
Cost-effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma

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Background: Specific immunotherapy is the only potentially curative treatment in patients with allergic rhinitis and allergic asthma. Health economic evaluations on this treatment, particularly in a German context, are sparse.

Objective: To evaluate the cost-effectiveness of specific subcutaneous immunotherapy (SCIT) in addition to symptomatic treatment (ST) compared with ST alone in a German health care setting.

Methods: The analysis was performed as a health economic model calculation based on Markov models. In addition, we performed a concomitant expert board composed of allergy experts in pediatrics, dermatology, pneumology, and otolaryngology. The primary perspective of the study was societal. Additional sensitivity analyses were performed to prove our results for robustness.

Results: The SCIT and ST combination was associated with annual cost savings of €140 per patient. After 10 years of disease duration, SCIT and ST reach the breakeven point. The overall incremental cost-effectiveness ratio (ICER) was €–19,787 per quality-adjusted life-year (QALY), with a range that depended on patient age (adults, €–22,196; adolescents, €–14,747; children, €–12,750). From a third-party payer's perspective, SCIT was associated with slightly additional costs. Thus, the resulting ICER was €8,308 per QALY for all patients.

Conclusions: Additional SCIT was associated with improved medical outcomes and cost savings compared with symptomatic treatment alone according to a societal perspective. Taking a European accepted ICER threshold of up to €50,000 per QALY into account, additional SCIT is considered clearly cost-effective compared with routine care in Germany. The degree of cost-effectiveness is strongly affected by costs related to SCIT and the target population receiving such treatment.

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INTRODUCTION

Allergic rhinitis is a frequent chronic disease and is associated with a number of symptoms that reduce the patient's quality of life.¹ Often, the disease manifestation begins in early childhood. A prevalence of allergic rhinitis of 15% has been observed in children up to 7 years of age.² However, the proportion of patients with this condition increases to 25% in adults.^{3,4}

Since the 1970s, in Western societies a continuous increase of newly diseased patients was observed, which seems to be currently stabilized.⁵ The relation between allergic rhinitis and allergic asthma should be an important factor in the evaluation of treatments for allergic rhinitis. A number of

studies have suggested that allergic rhinitis precedes the development of allergic asthma.⁵ Other studies indicate that 80% of patients with allergic asthma also have allergic rhinitis.⁶ Thus, allergic asthma can be seen as a severe complication of allergic rhinitis.⁷

Specific subcutaneous immunotherapy (SCIT) is a well-established treatment for type 1 allergy. The efficacy of SCIT was confirmed in several studies.⁸ SCIT is deemed to be the only causal therapy of allergic rhinitis and was evaluated as a preventive treatment regarding the development of rhinitis-related allergic asthma.^{9,10} Currently, economic evaluations on this treatment, particularly in a German context, are sparse.

The aim of the present study was to evaluate the cost-effectiveness of SCIT in addition to symptomatic treatment (ST) compared with ST alone. Therefore, it was assumed that all patients receiving SCIT would also use symptomatic medication if their health state worsened. The health economic model was customized for the German health care setting.

METHODS

Design

The present analysis was performed as a health economic model calculation based on Markov models. The model consists of 3 modules (Fig 1). Model calculations are character-

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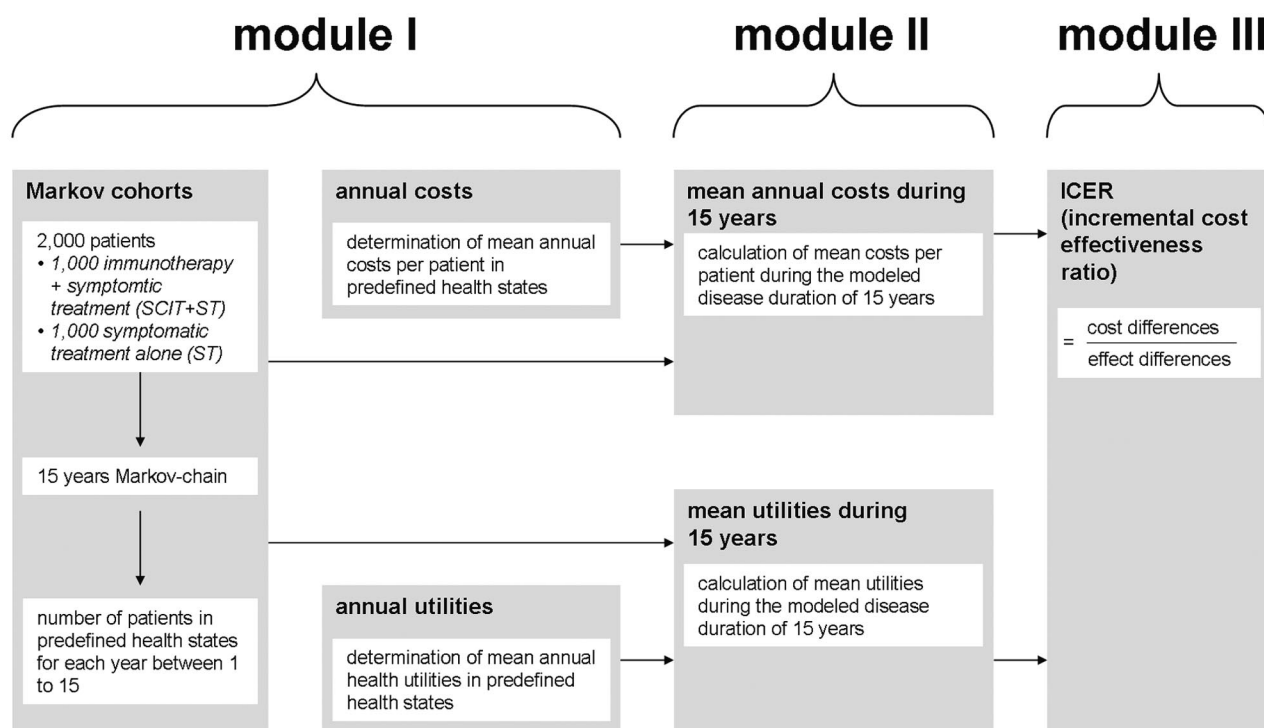


Figure 1. Model overview and basic methods of group comparisons. SCIT indicates subcutaneous immunotherapy; ST, symptomatic therapy.

ized by the need for robust assumptions, where epidemiologic data are missing. Thus, we formed a concomitant expert board composed of experts in pediatrics, dermatology, allergy, pneumology, and otolaryngology. Model assumptions that could not be validated by any literature sources were based on expert board consensus.

The primary perspective of the analyses was societal. In addition, the results are presented from a third-party payer's point of view. Future costs and effects were discounted by a rate of 3% per year. The choice of this rate varied in additional sensitivity analyses.

Module 1

Markov cohorts. In module 1, the central element of the model calculation was the use of Markov chains to portray the long-term course of allergic rhinitis or allergic asthma. This approach has been chosen because either directly after the manifestation of allergic rhinitis or during the disease either a worsening (eg, development of serious allergic rhinitis) or an improvement (such as spontaneous healing) was possible.^{11–13} Allowing for certain methodologic restrictions, this path through different states of disease can be effectively reflected by Markov chains. The Markov cycle length in our model was 1 year. The following disease states were classified: [A] mild allergic rhinitis, [B] moderate to severe allergic rhinitis, [C] moderate to severe allergic rhinitis and mild allergic asthma, [D] moderate to severe allergic rhinitis and moderate to severe allergic asthma, [E] no symptoms, and [F]

dead. The transition probabilities between the predefined states were obtained directly or from published literature sources.^{11,12,14–18} Some of these studies reported the number of patients who had the considered conditions at different time points (eg, at the year of therapy onset and 10 years after). For extracting the annual transition probabilities, we assumed a steady change during the time. For example, a study reported the number of healed patients 10 years after SCIT was performed. We assumed that this number of healed patients was reached because of a steady change over time and recalculated the annual proportion that was necessary to achieve the reported number of healed patients 10 years after treatment onset. The model differs among treatment types (ST, SCIT and ST) and age groups (children 6–12 years, adolescents 13–18 years, and adults 19–65 years).

In this form, only 1 seasonal disease episode was assumed. To account for perennial disease forms, the improvement probabilities of 2 seasonal Markov models were combined. If, for example, a patient with moderate to severe seasonal allergic rhinitis has a 30% probability rate that his or her condition will improve within the next year, this probability would be reduced to 9% for a perennially diseased patient ($30 \times 30 = 9\%$). Thus, it was assumed that seasonal and chronic forms occur in a ratio of 4:1.¹⁹

In the cohort calculation, the disease progression (during a period of 15 years) of 2 hypothetical cohorts of 1,000 newly diseased people each was simulated. It was assumed that

1,000 patients would be treated symptomatically and 1,000 would in addition receive SCIT. The model allows calculating the number of people in each of the predefined states for each of the 15 years. The model comprises those patients who already had contacted their physician.

Annual costs. The calculation of the average annual cost per patient in each of the illness states was based on a German study by Schramm et al.²⁰ This study provided direct and indirect costs (attributable to disability, early retirement, and loss of work by patients and caregivers) stratified by severity, which were derived from retrospective interviews on physician-recruited patients. Figure 2 provides the basic cost components. The sensitivity analyses include 1 scenario of extending SCIT to all patients (even those who, because of their relatively few complications, had never contacted a physician).

SCIT lasts 3 years on average, at an additional cost of €600 per patient per allergy season in the first year. In the second and third years, the additional cost decreases to approximately €540 per patient per allergy season. For treating

patients with perennial complications, SCIT costs will increase by a factor of 1.5.¹⁶

Annual utilities. To perform cost-utility analyses, it was necessary to identify a German outcome parameter. To this end, the measured utilities of a large German pilot project on acupuncture, which also examined patients with different allergic diseases, were incorporated.²¹ Thus, for the present model, we used the following annual health state utilities: mild allergic rhinitis, 0.7579; moderate to severe allergic rhinitis, 0.7378; severe allergic rhinitis and mild allergic asthma, 0.7317; severe allergic rhinitis and moderate to severe allergic asthma, 0.6985; no symptoms, 0.7841; and death, 0.0.

Module 2

Mean annual costs during 15 years. Average annual costs per patient were calculated from the results of the Markov cohort calculation and the basic annual costs of the illness, adhering to the disease stages outlined above (Ø annual costs per patient):

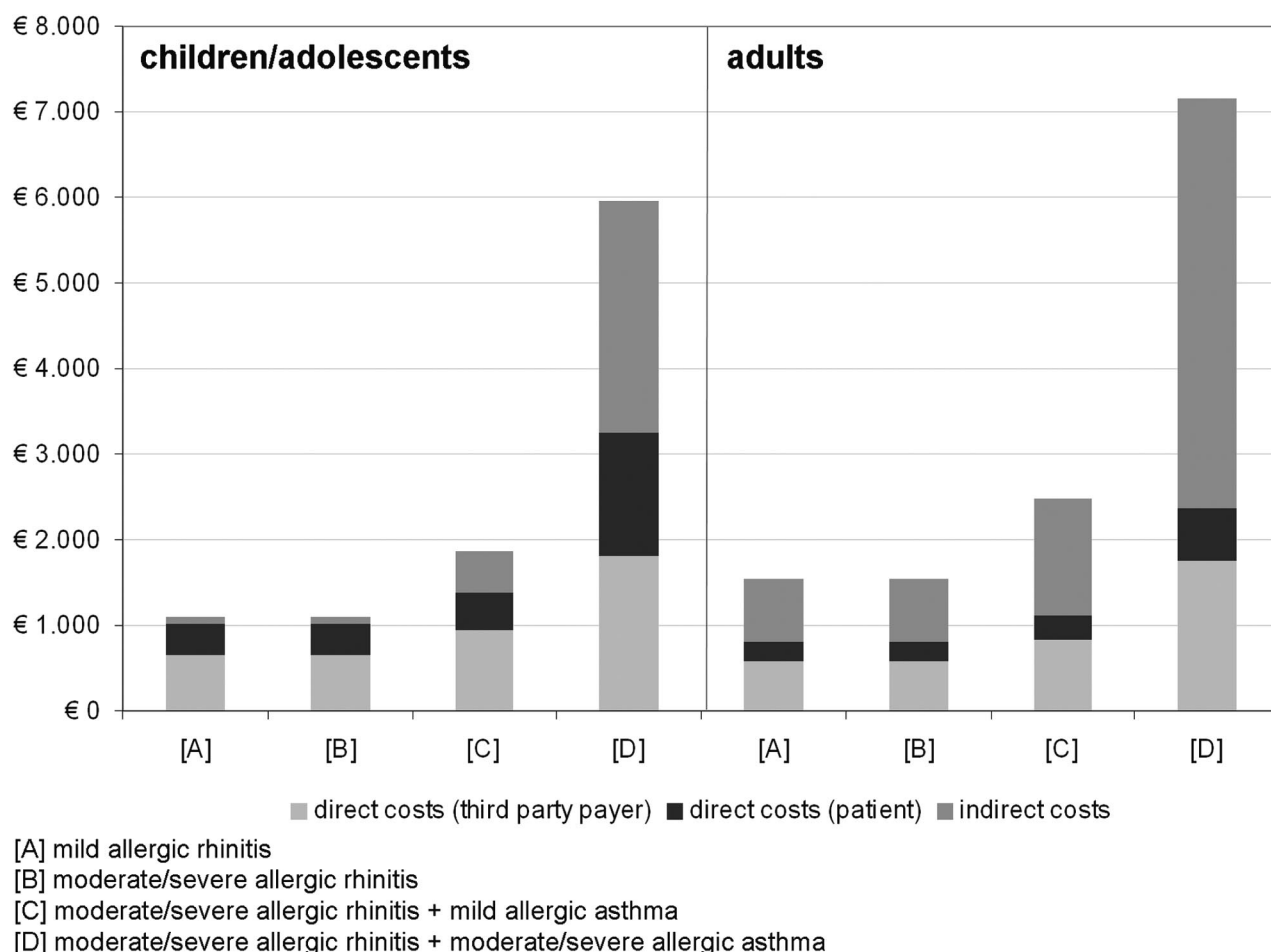


Figure 2. Costs for different disease stages used in the model calculation.

$$\left(\frac{\emptyset \text{ Annual Cost}}{\text{Patient}} \right)_{\text{SIT+ST,ST}} = \left(\sum_{i=1}^{15} \frac{\text{Cost of the Cohort } t_i}{\text{Number of Patients } t_i} \right) \times \frac{1}{15 \text{ Years}} \quad (1)$$

where $i = 1$ indicates that the summation starts in year 1, and t_i indicates that the formula refers to each of the years 1 through 15.

These average annual costs reflect the progression of a patient through each of the different stages of disease.

Mean health state utilities during 15 years. The mean utilities of the different treatments were derived from the results of the Markov cohorts and from the base utilities of the predefined health stages:

$$\emptyset \text{ Utility}_{\text{SIT+ST,ST}} = \left(\sum_{i=1}^{15} \left[\frac{\text{Number of Patients (Health States [A] to [F]) } t_i \times \text{Utility (Health States [A] to [F]) } t_i}{\text{All Patients per Year } t_i} \right] \right) \times \frac{1}{15 \text{ Years}} \quad (2)$$

Module 3

Incremental Cost-effectiveness Ratio. The incremental cost-effectiveness ratio (ICER) is the result of dividing the cost differences of the treatment groups and the respective effect differences (according to a predetermined utility).

$$\text{ICER} = \frac{\left(\frac{\emptyset \text{ Annual Cost}}{\text{Patient}} \right)_{\text{SIT+ST}} - \left(\frac{\emptyset \text{ Annual Cost}}{\text{Patient}} \right)_{\text{ST}}}{\emptyset \text{ Utility}_{\text{SIT+ST}} - \emptyset \text{ Utility}_{\text{ST}}} \quad (3)$$

It specifies the added costs involved in attaining an additional quality-adjusted life-year (QALY). Hence, low values are considered more cost-effective.

Sensitivity Analyses

Additional sensitivity analyses were performed in which we varied different model assumptions to analyze our results for robustness.

In the base-case scenario, it was assumed that the average length of SCIT is approximately 3 years. It is, however, expected that a number of patients stop therapy earlier because of, for example, lack of compliance. This consideration led to a shortening of the expected treatment length to 2 years in the sensitivity analysis.

In addition, the costs of SCIT should influence the cost-effectiveness of this therapy. Contrary to the base-case scenario, we varied the price of SCIT according to the price used in another German publication by Greiner et al.²² The costs

they used for SCIT were €254 for treatment costs and €374 for medication costs.

The discount rate of 3% for future costs and effects was varied in the sensitivity analysis between 0% and 10%.

In the base-case scenario, it was assumed that all treated patients had initial physician contact. A further sensitivity analysis examined the economic effect of extending additional SCIT to all patients with allergic rhinitis or allergic asthma. Therefore, all health stage-specific cost components that resulted from physician contacts, such as prescription medicines or rehabilitation, were subtracted according to the proportion of patients who never consulted a physician.

RESULTS

Effects on Disease Course

At the beginning of disease manifestation, most patients suffer from mild allergic rhinitis (Fig 3). During the disease duration, we observed a clinical relevant difference between symptomatic treated patients and patient who receive additional SCIT. Figure 4 shows the group differences in the number of patients in different disease stages at the end of the modeling period. After 15 years, there were more patients without symptoms in the SCIT and ST group (group difference of 163 patients). In contrast, the patients treated only symptomatically were more likely to develop mild asthma (group difference of 105 patients) or moderate to severe forms of asthma (difference of 93 patients). SCIT was able to avoid more severe disease stages compared with symptomatic treatment alone.

Economic Evaluation

From a societal perspective, the additional SCIT and ST combination was associated with cost savings. The total costs per patient after 15 years of disease were approximately €26,100 for symptomatically treated patients and approximately €24,000 for patients receiving additional SCIT. This finding was equivalent to annual cost savings of approximately €140 per SCIT-treated patient. After 10 years of disease duration, the SCIT and ST treatment reaches the breakeven point. If the costs of SCIT were excluded, SCIT was associated with cost savings from the outset of the therapy.

From a third-party payer's perspective, we calculated additional costs for the SCIT and ST combination. A patient treated with SCIT and ST incurred annual costs of approximately €750 compared with €690 of those receiving only ST. This result was highly affected by the SCIT and ST related costs. After excluding this cost component, a direct cost saving of €60 per year would be realizable.

The results on cost-effectiveness are presented in Table 1. From a society perspective, SCIT reaches an overall ICER of €−19,787 per additional QALY. That means SCIT and ST were both more effective and less costly compared with symptomatic treatment only. We also observed a range of results, depending on the patient's age. The ICER was better in adult patients (€−22,196 per QALY) than in children

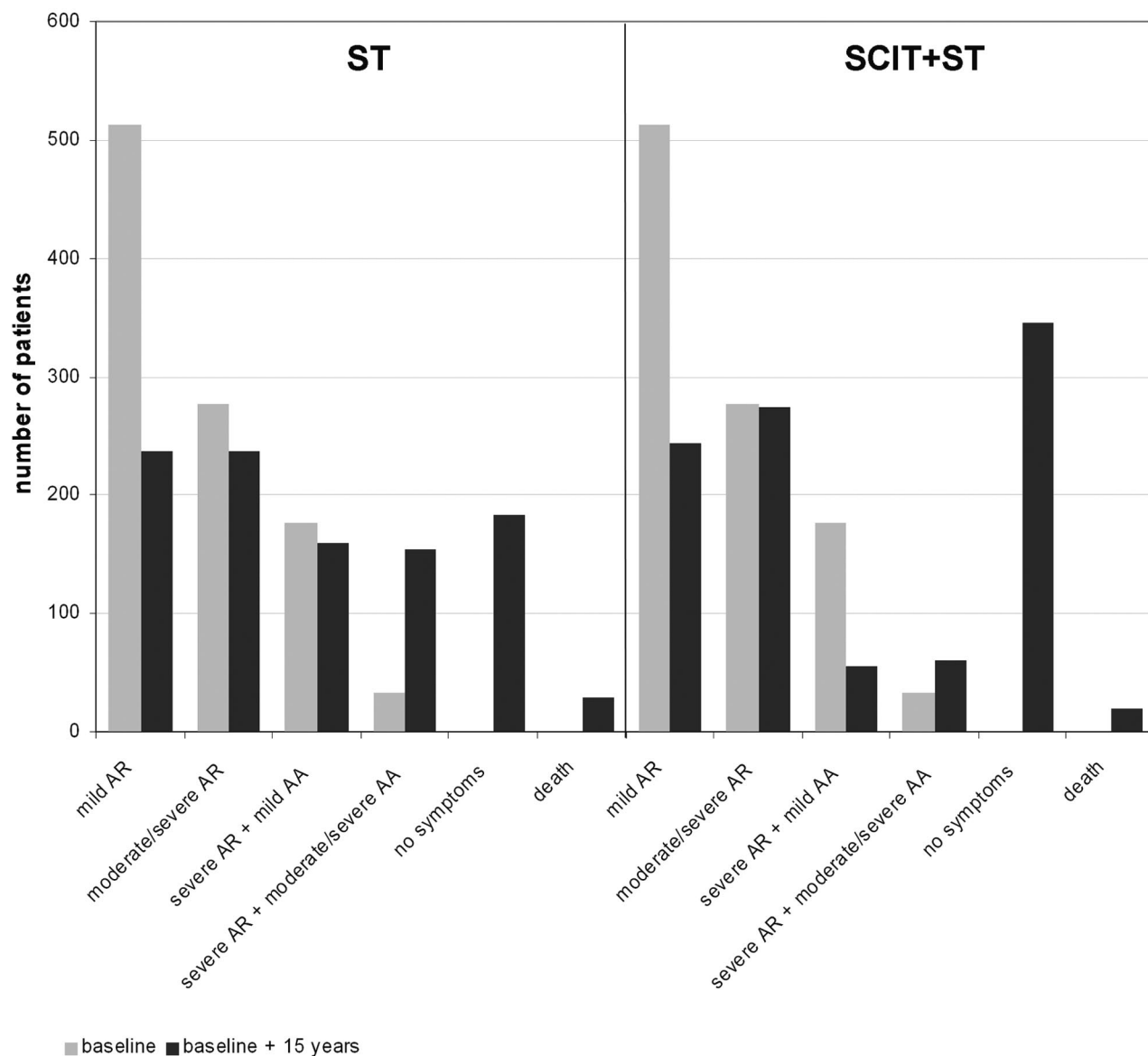


Figure 3. Comparison of cohort's severity levels (1,000 patients per treatment group) of additional immunotherapy (subcutaneous immunotherapy [SCIT] and symptomatic therapy [ST]) vs ST alone at baseline and after 15 years. AA indicates allergic asthma; AR, allergic rhinitis.

(€–12,750 per QALY) or adolescents (€–14,747 per QALY). This finding was mainly affected due to the reduction in indirect costs, which are a more important factor in the working population. If only the effectiveness of SCIT and ST was observed, the treatment is more effective in children (QALY group difference, 0.00764) compared with an adult population (QALY group difference, 0.00718).

From a third-party payer's perspective, SCIT was associated with slightly additional costs. Thus, the resulting ICER was positive for all patients (€8,308 per QALY). In European countries, even an ICER up to €50,000 per QALY will be

rated as cost-effective. Against this background, the SCIT is an indisputably cost-effective treatment.

Sensitivity Analyses

The main results on sensitivity analyses are given in Table 2. The cost-effectiveness of SCIT would be improved if the treatment duration could be reduced without any reduction in clinical benefits. The present model calculates a new ICER of €–24,917 per additional QALY, if the treatment was performed within 2 years instead of 3 years. Nevertheless, in reality we would also expect a decrease in clinical effective-

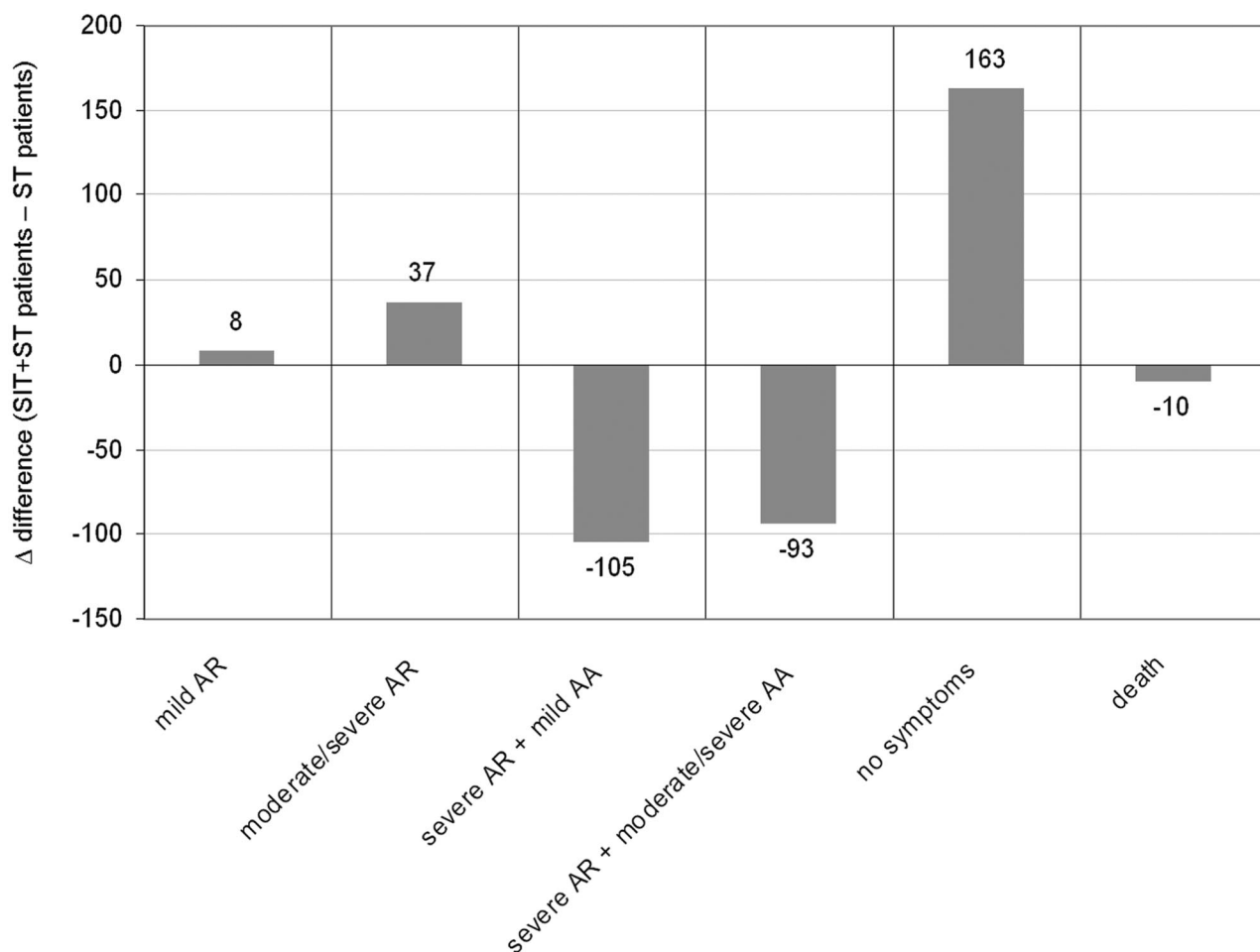


Figure 4. Severity level differences between 1,000 patients receiving symptomatic treatment (ST) alone and 1,000 patients receiving both subcutaneous immunotherapy (SCIT) and ST after 15 years of treatment duration. AA indicates allergic asthma; AR, allergic rhinitis.

Table 1. Cost-effectiveness of Additional SCIT, Depending on the Cost Perspective

	Children	Adolescents	Adults	Total ^a
Societal perspective				
Δ Annual cost, €	-97.08	-112.01	-159.46	-144.47
Δ Utility	0.00764	0.00760	0.00718	0.00730
ICER	-12,750	-14,747	-22,196	-19,787
Third-party payer's perspective				
Δ Annual cost, €	67.81	62.37	58.87	60.65
Δ Utility	0.00764	0.00760	0.00718	0.00730
ICER	8,874	8,212	8,194	8,308

Abbreviations: ICER, incremental cost-effectiveness ratio; SCIT, subcutaneous immunotherapy.

^a Adjusted for the proportion of the age groups in the German population.

ness, so this result is more a theoretical than a realistic prediction.

In addition, the price of SCIT was varied. As a result, direct cost saving could be reached from a societal perspective and from the perspective of third-party payers. So the overall ICER from a statutory health insurance view was

€-1,848 with differences in age groups (children, €-827; adolescents, €-1,539; adults, €-2,129). ICERs from a societal perspective are presented in Table 2.

The choice of discount rate also has a marked influence in the evaluation of cost-effectiveness. Therefore, the ICER ranks between €-23,478 without discounting and €-8,339

Table 2. Results of Sensitivity Analyses on Cost-effectiveness of Additional SCIT From a Societal Perspective

	Children	Adolescents	Adults	Total ^a
Mean treatment duration of 2 years				
Δ Annual cost, €	–134.44	–149.41	–196.94	–181.92
Δ Utility	0.00764	0.00760	0.00718	0.00730
ICER	–17,593	–19,671	–27,413	–24,917
Lower treatment costs for SCIT				
Δ Annual cost, €	–171.22	–186.07	–233.63	–218.62
Δ Utility	0.00764	0.00760	0.00718	0.00730
ICER	–22,405	–24,498	–32,519	–29,943
Discount rate of 0%				
Δ Annual cost, €	–165.15	–184.04	–245.83	–226.39
Δ Utility	0.01010	0.01005	0.00948	0.00964
ICER	–16,345	–18,312	–25,923	–23,478
Discount rate of 10%				
Δ Annual cost, €	–5.95	–15.32	–42.89	–34.07
Δ Utility	0.00426	0.00423	0.00403	0.00409
ICER	–1,394	–3,622	–10,655	–8,339
Hypothetical extension of SCIT to all patients with allergic rhinitis				
Δ Annual cost, €	53.77	46.67	18.48	27.11
Δ Utility	0.00764	0.00760	0.00718	0.00730
ICER	7,036	6,144	2,572	3,713

Abbreviations: ICER, incremental cost-effectiveness ratio; SCIT, subcutaneous immunotherapy.

^a Adjusted for the proportion of the age groups in the German population.

using a 10% discount rate. This observation was mainly affected because of the long-term modeling period (see “Discussion” section).

The theoretical extension of SCIT and ST to all patients (also to patients without prior physician contact because of allergic rhinitis or allergic asthma) would reduce the treatments cost-effectiveness. Therefore, the observed overall ICER was €3,713. This finding is because patients never treated by a physician involve lower costs compared with patients already in treatment. Consequently, the potential for cost reduction of SCIT will also be reduced, which affects the cost-effectiveness of this therapy.

DISCUSSION

Our results indicate that from a societal perspective the combination of SCIT and ST has the potential to achieve a reduction in costs compared with ST alone. From a third-party payer’s perspective, SCIT was associated with slightly additional costs and increased benefits. The resulting ICER was positive for all patients (€8,308 per QALY). In European countries, an ICER between €40,000 and €50,000 per QALY is rated as cost-effective. Against this background, SCIT is an indisputable cost-effective treatment. The cost-reducing factors shown in our study are essentially because the disease does not tend to progress to severe disease stages compared with symptomatic treatment. This accordingly results in a decreased demand on medical resources and a smaller loss of productivity.

A fundamental strength of our study is the use of a conservative model approach and empirical data regarding the

health utility evaluation in different health states. The results of our calculation are in line with other studies. A German analysis observed cost savings of approximately €600 per patient during a period of 25 years.²² An Italian study also found that supplementary specific sublingual immunotherapy (SLIT) could lead to cost reduction and improved medical care.²³ Furthermore, recently published studies that focused on the cost-effectiveness of SLIT compared with symptomatic treatment support our findings.^{24,25} Bachert et al²⁴ calculated an ICER of €18,263 per QALY from a German society’s perspective. Assuming that SLIT and SCIT reach comparable levels of effectiveness, which is supported by original studies^{26,27} and a recently published review article,²⁸ our study results where SCIT is both a cost-effective and cost-saving treatment in addition to ST also seem to be sensible and robust.

The model calculation was based on Markov models because these can be more appropriately applied to the long-term modeling of complex chronic illnesses than decision tree models.^{29,30} A limitation is that in applying Markov models, the greater effect of the SCIT, particularly in the first years of treatment, is underestimated. This means that the results presented should be considered a conservative estimate. In reality, superior cost-effectiveness is probable. Another criticism of this modeling approach, however, is that Markov models always assume constant annual transition probabilities among individual disease states over time (the so-called Markovian assumption).^{23,29} In reality, this probability is also influenced by specific corresponding factors, for example, the length of time spent by a patient in a particular disease state

has an effect on the transition probability to another state. By applying so-called Markov processes, adjustments could have been implemented. However, this in turn would have required a wide range of additional clinical long-term information that was not available. Hence, the Markovian assumption was kept. This approach is a widely used method in economic evaluation.

Another point of discussion is the model duration of 15 years, which also has an impact on the results. Under the current model assumptions, a longer period would lead to better results for SCIT, and a shorter duration would lead to better results for symptomatic treatment. The period of 15 years was chosen to reflect at least the median illness duration and to prevent a loss of accuracy when progressing through later stages of the illness.

A model is a simplified simulation of a real situation and is thus transferable only to a limited degree. The Markov models, for example, were derived from published data from various sources and surveys. These data have been transferred to the German situation without exploring possible differences among the target countries. Model calculations are also characterized by the challenge of achieving an accurate portrayal of reality and the balance of necessary pragmatism. To be as realistic as possible more data are required, or if these data are not available, the number of fundamental assumptions required is higher. Numerous assumptions were necessary for this study, and the advice of an interdisciplinary committee of experts was sought to ensure the reliability of the data.

To determine the direct costs, the human capital approach was applied. This method is controversial because it assumes that only those in an earning capacity incur indirect costs and that these (particularly in view of high unemployment rates) are rated too highly because in reality brief employment interruptions are compensated for by other employees.³¹ The so-called friction cost method, which tries to avoid the problem of short-term work loss, was deliberately not applied here for the sake of better comparability because most health-economic analyses are based on the human capital approach. In Germany, application of the human capital approach is recommended by the Hanover consensus group.³²

A further fundamental problem is that of discounting, particularly the choice of the discount rate. Discounting is a widely used method in health economic research. It is the process of finding the current value of future costs and savings (alternatively future medical impairments or benefits). For example, possible cost savings of €1,000 in future years are considered less valuable compared with savings of €1,000 at present (eg, because of monetary inflation or individual time preference). Using a discount rate of 3%, a cost reduction of €1,000 in 1 year would be associated with a current value of €970. Consequently, future savings would be valued lower than those costs incurred in the near future (eg, the cost of SCIT). Discounting is unlikely to have a relevant effect in the immediate future, but in the case of changes occurring during a long period results may be significantly

affected. However, our results were robust to changes in discount rates.

In conclusion, for the German society, additional SCIT is associated with improved medical outcomes and cost savings compared with symptomatic treatment alone. From a German statutory health insurance perspective, the improved effectiveness is associated with negligible higher costs. Taking a European accepted ICER threshold of up to €50,000 per QALY into account, additional SCIT has been considered to be clearly cost-effective compared with routine care in Germany. The degree of cost-effectiveness was strongly affected by costs related to SCIT and the target population receiving such treatment. A prospective and long-term real-life study is suggested to support the robustness of the long-term forecast for the German context.

REFERENCES

1. Ng ML, Warlow RS, Chrisanthan N, Ellis C, Walls R. Preliminary criteria for the definition of allergic rhinitis: a systematic evaluation of clinical parameters in a disease cohort (I). *Clin Exp Allergy*. 2000;30(9):1314–1331.
2. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol*. 2000;106(5):832–839.
3. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. 2004;24(5):758–764.
4. Public Use File BGS98. Berlin, Germany: Bundes-Gesundheitssurvey; 1998.
5. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. *Respir Res*. 2005;6:153.
6. Gillissen A, Hoffken G, Juergens UR. A connection between allergic rhinitis and allergic asthma? the “one-airway-one-disease”-hypothesis. *Pneumologie*. 2005;59(2):112–119.
7. Skoner DP. Complications of allergic rhinitis. *J Allergy Clin Immunol*. 2000;105(suppl 6):605–609.
8. Niggemann B, Jacobsen L, Dreborg S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy*. 2006;61(7):855–859.
9. Bousquet J, Demoly P, Michel FB. Specific immunotherapy in rhinitis and asthma. *Ann Allergy Asthma Immunol*. 2001;87(1 suppl 1):38–42.
10. Gillissen A, Bergmann KC, Kleine-Tebbe J, et al. Specific immunotherapy in allergic asthma. *Dtsch Med Wochenschr*. 2003;128(5):204–209.
11. Bodtger U, Linneberg A. Remission of allergic rhinitis: an 8-year observational study. *J Allergy Clin Immunol*. 2004;114(6):1384–1388.
12. Ronmark E, Jonsson E, Lundback B. Remission of asthma in the middle aged and elderly: report from the Obstructive Lung Disease in Northern Sweden study. *Thorax*. 1999;54(7):611–613.
13. Corren J. The connection between allergic rhinitis and bronchial asthma. *Curr Opin Pulm Med*. 2007;13(1):13–18.
14. de Marco R, Locatelli F, Cazzoletti L, Bugiano M, Carosso A, Marinoni A. Incidence of asthma and mortality in a cohort of young adults: a 7-year prospective study. *Respir Res*. 2005;6:95.
15. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. *Clin Ther*. 2000;22(3):342–350.
16. Schaedlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics*. 2000;17(1):37–52.
17. Sterbetafel 2003/2005. Wiesbaden, Germany: Statistisches Bundesamt; 2006.
18. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunother-

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- apy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther.* 2000;22(3):329–341.
19. Riemann E. *Allergie und Rhinitis Allergica*. Frankfurt am Main, Germany: HNO-Klinik-Hoechst; 2005.
20. Schramm B, Ehlken B, Smala A, Quednau K, Berger K, Nowak D. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J.* 2003;21(1):116–122.
21. Witt CM, Brinkhaus B, Jena S, Selim D, Straub C, Willich SN. Wirksamkeit, Sicherheit und Wirtschaftlichkeit der Akupunktur - Ein Modellvorhaben mit der Techniker Krankenkasse. *Dtsch Arztebl.* 2006;103(4):A-196/B-169/C-167.
22. Greiner WSJA. Kosten und Nutzen der Hyposensibilisierung bei allergischem Asthma und Rhinitis. *Gesundh ökon Qual manag.* 2002;1700(3):179–186.
23. Berto P, Passalacqua G, Crimi N, et al. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol.* 2006;97:615–621.
24. Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX(R)) for the prevention of seasonal grass pollen induced rhinoconjunctivitis: a Northern European perspective. *Clin Exp Allergy.* 2007;37(5):772–779.
25. Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX(R) for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med.* 2007.
26. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy.* 2004;59(1):45–53.
27. Mauro M, Russello M, Incorvaia C, Gazzola GB, Di CG, Frati F. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. *Allerg Immunol (Paris).* 2007;39(4):119–122.
28. Erny-Albrecht K, Valentine WJ, Christensen J, Vestenbaek U, Palmer AJ. Sublingual immunotherapy in allergic rhinitis and asthma: a review of recent clinical evidence. *J Appl Res.* 2007;7(1):17–31.
29. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics.* 1998;13(4):397–409.
30. Kobelt G. Modelle als Instrument der Gesundheitsökonomie. *Gesundh Ökon Qual Manag.* 2005;suppl 2(10):37–44.
31. Rychlik R. Gesundheitsökonomie - Grundlagen und Praxis. Stuttgart, Germany: Enke; 1999.
32. Hanoverian Consensus Group. German Recommendations for health economic evaluations - revised version of the Hanover Consensus. *Gesundh Ökon Qual Manag.* 1999;4:A62–A65.
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