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Cost-effectiveness analysis of grass pollen specific immunotherapy in children with allergic rhinitis compared to the standard of care symptomatic treatment in Portugal

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Key words

Allergen immunotherapy; allergic rhinitis; children; cost-effectiveness; grass pollen.

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Impact statement

Allergen immunotherapy is cost-effective in children with grass pollen allergic rhinitis due to an increase in quality-of-life and asthma prevention, especially for the subcutaneous route.

Summary

Background. *Cost-effectiveness studies evaluating allergen immunotherapy (AIT) in children are scarce. We aim to compare the cost-effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) against standard-of-care (SOC) treatment in children with grass pollen allergic rhinitis.* ***Methods.*** *We created a Markov model to compare the three strategies over a 10-year horizon. SOC was the reference to calculate the incremental cost-effectiveness ratio (ICER). Deterministic and probabilistic sensitivity analysis were used to assess models' uncertainty.* ***Results.*** *We obtained an ICER of 12,605€ and 6,318€ for SLIT and SCIT, respectively. In sensitivity analysis, SCIT was more cost-effective than SLIT.* ***Conclusions.*** *AIT is cost-effective in children with grass pollen allergic rhinitis, especially for the subcutaneous route.*

Introduction

Allergen specific immunotherapy (AIT) is a treatment aiming to improve the health and quality of life of patients suffering from allergic conditions such as rhinitis, rhinoconjunctivitis, food allergy, and asthma (1-4). Beyond the symptomatic treatment, AIT is an effective option in the long-term because it may alter the natural course of the disease by inducing allergen-specific immune tolerance and suppressing allergic inflammation (5, 6). The main routes of administration are subcutaneous injections (SCIT) and sublingual preparations (SLIT) as tablets or drops, hereafter referred together as AIT, which are ideally administered for at least three years to maximize efficacy (1, 4). But other delivery routes are emerging, such as oral mucosal, epicutaneous, and intralymphatic, that may also target other IgE mediated hypersensitivities besides aeroallergies while meeting patients' expectations of tolerability, effectiveness, and adherence (7, 8). However, the acquisition costs of AIT are not currently reimbursed by the Portuguese National Health System, except for persons under other subsystems or health insurances, compromising its use due to high costs and contributing to health inequalities (9).

Cost-effectiveness analysis (CEA) is a recognized approach to estimate short- and long-term consequences on costs and the health of a specific treatment (10). Pharmacoeconomics, a branch of health economics, is highly important in health policy making because it allows the comparison and analysis of the value of a certain policy or treatment with another. Quality-adjusted life years (QALYs) are used to quantify, on a scale from zero to one, the outcome of health in economic evaluations allowing comparisons across interventions since it can be applied in all models independently of the kind of drugs, interventions, or diseases (10). CEA studies are important to inform costs and health gains of an intervention, over a time-specific horizon, translating the knowledge of clinical efficacy trials and real-world studies (11). The results provided by these studies allow to drive political decisions, as reimbursement of therapies, and to implement policies contributing to the improvement of patients' lives while reducing health inequalities regarding drugs' assessment.

A review on CEA studies published in the literature of AIT effects on allergic rhinitis and asthma has been published recently (12). Briefly, although AIT shows to be cost-effective in most scenarios, the studies performed in children and incorporating real-life compliance information comparing SCIT and SLIT therapies are scarce (12). Moreover, there are no studies performed within the context of the Portuguese healthcare system. Children are an important population to assess because AIT can modify the natural course of the disease, especially at an early age, and prevent the development of asthma (6, 13, 14). The prevalence of allergic rhinitis is around 25% in Portuguese children and adolescents, with grass pollen being a relevant allergen in the country and 70% of cases also presenting conjunctivitis symptoms (15, 16). Having in mind the perspective of the Portuguese healthcare system, we aim to compare SCIT and SLIT therapies for children with grass pollen allergic rhinitis using a mathematical modelling approach and parameters from multiple sources, including randomized controlled trials and real-world data, such as compliance.

Materials and methods

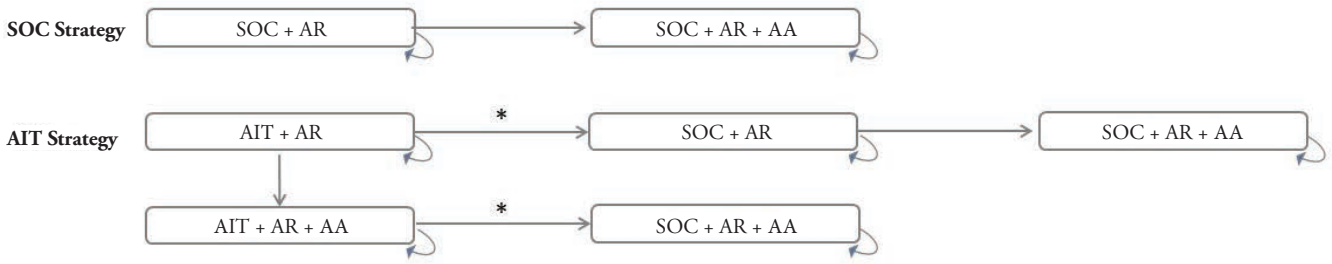
This cost-effectiveness analysis was based on previous modelling cost-analysis studies conducted in adults with allergic rhinitis/rhinoconjunctivitis (17). We developed a Markov model framework with three strategies to compare costs and health-related quality-of-life outcomes in children with grass allergic rhinitis treated with SLIT or SCIT plus symptomatic treatment *versus* children treated with pharmacotherapy alone, over a 10-year horizon, according to the Portuguese healthcare system perspective.

Model assumptions

For the Markov state-transition model, we simulated a hypothetical cohort of 8-years old patients, one thousand per strategy, over a 10-year time horizon divided into cycles of one year. The inclusion criteria of patients were a diagnosis of moderate persistent allergic rhinitis (AR) eligible for AIT (18), and a positive skin-prick test to grass pollen. Patients were modelled across different mutually exclusive health states. At baseline, none of the children had a diagnosis of asthma, however, throughout the model the probability of developing allergic asthma (AA) was considered and accounted as an effectiveness parameter. We assumed that AIT plus pharmacotherapy would generate a decrease in AR medication and symptoms, and a reduction of AA cases when compared to the standard-of-care (SOC) pharmacotherapy strategy. The SOC strategy had three possible health states: allergic rhinitis ("SOC + AR"), allergic rhinitis plus asthma ("SOC + AR + AA"), and any-cause death (**figure 1**). Allergen immunotherapy strategies, sublingual (SLIT) and subcutaneous (SCIT), were defined by five health states each: two states according to AIT administration, namely, AIT and rhinitis ("SLIT/SCIT + AR"), and AIT with rhinitis and asthma ("SLIT/SCIT + AR + AA"), plus the three health states mentioned for the SOC arm (**figure 1**).

At the beginning of the intervention, all patients were in the health state of "SOC + AR" or "SLIT/SCIT + AR", if assigned to any of the AIT strategies. In the two intervention strategies, the health states representing AIT administration were also characterized by the concomitant use of symptomatic SOC therapy for AR. We accounted for the possibility of therapy discontinuation as it happens in the real world (19). Patients who discontinued AIT were allocated to the corresponding health state as in the SOC arm, taking only symptomatic therapy ("SOC + AR" or "SOC + AR + AA"), and this therapy regimen was allowed for

Figure 1 - *Basic structure of the Markov model. The risk of death is not shown (in order to simplify representation) but all patients, in any health state, are in risk of any-cause death. Patients under intervention (AIT administration) may discontinue treatment at any time; at that time patients follow the transitions and health states represented for the SOC arm. The same happens when treatment ends (after 3 years). The previous situations are explained in the scheme with an asterisk (*). AIT represents SCIT and SLIT strategies. All patients under the AIT strategy start, at baseline, in "AIT + AR" health state; all patients under the SOC strategy start, at baseline, in "SOC + AR" health state.*



AA: allergic asthma; AIT: allergen immunotherapy; AR: allergic rhinitis; SOC: standard-of-care treatment; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

the remaining time horizon. After treatment discontinuation, patients were not allowed to return to any AIT health-state. Patients were allowed to discontinue at any time of the year; thus, to account for this assumption, AIT costs corresponding to six months of administration were considered during the year before discontinuation. For these patients, AIT effects on medication and utilities were not considered once treatment was discontinued, and SOC values were considered instead. AIT was ideally administered for three years, as recommended, and patients who completed AIT continued pharmacotherapy alone for the remaining cycles; the AIT effects on costs and utilities remained the same after the end of therapy as described in literature (14). The effect of AIT on AA prevention was only considered for the years of AIT administration assuming, then, the value for the SOC strategy (6, 13, 20). When a patient developed asthma, it was not possible to return to a health state with AR only.

Model inputs

Each health state had an associated cost and utility value. After each Markov cycle, the cohort was re-distributed across the possible health-states based on transition probabilities derived from the literature. In the end, health-state costs and utilities were accumulated according to the number of patients, in each cycle, and over the time horizon. The effectiveness of strategies was measured by the reduction of symptomatic treatment and the development of asthma. The transition probabilities, disease-related costs, and utilities reflect the effect of strategies in the sample according to different sources for clinical data input. We conducted a literature review and meta-analysis to obtain the effectiveness parameters of both SLIT and SCIT on asthma prevention for grass pollen allergic patients to avoid the overestimation of effects if data were retrieved from a single study (**online supplements table IS**). The protective effect was higher for SCIT than for SLIT (OR, 95%CI, n studies: 0.50, 0.28-0.88, 3 *vs* 0.81, 0.67-0.97, 5) (**online supplements table IS**). For the SOC strategy, the probability of developing asthma was extracted from the control arm of the grass sublingual immunotherapy tablet asthma prevention (GAP) trial that was conducted in children with grass pollen allergy over 5 years (20). Asthma was reported if a patient had experienced asthma symptoms and medication use during the year leading up to the visit. The probability of discontinuation was retrieved from a recent real-world study conducted in German children with pollen allergic rhinitis taking SLIT or SCIT (19). Cumulative non-adherence for 3 years of therapy was 66% and 53% for SLIT and SCIT, respectively. Any-cause death probability was estimated based on country-specific data from 2019, for 8-years old children, using data from the Portuguese national institute of statistics (21). Cumulative probabilities were converted as rates using their periodicity and re-expressed as probabilities within 1 year (cycle length) (22, 23).

Costs were defined for each health state, per year, to express differences in medication and healthcare resources use between strategies (**table I**). AR treatment followed ARIA recommendations (18) and the duration of the pollen season was estimated at 4 months (120 days) (24). We assumed full adherence to the AR symptomatic treatment in all strategies. The cost of symptomatic treatment was calculated based on drug total costs for 4 months; patients were under nasal corticosteroids and oral antihistamines (18, 25). For both AIT strategies, the costs of AR symptomatic drugs were reduced by 27% according to the mean reduction effect found in the GAP trial and this effect remained after AIT completion (14, 20, 26). AIT costs for one year of SLIT (Sulgen) and SCIT (Allergovac Poliplus) were based on the price list of the pharmaceutical company Roxall, for Portugal (27). In the case of SCIT, we considered administration costs of the therapy at the hospital assuming the con-

tracted costs for Portuguese public hospitals in 2020 (28). In the case of AIT discontinuation, we considered a reduction of 50% in the AIT cost in the year in which treatment was discontinued (representing a mean of six months of immunotherapy the year before discontinuation). Asthma symptomatic drug costs were calculated according to the price of drugs in the country; patients were stratified by GINA guidelines in steps 2, 3, and 4 in equal proportions to calculate a mean value for drug's costs (25, 29). We also considered costs related to asthma moderate and severe exacerbations according to the probability of emergency department (ED) visits and hospitalizations, respectively, based on contracted values for Portuguese public hospitals (28). For both AIT strategies, asthma medication costs and exacerbations were reduced based on literature findings; the use of drugs was reduced by 34% and exacerbations leading to ED visits or hospitalizations due to asthma were reduced by 74% (20, 30). The previous effects on asthma were included in the model for patients taking and completing three years of immunotherapy. In all strategies, we considered two scheduled medical visits (including medical tests), per year, and SPT testing was considered only in SLIT and SCIT strategies, at the first visit, to confirm the diagnosis of grass allergy (31).

Quality-adjusted life years (QALYs) was the outcome used to translate efficacy in health gains. QALYs were extrapolated from a study conducted in children with grass pollen rhinoconjunctivitis with or without well to partially controlled allergic asthma (32). The effect was assumed to be the same for SLIT and SCIT since we did not find specific data for children by the AIT administration route. The QALYs are presented in **table I**. Alternative QALYs values were retrieved from another study conducted in adults with a grass pollen allergy that stratified SLIT and SCIT effects on symptoms (17). The authors applied the multi-attribute Rhinitis Symptom Utility Index (RSUI) to convert symptoms severity in utilities (33). Symptoms severity was evaluated through the rhinoconjunctivitis total symptom scores (RTSS) reported in a meta-analysis (34, 35). To adjust these data from a single condition, we further considered the patient's age and co-existing asthma utilities values to better describe our pediatric population using a multiplicative function (17, 36). Thus, we used as reference a value for "perfect health" valid for children (0.960) and incorporated asthma comorbidity into utilities by attributing a utility of 0.737, as described (17, 37). These adjusted QALYs were applied in an alternative scenario analysis.

Model calculation

Cost-effectiveness was established by the calculation of the incremental cost-effectiveness ratio (ICER) as incremental costs divided by incremental QALYs assuming the SOC strategy as reference. Costs and QALYs were discounted at 3% per year as performed in previous studies (10, 17, 38). The cost-effectiveness threshold was based on literature; the WHO recommends a threshold of up to three times the gross domestic product (GDP) per capita of the country (39). However, this threshold has been widely discussed because it is very high and a lower value, corresponding to the lower category suggested by WHO, specifically, up to one time the GDP *per capita*, was adopted in this analysis (39, 40). Therefore, in Portugal, the GDP *per capita* in 2020 was set at 22,488.62 USD (corresponding to 18,482.80€; data converted on June 7th, 2021). All the analyses were performed in RStudio Software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) using the heemod package (22).

Sensitivity analysis

A deterministic sensitivity analysis (DSA) was performed to check the uncertainty of each parameter, allowing to determine an ICER range due to lower and higher changes in the input parameters in comparison to the base case scenario (10). For the efficacy parameter of asthma development in both AIT strategies, the range of values for DSA was defined based on the 95% confidence interval. For QALYs and remaining parameters we considered a margin of error of ± 10% and ± 20%, respectively (**table I**). A Tornado diagram was developed to summarize the relative contribution of each parameter to ICER variation (11).

A probabilistic sensitivity analysis (PSA) was performed by running 1,000 Monte Carlo simulations (10, 11). These multiple repetitions of ICER calculations were drawn randomly according to the defined distribution for utilities and transition probabilities parameters (11, 41). Utilities followed a beta distribution while transition probabilities followed a binomial distribution. Costs were point estimates since their calculation was based on market prices and did not follow any specific distribution. PSA results were represented graphically, in a cost-effectiveness plane, to evaluate the extent of uncertainty (11). Based on those results, a cost-effectiveness acceptability curve (CEAC) was created showing the probability of the intervention being cost-effective compared to the symptomatic arm for different threshold values of willingness-to-pay (WTP) (11).

In the end, other plausible scenarios were considered to analyze alternative assumptions that might happen or be improved in clinical practice (23). Thus, we considered the following alternative scenarios (the values changed in the model for each scenario are shown in parentheses) to the base case model:

1. Asthma medication costs calculated based only on step 2 GINA guidelines, assuming that all patients who developed asthma were considered to be mild cases (SOC: 153€; AIT: 59€).
2. Equal asthma costs across all strategies (do not consider AIT effects on asthma) (SOC: 451€; AIT: 451€).
3. Adherence of 50% to AR symptomatic treatment across all strategies (SOC: 14€; AIT: 10€).
4. Different time horizons, 5 years to ensure the short-term effect found in the literature review, and 15 years assuming that effects are longer.

Table I *- Parameters of the Markov model for the three strategies (SOC, SLIT and SCIT).*

Parameter	Base case value (Symptomatic arm)	Base case value (AIT arm, SLIT or SCIT)	Range for DSA		Distribution	Ref.
			Lower	Upper		
Time horizon	10 years					
Age at baseline	8 years					
Number of health states	3	5	-	-	-	-
Initial Health State (t0)	SOC + AR (n = 1,000)	SLIT/SCIT + AR (n = 1,000)	-	-	-	-
Annual discount rate (costs/QALYs)	3% (range 0%-6%)					
Time of a Markov cycle	1 year					
Transition probabilities						
Disease progression (SOC + AR --> SOC + AR + AA)	0.021287		0	0.068850	Binomial	20
Disease progression (AIT + AR --> AIT + AR + AA)	-	SCIT: 0.010643 SLIT: 0.014262	SCIT: 0.005960* SLIT: 0.012985*	SCIT: 0.018732* SLIT: 0.020648*	Binomial	Meta-analysis
AIT discontinuation	-	SCIT: 0.22250 SLIT: 0.302047	SCIT: 0.124966 SLIT: 0.185674	SCIT: 0.353670 SLIT: 0.480750	Binomial	19
Annual mortality						
All-cause mortality (any state to death)	0.000066				-	21
Costs (1 year)						
SPT testing (t = 0)	-	31€	-	-	-	28
Scheduled visits + additional tests	150€ (2 visits/year)		-	-	-	28
Medication AR	28.86€	21.00€	SOC: 23.86€ AIT: 16.80€	SOC: 34.63€ AIT: 25.2€	-	18, 20, 25
Asthma costs	451€	180€	SOC: 361€ AIT: 144€	SOC: 541€ AIT: 216€	-	20, 25, 29
AIT	-	SCIT: 300€ SLIT: 860€	SCIT: 240€ SLIT: 688€	SCIT: 360€ SLIT: 1,032€	-	27
AIT administration	-	SCIT: 252€	-	-	-	28
QALYs						
SOC + AR	0.671		0.604**	0.738**	Beta	31
SOC + AR + AA	0.666		0.599**	0.733**	Beta	
SLIT/SCIT + AR	-	0.705	0.635**	0.776**	Beta	
SLIT/SCIT + AR + AA	-	0.677	0.609**	0.745**	Beta	
Death	0		-	-	-	-

*Value obtained based on the 95% confidence interval; **value obtained based on a margin error of 10%; the range for DSA analysis was calculated based on a margin error of 20% unless otherwise stated.

Table II *- Base case results of costs and health gains for SOC, SLIT, and SCIT strategies at the end of the model calculation (10-year horizon).*

Base case scenario	SOC	SLIT	SCIT
AR costs	288,495€	257,814€	248,095€
AIT costs	0€	1,571,120€	1,144,970€
AA costs	495,501€	334,882€	282,076€
Healthcare resource costs	1,500,002€	1,531,000€	1,531,000€
Total cost	2,283,999€	3,694,815€	3,206,141€
Total cost (discount rate)	1,988,279€	3,396,562€	2,921,615€
QALYs	6,702	6,827	6,868
QALYs (discount rate)	5,889	6,001	6,037
Cost difference	Ref	1,408€	933€
Effect difference	Ref	0.112	0.148
ICER	**Ref**	**12,605€**	**6,318€**

AA: allergic asthma; AIT: allergen immunotherapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-years; Ref: reference; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SOC: standard-of-care.

Table III *- Distribution of participants according to specific Markov cycles (cycles 0, 3, and 10) by health state.*

Cycle	SOC + AR	SOC + AR+AA	AIT + AR	AIT + AR + AA	Death
t = 0					
SOC	1,000	-	-	-	0
SLIT	-	-	1,000	-	0
SCIT	-	-	1,000	-	0
t = 3					
SOC	937	63	-	-	0
SLIT	634	27	319	20	0
SCIT	511	19	451	19	0
t = 10					
SOC	806	193	-	-	1
SLIT	543	116	275*	65*	1
SCIT	439	90	388*	82*	1

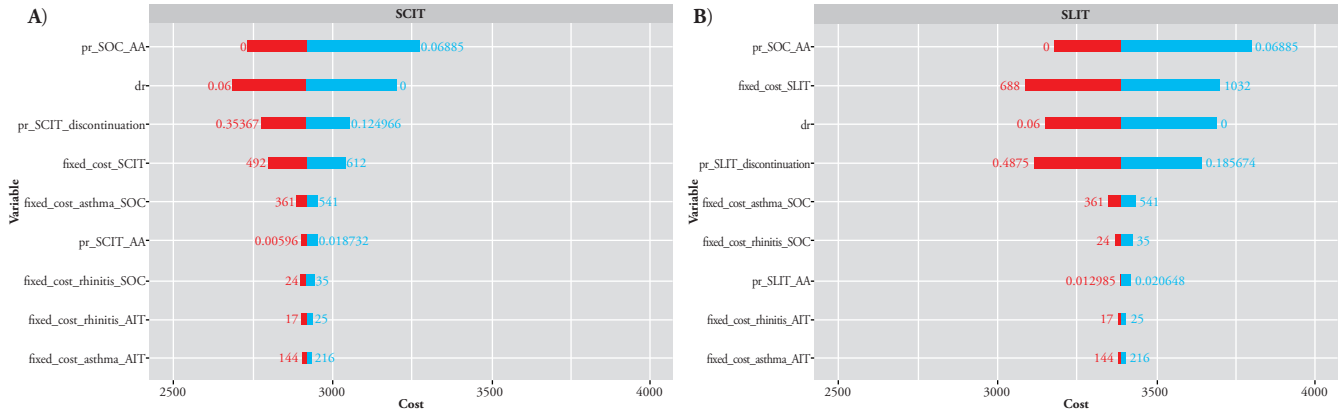
AA: allergic asthma; AIT: allergen immunotherapy; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SOC: standard-of-care; *patients who completed AIT (t = 3) were assumed to remain in the same state to consider long-term effects of AIT in medication and symptoms, however, the probability of developing asthma was assumed to be equal to the SOC arm since long-term effects are still under evaluation.

5. Long-term effect of AIT on asthma prevention.
6. Full adherence to AIT (no possibility of AIT discontinuation).
7. Discount of 50% in AIT acquisition costs (SLIT: 430€; SCIT: 402€).
8. Different utilities values, adjusted for SLIT and SCIT ("SOC + AR": 0.748; "SOC + AR + AA": 0.551; "SLIT + AR": 0.797; "SLIT + AR + AA": 0.587; "SCIT + AR": 0.817; "SCIT + AR + AA": 0.602).

Results

The base case analysis shows an incremental cost of 1,408€ and 933€ per patient for SLIT and SCIT, respectively, and a correspondent incremental QALYs of 0.112 and 0.148 per patient, causing an ICER of 12,605€ and 6,318€ per QALY gained (**table II**). SCIT strategy was more cost-effective than SLIT, but both strategies are lower than the willingness-to-pay threshold assumed for Portugal. SCIT demonstrated to be less costly than SLIT mainly due to savings in asthma costs and AIT price. Over

Figure 2 *- Tornado plot resulting from the deterministic sensitivity analysis.*



Blue and red bars represent an increase or decrease in costs, respectively, according to changes in variables (the range of values is represented in each side of the bars). **(A)** Subcutaneous strategy; **(B)** Sublingual strategy. AIT: allergen immunotherapy; dr: discount rate; fixed_cost_asthma_AIT: asthma-related costs in AIT arm; fixed_cost_asthma_SOC: asthma-related costs in SOC arm; fixed _cost_rhinitis_AIT: rhinitis-related costs in AIT arm; fixed_cost_rhinitis_SOC: rhinitis-related costs in SOC arm; fixed_cost_SCIT/SLIT: cost of AIT according to the administration route, subcutaneous or sublingual; pr_SCIT/SLIT_AA: probability of developing asthma in AIT arm; pr_SCIT/SLIT_discontinuation: probability of AIT discontinuation; pr_SOC_AA: probability of developing asthma in the SOC strategy.

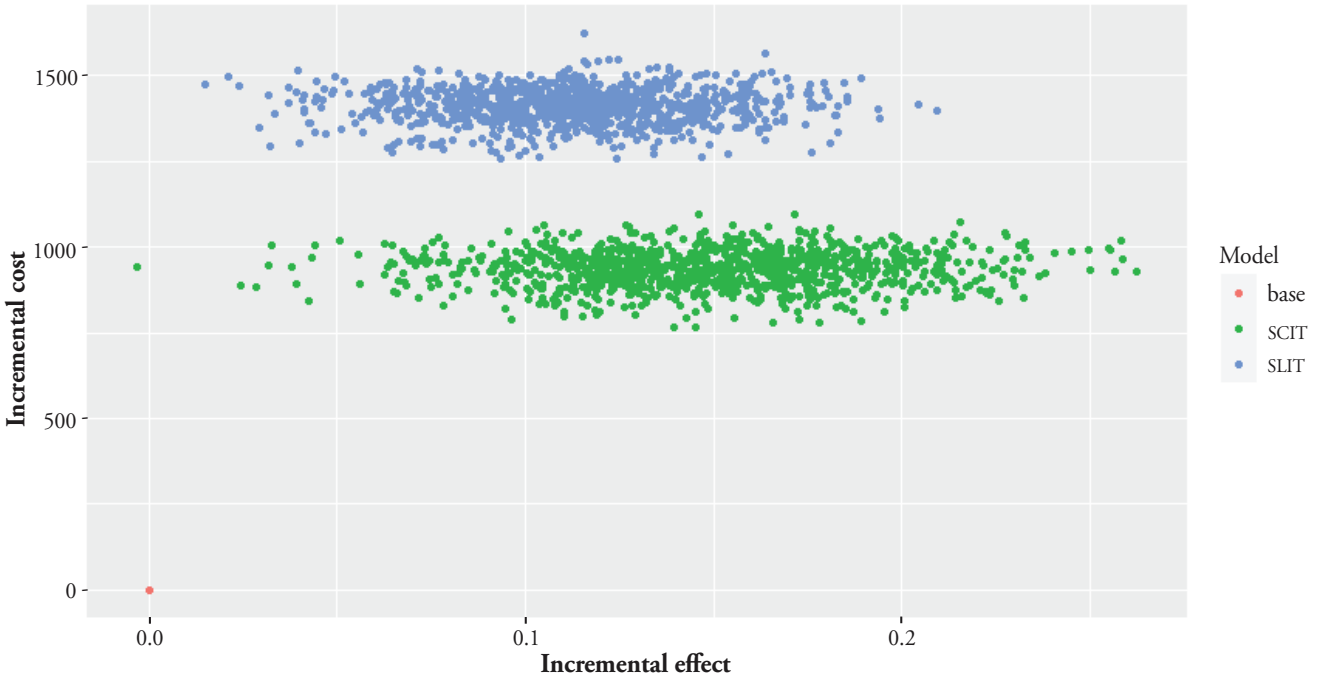
the 10-year horizon, the number of patients experiencing allergic asthma were 193, 181, and 172 in SOC, SLIT, and SCIT strategies, respectively (**table III** and **online supplements figure 1S**). According to the model, 339 and 470 patients completed three years of immunotherapy (SLIT and SCIT, respectively). For these patients, the reduction of medication and allergic symptoms remained the same until the end of the analysis.

The robustness of the results was assessed in a sensitivity analysis. The DSA showed the parameters with the greatest contribution for the estimation of costs; specifically, for both AIT strategies, the natural probability of asthma development (assumed in the SOC arm) over the years was the main driver for change in costs, followed by annual discount rate, treatment discontinuation, and AIT costs (particularly, in SLIT arm) (**figure 2**). The variation of model parameters resulted in a range of ICER values varying between 4,185€ and 20,290€ for SLIT, and 2,093€ and 8,417€ for SCIT. The full list of ICER values according to individual variation of parameters is presented in the supplemental material (**online supplements tables IIS, IIIS**).

The PSA showed the uncertainty surrounding the point estimates of the base case analysis and is graphically represented in **figure 3** (each dot represents a Monte Carlo iteration of PSA). Both strategies showed to be cost-effective as QALYs increase, the costs remain similar, decreasing ICER; still, SCIT presented higher values for QALYs and lower costs which translates to a lower ICER value. The mean ICER after Monte Carlo simulation was 12,599€ and 6,249€ for SLIT and SCIT interventions, respectively (**online supplements table IVS**). These values are very similar to those from the base case scenario. These data were used to compute the cost-effectiveness acceptability curves (CEAC) according to a range of WTP thresholds. The graphs are presented in the supplemental material (**online supplements figure 2S**) and show the probability of AIT to be cost-effective considering different WTP threshold values; for example, considering a WTP limit of 10,000€ the probability of being cost-effective is 20% (SLIT) and 90% (SCIT), but increasing this limit to 20,000€, which is a similar value to the WTP that we assumed for Portugal, the values increase to 60% and 98%, respectively.

Uncertainty of the model was also assessed by varying model parameters according to possible circumstances that might happen in the real-world (**online supplements table VS**). The ICER remained similar to the base case when AA and AR costs varied. As expected, ICER values were higher when considering a short-time horizon and lower for a long-time horizon; both strategies were cost-effective for a higher follow-up of patients mainly due to the accumulated QALYs over years since costs were marginally reduced compared to the base case. If the probability of AA prevention remains after AIT completion, ICER results did not vary significantly. The possible scenarios related to full-adherence to AIT and a 50% discount on AIT acquisition costs had a significant effect on ICER as the probability of SLIT and SCIT being cost-effective increase to 77% and 97% (full-adherence), and 92% and 98% (50% discount), respectively. The previous probabilities are for a WTP of 10,000€, which is almost half of the WTP threshold value considered for Portugal. The last scenario analysis considered different utility values as the values found in the literature vary (the values assumed are described in

Figure 3 *- Results of the probabilistic sensitivity analysis graphically represented on a cost-effectiveness plan.*



Green: subcutaneous immunotherapy; blue: sublingual immunotherapy; orange: standard-of-care (reference).

Methods section). These values were adjusted for the patient's age and administration route of AIT according to the method described previously. The results were significantly lower being both strategies cost-effective at a WTP of 10,000€.

Discussion

Over a 10-year time horizon, grass sublingual and subcutaneous immunotherapy seems to be cost-effective in children with grass pollen-induced allergic rhinitis considering a WTP threshold of 18,482.80€. Specifically, SCIT showed robust results for all sensitivity analyses and different scenarios. The key drivers were the reduced asthma-related costs due to the prevention of more asthma cases and the lower acquisition price of SCIT. Sensitivity analysis evidenced the core parameters that might improve the cost-effectiveness of both strategies; namely, a reduction in AIT acquisition prices and an increase of AIT adherence. The results were sensitive to changes in utilities showing the importance to improve evidence of AIT effects on QALYs in younger populations. Still, the conclusions remained the same for this alternative scenario.

To our knowledge, this is the first cost-effectiveness study conducted in children with grass pollen allergic rhinitis that evaluated two different administration routes of allergen immunotherapy relative to the standard symptomatic treatment. Vogelberg and colleagues conducted a similar analysis in children for sublingual immunotherapy (38). Our results were similar in terms of QALYs gained per patient and higher regarding costs resulting in a relatively higher ICER value. Differences in costs can be due to some assumptions that differed between studies; Vogelberg *et al.* (38) considered only mild cases of asthma and an additional health-state to account for improvement of rhinitis severity (mild rhinitis) which may result in a lower cost per patient treated with SLIT. Still, our study reinforces the result previously obtained for SLIT in children (38). Additionally, our study evaluated for the first-time grass pollen SCIT in a pediatric cohort and demonstrated to be more cost-effective than SLIT, especially when assessing sensitivity analysis and alternative scenarios. The main reasons for this effect are the lower costs of AIT and the larger effect on asthma prevention and, consequently, in asthma-related costs. This study assumes a higher relevance because it simulates a pediatric cohort of patients in which preventive effects might be more prominent; when evaluating studies conducted in adult patients, the ICER results usually are higher for both strategies evidencing the greater long-term effects if administered early in life (17, 42). QALYs estimation for children may also impact this hypothesis since values differed greatly from adults highlighting the scarcity of studies conducted in children (32).

This study has several strengths. The base case model outcomes can be considered conservative due to different assumptions

considered for model input. First, despite the productivity losses of children in school and absenteeism not being accounted, because we considered in the analysis direct costs, the inclusion of those parameters would reduce the ICER estimates which strengths the conclusions of this simulation (17). Second, the effect of AIT on asthma prevention was assumed only for the years of treatment, but if we assume this effect in an alternative scenario for the remain time-horizon, in patients completing three years of treatment, the results do not differ significantly. Third, asthma prevention effects of AIT were retrieved from a meta-analysis conducted by the team synthesizing multiple data sources to improve the precision of pooled estimates resulting in a less optimistic estimate when compared to previous studies avoiding the overestimation of the results (31, 38). Fourth, whenever possible, we included data from real-world studies, such as the discontinuation rates. Fifth, patients who discontinue AIT earlier than the recommended duration were assumed to not receive any benefit from AIT (medication, QALYs, asthma prevention). Lastly, we conducted an extensive sensitivity analysis (deterministic and probabilistic) to account for the uncertainty of parameters and considering different scenarios in alternative analysis to the base case model, strengthening the results and evidencing key parameters to improve the cost-effectiveness of strategies in practice and drive policy decisions.

There are limitations that we should address. As a direct limitation of Markov models, we should be aware that we calculated expected costs and health benefits by simulating disease progression based on literature findings and we are not following each patient since the model is memoryless (10). Although we proposed a WTP threshold based on the lower limit suggested by the WHO, this limit should be interpreted cautiously since the Portuguese authorities may consider another value (39). Nonetheless, the extensive presentation of the results allows the interpretation using different WTP thresholds. The efficacy of AIT on allergic rhinitis symptoms and medication use was assumed to be the same for both strategies based on a study conducted only for SLIT (20). However, a meta-analysis revealed no differences between SCIT and SLIT on standardized mean differences for rhinitis medication scores in children (26) and there are no head-to-head comparisons of SLIT and SCIT efficacy. We also assumed that AIT had effects on reducing moderate and severe asthma exacerbations in children completing three years of immunotherapy but still developed asthma (65 and 82 for SCIT and SLIT arms, respectively). The evidence to support this assumption is very limited and we should be aware that this effect may be not significant as we expected. The key assumption underpinning our choice are the known effects of AIT in patients with asthma while the extrapolation for the remaining time-horizon was the sustained efficacy of AIT on symptoms and medication demonstrated previously in GAP trial (20). In a complementary analysis, assuming no effects of AIT on reducing asthma medication and exacerbations in children who developed asthma, asthma-related costs would be 495,501€, 400,458€, and 437,790€ for SOC, SCIT, and SLIT, respectively, leading to an ICER value of 6,989€ (SCIT) and 13,384€ (SLIT). As discussed, the results are highly dependent on the underlying assumptions retrieved from the literature. Thus, the long-term effects of AIT on allergic rhinitis and asthma, in children, should be demonstrated in higher-quality studies since published studies are inconsistent and limited, especially for AR patients that develop asthma under AIT completion. Therefore, we varied model parameters to allow interpretation of the results under different assumptions. We did not incorporate nonmedical costs such as transportation to the hospital for SCIT administration which may underestimate the ICER for this strategy at some extent (17). The management of adverse events due AIT was not considered. We believe that the impact of this parameter would be low because the differences found in randomized controlled trials between AIT and placebo are not statistically significant (6, 20). The analysis is also limited to a 10-year time horizon, and we cannot predict the long-term effect of asthma development in adulthood as well as asthma severity of those who developed asthma. We assumed SPT to be enough to identify grass pollen patients eligible for AIT, but the pattern of the pollen season can be very heterogeneous as well as the sensitization profiles of patients (43, 44). These situations usually require the use of molecular diagnostic tests which may increase the costs associated to the AIT arms and the reported ICER. We assumed that SPT would be performed only in children of AIT strategies to confirm the diagnosis of grass allergy prior to AIT initiation and to allow the comparison with other studies (31). A complementary analysis assuming skin-prick testing in children of SOC group showed a decrease in ICER for both SLIT and SCIT (12,328€ and 6,108€, respectively). Finally, the analysis is limited to the Portuguese context but the model can be applicable to other countries and realities according to the available data to fulfil the model parameters.

Despite variations underlying model assumptions, we sought to assess which strategy is more cost-effective in a pediatric population. Different sensitivity and scenario analysis demonstrated a favorable result to SCIT mainly due to the lower acquisition costs, higher effect on asthma prevention and related costs, and lower discontinuation rates. However, SCIT is not always the preferred route of administration in children due to frequent hospital visits and discomfort and constraints intrinsically related to the administration of injections. New routes of AIT administration are being developed and evaluated, such as epicutaneous, intradermal, and intralymphatic (8), but there is limited evidence of effectiveness, especially in young children in which AIT is more likely to prevent new sensitizations and asthma.

The present study highlights the scarcity of cost-effectiveness studies conducted in pediatric populations and, considering the

Portuguese context for both children and adults. Despite the conservative framework adopted in this study, we cannot strongly conclude that both forms of AIT for grass pollen allergic rhinitis are cost-effective. However, SCIT showed consistent results across different scenarios and a high probability of being cost-effective which may drive future policy decisions and AIT prescribing habits. To perform reliable and accurate cost-effectiveness studies, AIT long-term effects should be addressed in high-quality studies as well as in head-to-head comparative studies. We also conclude that AIT adherence has a great impact on results highlighting the value of implementing strategies to promote adherence rates.

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Contributions

AM, JCR, MF: conceptualization. AM, LD: clinical data discussion and approval - as medical experts in the field. MF, IP, FCM: literature review. MF, JCR: implemented the model (data analysis). All authors: results interpretation and discussion, writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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Figure 1S *- Distribution of participants in each health state per strategy.*

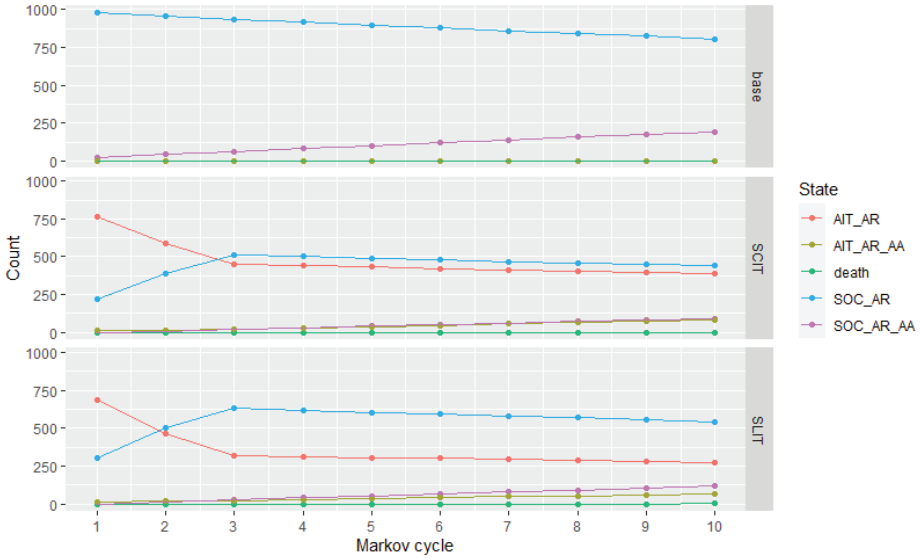
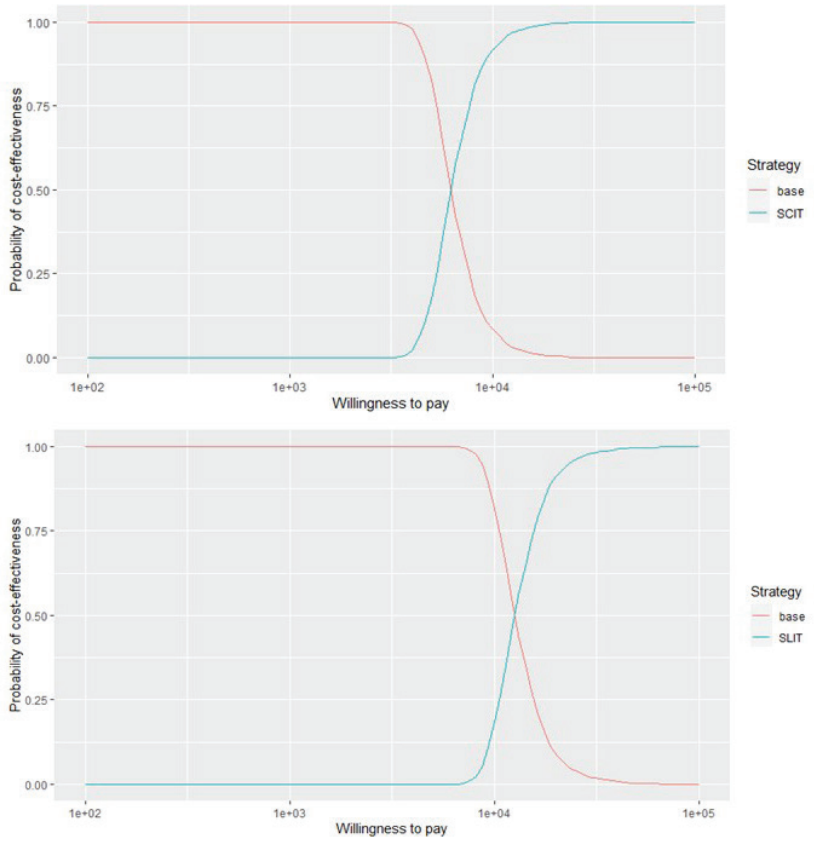


Figure 2S *- Cost-effectiveness acceptability curve for different willingness-to-pay (WTP) threshold values.*



(A) Subcutaneous strategy; **(B)** Sublingual strategy.

Table IS *- Results from the meta-analysis performed by our team to estimate the effect of AIT on asthma prevention. For each output is presented the corresponding OR (95%CI), heterogeneity parameters, and the number of studies included.*

Outcome	Meta-analysis, OR (95%CI)	Heterogeneity I2; Q (P-value)	n of studies analyzed
All studies (independently of allergen and population)			
SCIT	0.58 (0.37; 0.90)	26%; 6.72 (0.24)	6
SLIT	0.76 (0.62; 0.94)	23%; 10.45 (0.23)	9
Studies performed only in children			
SCIT	0.52 (0.18; 1.49)	0%; 0.14 (0.71)	2
SLIT	0.63 (0.29; 1.35)	33%; 5.93 (0.20)	5
Studies performed only in grass/ birch pollen allergic patients			
SCIT	0.50 (0.28; 0.88)	0%; 0.8 (0.67)	3
SLIT	0.81 (0.67; 0.97)	11%; 4.47 (0.35)	5

CI: confidence interval; I^2: Higgins I^2 statist; OR: Odds ratio; Q: Cochran's Q; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

Table IIS *- Costs and QALYs per patient and the respective ICER results according to changes in key parameters (deterministic sensitivity analysis) for the sublingual immunotherapy strategy.*

SLIT strategy	Cost difference	Effect difference	ICER
Base case scenario	**1,408€**	**0.112**	**12,605€**
dr – no annual discount	1,411€	0.125	11,320€
dr – annual discount 6%	1,403€	0.101	13,858€
Cost asthma AIT	1,397€	0.112	12,502€
	1,420€	0.112	12,709€
Cost asthma SOC	1,447€	0.112	12,954€
	1,369€	0.112	12,257€
Cost rhinitis AIT	1,394€	0.112	12,481€
	1,422€	0.112	12,730€
Cost rhinitis SOC	1,425€	0.112	12,757€
	1,387€	0.112	12,414€
AIT discontinuation	1,659€	0.165	10,082€
	1,129€	0.056	20,290€
Pr AA (AIT arm)	1,402€	0.112	12,509€
	1,435€	0.110	13,095€
Pr AA (SOC arm)	1,610€	0.113	14,206€
	1,053€	0.108	9,739€
AIT cost	1,100€	0.112	9,845€
	1,717€	0.112	15,366€
QALY SOC + AR	1,408€	0.316	4,452€
	1,408€	0.092	15,162€
QALY SOC + AR + AA	1,408€	0.141	10,007€
	1,408€	0.093	17,026€
QALY SLIT + AR	1,408€	0.110	12,818€
	1,408€	0.336	4,185€
QALY SLIT + AR + AA	1,408€	0.090	15,669€
	1,408€	0.134	10,544€

AA: allergic asthma; AIT: allergen immunotherapy; dr: discount rate; ICER: incremental cost-effectiveness ratio; pr: probability; QALY: quality-adjusted life-years; Ref: reference; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SOC: standard-of-care.

Table IIIS *- Costs and QALYs per patient and the respective ICER results according to changes in key parameters (deterministic sensitivity analysis) for the subcutaneous immunotherapy strategy.*

SCIT Strategy	Cost difference	Effect difference	ICER
Base case scenario	**933€**	**0.148**	**6,318€**
dr – no annual discount	922€	0.166	5,563€
dr – annual discount 6%	939€	0.133	7,058€
Cost asthma AIT	920€	0.148	6,228€
	947€	0.148	6,407€
Cost asthma SOC	983€	0.148	6,653€
	884€	0.148	5,982€
Cost rhinitis AIT	915€	0.148	6,194€
	952€	0.148	6,441€
Cost rhinitis SOC	956€	0.148	6,468€
	905€	0.148	6,128€
AIT discontinuation	1,068€	0.200	5,345€
	789€	0.094	8,413€
Pr AA (AIT arm)	914€	0.150	6,107€
	967€	0.145	6,690€
Pr AA (SOC arm)	1,163€	0.151	7,721€
	526€	0.142	3,715€
AIT cost	812€	0.148	5,493€
	1,055€	0.148	7,142€
QALY SOC + AR	933€	0.417	2,239€
	933€	0.121	7,693€
QALY SOC + AR + AA	933€	0.185	5,056€
	933€	0.111	8,417€
QALY SCIT + AR	933€	0.146	6,382€
	933€	0.446	2,093€
QALY SCIT + AR + AA	933€	0.123	7,598€
	933€	0.173	5,406€

AA: allergic asthma; AIT: allergen immunotherapy; dr: discount rate; ICER: incremental cost-effectiveness ratio; pr: probability; QALY: quality-adjusted life-years; Ref: reference; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SOC: standard-of-care.

Table IVS *- Results from the probabilistic sensitivity analysis (mean values).*

Strategy	Cost difference	QALY difference	ICER
SLIT	1,409€	0.112	12,618€
SCIT	934€	0.149	6,249€

ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

Table VS *- ICER results for SLIT and SCIT according to different scenarios.*

Scenarios	Cost difference	Effect difference	ICER
#1 – Lower asthma costs			
SLIT			
Base case	1,498€	0.112	13,412€
PSA (average)	1,500€	0.112	13,338€
PSA CEAC probability (10,000 WTP)	-	-	12.5%
SCIT			
Base case	1,053€	0.148	7,127€
PSA (average)	1,054€	0.148	7,127€
PSA CEAC probability (10,000 WTP)	--	-	85%
#2 – Equal asthma costs for all strategies			
SLIT			
Base case	1,495€	0.112	13,385€
PSA (average)	1,492€	0.111	13,407€
PSA CEAC probability (10,000 WTP)	-	-	12.5%
SCIT			
Base case	1,033€	0.148	6,989€
PSA (average)	1,036€	0.150	6,882€
PSA CEAC probability (10,000 WTP)	--	-	87%
#3 – 50% of adherence to AR symptomatic treatment for all strategies			
SLIT			
Base case	1,422€	0.112	12,726€
PSA (average)	1,422€	0.111	12,765€
PSA CEAC probability (10,000 WTP)	-	-	17.5%
SCIT			
Base case	951€	0.148	6,437€
PSA (average)	951€	0.147	6,446€
PSA CEAC probability (10,000 WTP)	--	-	90%

Scenarios	Cost difference	Effect difference	ICER
#4.1 – Shorter time-horizon (5 years)			
SLIT			
Base case	1,501€	0.069	21,647€
PSA (average)	1,503€	0.070	21,459€
PSA CEAC probability (10,000 WTP)	-	-	0%
SCIT			
Base case	1,060€	0.088	11,997€
PSA (average)	1,060€	0.087	12,103€
PSA CEAC probability (10,000 WTP)	--	-	25%
#4.2 – Longer time-horizon (15 years)			
SLIT			
Base case	1,302€	0.146	8,928€
PSA (average)	1,306€	0.145	9,010€
PSA CEAC probability (10,000 WTP)	-	-	62.5%
SCIT			
Base case	789€	0.196	4,032€
PSA (average)	797€	0.196	4,059€
PSA CEAC probability (10,000 WTP)	--	-	97%
#5 – Long-term effect of AIT on asthma prevention (10 years)			
SLIT			
Base case	1,400€	0.113	12,380€
PSA (average)	1,402€	0.114	12,341€
PSA CEAC probability (10,000 WTP)	-	-	62.5%
SCIT			
Base case	915€	0.151	6,074€
PSA (average)	914€	0.148	6,169€
PSA CEAC probability (10,000 WTP)	-	-	90%
#6 – 100% adherence to AIT			
SLIT			
Base case	2,190€	0.282	7,778€
PSA (average)	2,190€	0.283	7,725€
PSA CEAC probability (10,000 WTP)	-	-	77%

Scenarios	Cost difference	Effect difference	ICER
SCIT			
Base case	1,279€	0.284	4,506€
PSA (average)	1,278€	0.281	4,549€
PSA CEAC probability (10,000 WTP)	--	-	97%
#7 – Discount of 50% in AIT acquisition costs			
SLIT			
Base case	637€	0.112	5,704€
PSA (average)	638€	0.110	5,778€
PSA CEAC probability (10,000 WTP)	-	-	92%
SCIT			
Base case	629€	0.148	4,257€
PSA (average)	631€	0.144	4,380€
PSA CEAC probability (10,000 WTP)	-	-	98%
#8 – Different utilities, adjusted for SLIT and SCIT according to Di Bona et al. (20)			
SLIT			
Base case	1,408€	0.189	7,463€
PSA (average)	1,408€	0.188	7,505€
PSA CEAC probability (10,000 WTP)	-	-	88%
SCIT			
Base case	933€	0.345	2,708€
PSA (average)	936€	0.342	2,738€
PSA CEAC probability (10,000 WTP)	-	-	100%

AIT: allergen immunotherapy; AR: allergic rhinitis; CEAC: cost-effectiveness acceptability curve; WTP: willingness-to-pay threshold; PSA: probabilistic sensitivity analysis; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy.