W. Green[1], J. McMaster[1], R. Babela[2,3,4], S. Buchs[3]

Cost-effectiveness of the SQ HDM SLIT-tablet for the treatment of allergic asthma in three Eastern European Countries

[1]York Health Economics Consortium, Enterprise House, Innovation Way, University of York, Heslington, York, UK
[2]St. Elisabeth University, Institute of Healthcare Disciplines, Bratislava, Slovakia
[3]ALK-Abelló, Denmark
[4]R. Babela was an employee of ALK-Abelló at the time when this research was conducted.

Key words
cost-effectiveness; allergic asthma; allergy immunotherapy; sublingual immunotherapy; SQ HDM SLIT-tablet

Corresponding author
William Green
York Health Economics Consortium
Enterprise House, Innovation Way
University of York, Heslington
York, YO10 5NQ, UK
Phone: +44 (0)1904 32 4827
Fax: +44 (0)1904 32 3628
E-mail: william.green@york.ac.uk

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Summary

Background. *The SQ® house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet ACARIZAX®, ALK-Abelló A/S, Hørsholm, Denmark) is an allergy immunotherapy tablet for people with allergic respiratory disease. This analysis aims to assess the cost-effectiveness of the SQ HDM SLIT-tablet from the perspective of three Eastern European countries: Czech Republic, Poland and Slovakia.* ***Methods****. A cost-utility model per country was developed, which compared the SQ HDM SLIT-tablet as add-on to pharmacotherapy with pharmacotherapy alone in patients with HDM allergic asthma (AA) over a five year time horizon. The effectiveness of the two interventions was based on the results from a large-scale randomised controlled trial. In the models, annual costs and quality-adjusted life year (QALY) scores from the trial were extrapolated over a five year period, and the incremental cost-effectiveness ratios (ICERs) were estimated. One-way deterministic sensitivity and scenario analyses were undertaken.* ***Results.*** *The SQ HDM SLIT-tablet is cost-effective in all three markets over the five year time horizon (ICERs of less than € 10,000 per additional QALY). Treatment with the SQ HDM SLIT-tablet improves patient outcomes, with QALY gains of 0.35, versus pharmacotherapy only. In all three countries, the SQ HDM SLIT-tablet also incurs increased costs compared to pharmacotherapy treatment only. The sensitivity analysis identified utility values from the clinical trial as the main driver of the model results.* ***Conclusion.*** *The SQ HDM SLIT-tablet is a cost-effective treatment option for people with HDM AA in three different health care settings in Eastern Europe.*

Introduction

Asthma is a global health problem affecting 300 million people worldwide, a number expected to rise to 400 million people by 2025 (1). In Poland, Czech Republic and Slovakia, it is estimated that 5 to 8% of the population have asthma (2,3). Allergic Asthma (AA), usually defined by the presence of sensitisation to environmental allergens, accounts for approximately 50% of all asthma (4). House dust mites (HDM) are a significant factor underlying AA, with sensitisation to HDM present in 50% to 85% of people with asthma (5,6). In most cases of HDM AA, the disease is accompanied by allergic rhinitis (AR) (7). Close to 30% of people are sensitized to HDM in Poland and Slovakia (8,9).

The symptoms of asthma include breathlessness, chest tightness, wheezing and obstruction of airflow. The ever-present risk of severe exacerbations of symptoms, which may require emergency treatment and/or hospitalisation, can have a significant detrimental influence on daily quality of life. Quality of life can also be affected by limitation of daily activities, emotional functioning and lack of sleep (10). Overall, poor asthma control has been shown to reduce quality of life (11,12). A global survey among people with asthma reported poorer symptom control in Central and Eastern Europe, with 74% of people reporting

daytime symptoms compared to 56% in Western Europe (13). According to a Polish study, 47% of the population with asthma reported their symptoms to be partly controlled and 32% reported that their asthma was uncontrolled. A similar study in Czech Republic reported that 32% have partly controlled and 57% have uncontrolled asthma (12,14).

Asthma is associated not only with poor quality of life but also with significant health resource utilisation. In Europe the annual costs for an adult with asthma are estimated at € 1,583 and these costs increase with reduced asthma control (15). The cost of a single asthma exacerbation was estimated to range from € 737 to € 1,074, depending on asthma severity (16). Hospitalisation and medications have been identified as the most significant drivers in regards to direct costs. A systematic literature review reported that 52% to 86% of direct asthma-related costs come from in-patient hospitalisation (17). Absence from work or school are also significant contributors to indirect costs. Previous research indicates that 23% of adults in Central and Eastern Europe lost workdays due to asthma, as reported in the worldwide survey on asthma severity and control, compared to 17% in Western Europe (13).

For certain patients, symptoms of asthma can be controlled and relieved by allergen avoidance and controller medications, such as inhaled corticosteroids (ICS) or long-acting beta agonists (LABA), as well as asthma relievers such as short-acting beta agonists (SABA). For more severe asthma, IgE anti-bodies or Il-5 receptor agonists are add-on treatment options. Allergy immunotherapy (AIT) is the only treatment option for allergic diseases which aims to have a disease-modifying effect to limit disease progression and facilitate a long-term reduction in symptoms of the disease. The Global Initiative for Asthma (GINA) has included treatment with HDM sublingual immunotherapy (SLIT) in their latest strategy for asthma management (18). The SQ® HDM SLIT-tablet (ACARIZAX®, ALK-Abelló A/S, Hørsholm, Denmark) is a sublingual AIT that contains a 1:1 mixture of allergen extract from the 2 major mite species *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae.* It is indicated for people with HDM AA whose symptoms are not well controlled despite the use of ICS. The results from the MITRA trial (MT-04; NCT01433523), a large-scale (n = 834) phase III double-blind, randomised controlled trial, which assessed two doses for the HDM SLIT-tablet (6 SQ-HDM and 12 SQ-HDM) indicate that the 12 SQ HDM SLIT tablet significantly reduces the risk of moderate to severe asthma exacerbation compared with placebo (hazard ratio 0.69; 95% CI 0.50 to 0.96) (19). Based on the findings from this trial it has previously been shown that the 12 SQ HDM SLIT-tablet is a cost-effective treatment for AA in the German setting (20).

The SQ HDM SLIT-tablet is now available as a treatment option for people whose asthma is not well controlled in Czech Republic, Poland and Slovakia. The aim of the analysis was, therefore, to assess the cost-effectiveness of the 12 SQ HDM SLIT-tablet plus pharmacotherapy versus pharmacotherapy alone in the treatment of AA from the perspective of these three Eastern European countries.

Methods

Three cost-utility models were developed, to compare the costs and outcomes associated with patients with AA treated with SQ HDM SLIT-tablet plus pharmacotherapy versus patients treated with pharmacotherapy only over a five-year time horizon in the 3 countries of interest. The decision-tree model structure was based on a modelling approach described previously (20). The same model structure was applied for all three countries, with certain input parameters changed to reflect local variations (e.g. distinct unit costs for healthcare resources). For the model it was assumed that patients treated with the SQ HDM SLIT-tablet stay on treatment for 3 years, as per recommendations, and afterwards pharmacotherapy could be continued to be used as needed for the remaining time horizon. For patients using pharmacotherapy only, it was assumed that there were no changes in treatment throughout the time horizon of the model. The following cost inputs were included in the models: the cost of the SQ HDM SLIT-tablet (treatment arm only), specialist/general physician visits, emergency room visits, ICS use and SABA use (**table I**). The total usage of these resources was based on data recorded in the MT-04 trial per treatment arm and extrapolated over the full time horizon. The total annual costs were estimated by combining the resource use with country specific cost data and prices (21-26). To reflect the local health care setting and treatment practice, some adjustments had to be made to the different models. For Poland, emergency room visits are not applicable in the model as hospitals are paid a flat-fee for emergency treatment and not per patient or per visit, i.e. additional emergency room visits do not incur measurable extra cost to the health care system. Based on local guidelines and expert input the number of physician visits required for patients receiving the SQ HDM SLIT-tablet was adjusted by country (**table II**). For example, local experts suggest that in Poland and Slovakia patients should see their physician twice a year while treated with a SLIT-tablet, while this is not standard of care in Czech Republic. For all the countries, an extra visit for the first administration of the SQ HDM SLIT-tablet, which is required by the product label, was also added in the first year of treatment. Finally, for the Czech and Polish analyses the costs were converted from local currencies into Euros, using exchange rates of 25.61 and 4.25, respectively (valid on 06/11/17), to ensure consistent reporting across the three country settings.

For the cost of the SQ HDM SLIT-tablet the prices in the Czech Republic and Slovakia are defined by reference prices that are updated biannually. Prices relevant to 2017 have been ad-

Table I *- Annual resource use and cost per country.*

Resource	Cost per unit[1]	Annual resource use		Cost per year	
		SQ HDM SLIT-tablet	pharmaco-therapy	SQ HDM SLIT-tablet	pharmaco-therapy
SQ tablet (unit value: per tablet)					
Czech Republic	€ 2.63	365 tablets	0 tablets	€ 959.95	€ 0.00
Poland	€ 2.63	365 tablets	0 tablets	€ 923.45	€ 0.00
Slovakia	€ 2.63	365 tablets	0 tablets	€ 959.95	€ 0.00
Physician visits (unit value: per visit)					
Czech Republic	€ 7.89	1.0 visits	1.0 visits	€ 7.89	€ 7.89
Poland	€ 8.39	0.17 visits	0.1 visits	€ 1.47	€ 0.88
Slovakia	€ 60.48	0.17 visits	0.1 visits	€ 10.57	€ 6.33
Emergency room visits (unit value: per visit)					
Czech Republic	€ 21.63	0.01 visits	0.03 visits	€ 0.22	€ 0.55
Poland	N/A	N/A	N/A	N/A	N/A
Slovakia	€ 54.00	0.01 visits	0.03 visits	€ 0.54	€ 1.36
ICS daily dose (unit value: see below)					
Czech Republic (40,000 µg)	€ 20.00	205.5 mg	202.6 mg	€ 101.58	€ 100.14
Poland (10,000 µg)	€ 5.18	205.5 mg	202.6 mg	€ 106.50	€ 104.99
Slovakia (3,375 µg)	€ 8.00	205.5 mg	202.6 mg	€ 164.40	€ 162.06
SABA intake (unit value: see below)					
Czech Republic (200 doses)	€ 8.60	266 doses	297 doses	€ 11.43	€ 12.75
Poland (600 doses)	€ 8.81	266 doses	297 doses	€ 3.90	€ 4.36
Slovakia (25 doses)	€ 59.28	266 doses	297 doses	€ 26.28	€ 29.32

[1]All unit costs were based on local 2017 prices.

Table II *- Extra physician visits per treatment year for patients treated with the SQ HDM SLIT-tablet.*

Country	Unit cost	Resource use			Total cost
		year 1	year 2	year 3	
Czech Republic	€ 7.89	1.00	0.00	0.00	€ 7.89
Poland	€ 8.39	3.00	2.00	2.00	€ 58.76
Slovakia	€ 60.48	3.00	2.00	2.00	€ 423.36

opted but are liable to change in the future. Further, at the time of the analysis the SQ HDM SLIT-tablet was not reimbursed nationally in Poland and therefore the same price as the other two countries was applied.

The effectiveness of the two interventions is captured via the impact on patients' health-related quality of life (HRQoL), as measured by utility. Utility is a measurement of patient wellbeing on a scale of zero to one and can be combined with time to estimate quality-adjusted life year (QALY) scores.

The utility values applied in the models are based on data recorded during the MT-04 trial (**table III**). The values were obtained by calculating the change from baseline to end of the maintenance period in the trial per treatment arm. Although there was a significant change from baseline to end of trial, the

Table III *- Utility values from MT-04 (Change from baseline and end of maintenance period values).*

	Placebo	SQ HDM SLIT-tablet
baseline utility for full sample	0.736	0.736
change in utility (p = 0.0318)	0.0059	0.0315
final utility for analysis	0.742	0.768

values from the end of the maintenance period are more reflective of a real-world setting than the following period. This is because after the maintenance period in the trial ICS was removed by 50% for 3 months and completely withdrawn for the last 3 months (19). Between the two treatment arms the difference in utility change from baseline to end of maintenance period was 0.026 (p = 0.0318). Further, to account for baseline differences in utility between the treatment arms, the average baseline utility for the full trial sample was calculated and the change from baseline to the end of the maintenance period for the two treatment arms were applied to obtain the utility values used in the cost-effectiveness analysis.

The utility values from MT-04 were used for the first year of the analysis. For the remaining four years of the time horizon the utilities were extrapolated based on the following assumptions:

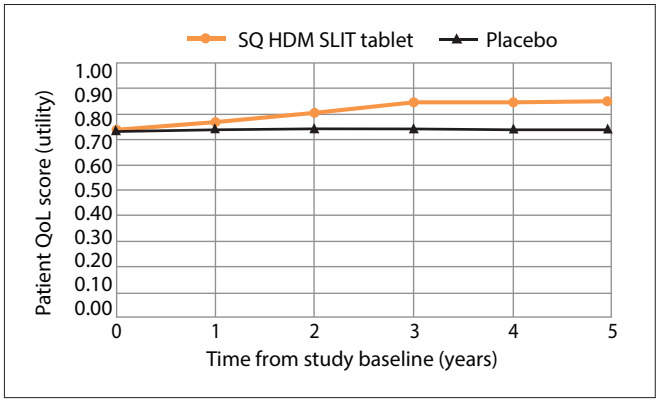
- in year 2-3 there will be an increased treatment effect and therefore further increase in utilities of 5% in the treatment arm;
- during year 4-5 this effect will be sustained due to the disease modifying effect.

These assumptions are based on the disease modifying effect of AIT, which has previously been evidenced when using AIT for respiratory allergies (27-30). For pharmacotherapy patients it has been conservatively assumed that the utility gains achieved in the trial remained throughout the time horizon, such that there is no change in utility from years one to five. The change in utility predicted over the course of the model time horizon for the two interventions is summarised in **figure 1**.

Cost-effectiveness was established by the estimation of the incremental cost-effectiveness ratio (ICER). The ICER is a standard measurement used in economic evaluations that facilitates a comparison of two interventions, taking into account the returns that could be achieved by spending the budget elsewhere in the healthcare system (i.e. the opportunity cost). The ICER equation is as follows:

$$ICER = \frac{Cost_{Treatment} - Cost_{Comparator}}{QALY_{Treatment} - QALY_{Comparator}} = \frac{\Delta Cost}{\Delta QALY}$$

Figure 1 *- Summary of utility changes over time.*



The interpretation of an ICER requires a cost-effectiveness threshold, which takes into account societies willingness to pay for new interventions, and thus formally quantifies whether the benefits achieved by an intervention is adequate given the cost consequences of that intervention and opportunity costs. To reflect local willingness-to-pay, cost-effectiveness thresholds based on local reimbursement guidelines were applied in the models. Costs as well as the QALYs estimated within each model were discounted based on local payer requirements. The cost-effectiveness thresholds, and discount rates, applied for each country setting are summarised in **table IV**.

To investigate first order uncertainty, one-way deterministic sensitivity analysis was undertaken by altering the values applied for individual model parameters to examine the impact on results. For all parameters a range of approximately +/-30% of the base case value was applied, based on guidelines for Slovakia and applied equally across the three countries to ensure consistency (31). The parameters tested were: unit cost of the SQ HDM

Table IV *- Summary of cost-effectiveness threshold and discount rates, by country.*

Parameter	Czech Republic	Poland	Slovakia
cost-effectiveness threshold (2017)[1]	€ 49,721	€ 30,626	€ 21,192
discount rate, costs	3.00%	5.00%	5.00%
discount rate, QALYs	3.00%	3.50%	5.00%
reference	(32)	(33)	(31)

[1]Cost-effectiveness threshold values for the Czech and Polish analyses were converted from local currencies into Euros, using exchange rates of 25.61 and 4.25, respectively.

SLIT-tablet, ICS dose, SABA intake and utility value. Emergency room visits and physician visits were not incorporated in the sensitivity analysis because the values obtained from the MT-04 trial were very low and, therefore, changes to these parameters were not expected to have a meaningful impact on the results unless unrealistic variations were tested.

To test the assumptions behind the extrapolation of utility data from the MT-04 trial to the five-year time horizon, alternative values were tested within the models via two scenarios. In the first scenario, a smaller improvement in utility for SQ HDM SLIT-tablet patients of 2% during years two and three was applied, whilst for the second scenario it was assumed there was a 0% change in utility for patients on active treatment during years two and three.

Results

The results of the economic analysis in the three countries are presented in **table V**. These results indicate that the SQ HDM SLIT-tablet is a cost-effective treatment for HDM allergic asthma in Czech Republic, Poland and Slovakia, as shown by the ICERs of less than € 10,000 per additional QALY in all three countries. Over the five-year time horizon, the SQ HDM SLIT-tablet is associated with higher overall costs of approximately € 2,500 to € 3,000, but also improves patient outcomes via QALY gains of approximately 0.35.

The results of the deterministic sensitivity analysis show that the results of the model are most sensitive to changes in utility for both intervention arms. Changes in utilities within the ranges examined, changed the direction of the results enough for the ICERs to be above the threshold in the three countries.

The results from the analyses, assessing different assumptions around the extrapolation of utilities over the time horizon, are presented in **table VI**. The results show that the ICERs increase as the utilities in year 2 and 3 are decreased. In both tested scenarios, the ICERs stay within the local cost-effectiveness thresholds, except for the Slovakian ICER in the second scenario.

Table V *- Results of the cost-effectiveness analysis (costs, QALYs and ICERs).*

	SQ HDM SLIT-tablet	Pharmaco-therapy	Difference
Czech Republic			
cost per patient	€ 3,283	€ 561	€ 2,722
QALYs per patient	3.76	3.40	0.37
cost-effectiveness threshold	-	-	€ 49,721
ICER	-	-	€ 7,455
Poland			
cost per patient	€ 3,152	€ 477	€ 2,675
QALYs per patient	3.71	3.35	0.36
cost-effectiveness threshold	-	-	€ 30,626
ICER	-	-	€ 7,492
Slovakia			
cost per patient	€ 3,875	€ 862	€ 3,013
QALYs per patient	3.55	3.21	0.34
cost-effectiveness threshold	-	-	€ 21,192
ICER	-	-	€ 8,814

Discussion

The results of the five-year analysis indicate that the SQ HDM SLIT-tablet plus pharmacotherapy is a cost-effective treatment option versus pharmacotherapy alone for people with allergic asthma in Czech Republic, Poland and Slovakia. All three analyses resulted in an ICER below € 10,000, which is substantially lower than the cost-effectiveness thresholds for each individual country (€ 49,721, € 30,626 and € 21,192 for Czech Republic, Poland and Slovakia, respectively). Consistent results were obtained despite the three country settings, with differences in local clinical practice, costs and payer requirements. Nevertheless, there were small variances in the results estimated for the three countries, driven mainly by different requirements for health economic analyses. In particular, the discount rate for QALYs was 5% in Slovakia, which was higher than the rates of 3% for the Czech Republic and 3.5% for Poland, and this reduced the QALY gains achieved by the SQ HDM SLIT-tablet in Slovakia. At the same time, the cost-effectiveness threshold was substantially lower for Slovakia compared to the other markets, meaning the values placed on the QALY gains are lower in this country. Overall, the results are in line with a previously published cost-effectiveness analysis for the SQ HDM SLIT-tablet in the treatment of AA in Germany (20).

Table VI *- Results of sensitivity analyses of long-term effect.*

Country	Base case ICER	Scenario 1 ICER	Scenario 2 ICER
Czech Republic	€ 7,455	€14,191	€22,861
Poland	€ 7,449	€14,164	€22,787
Slovakia	€ 8,814	€16,706	€26,766

The results of the sensitivity and scenario analyses indicate that the model is most sensitive to changes in the utility values in the model, including how utility changes during years 2 and 3 following treatment with the SQ HDM SLIT-tablet. The utility data applied in the model were taken from a large-scale, double blind randomised controlled trial. Given the robust trial design, this source should ensure that values adopted are valid and accurate reflections of patient HRQoL and should also provide reliable estimates of efficacy for both the SQ HDM SLIT-tablet and pharmacotherapy.

To estimate the long-term impact of the SQ HDM SLIT-tablet it was necessary to make a small number of assumptions regarding HRQoL change over five years. These assumptions were based on the disease-modifying properties of AIT, which address the underlying disease and induce tolerance to the allergen in question. Evidence shows that the effect of AIT improves throughout a full three-year course of treatment and that this effect can last for up to 7 years after finalizing treatment (27-30). Therefore, the SQ HDM SLIT-tablet may continue to benefit patients after the five-year time horizon considered here. For pharmacotherapy patients it has been conservatively assumed that the utility gains achieved in the trial remained throughout the time horizon, such that there is no change in utility from years one to five. However, the improvements measured in the trial may have occurred due to the placebo effect, in which case the long-term difference in patient HRQoL between the SQ HDM SLIT-tablet and placebo patients would be greater than modelled here.

One limitation of the model is that the resource use values applied in order to estimate the total cost burden for patients are based on the values reported in the MT-04 trial, which are protocol driven and may not reflect healthcare utilisation rates in real clinical settings. This approach was necessary due to a paucity of relevant local data and may lead to an underestimation of the cost difference between SQ HDM SLIT-tablet and pharmacotherapy patients. For example, if the SQ HDM SLIT-tablet leads to greater disease control, then this is likely to reduce the risk of hospital inpatient admissions, which are associated with large costs to the healthcare system. Besides from health care utilization, asthma and allergic rhinitis are also known to cause an indirect cost burden to society due to absenteeism and presenteeism, which is known to be particularly large in Eastern Europe (13). The impact of treatment on these societal costs was not captured in this model, due to a lack of specific local data.

Allergic asthma is a transient condition and disease control can vary on a day-by-day basis, sometimes resulting in asthma exacerbations which are costly and have a detrimental impact on HRQoL. While the MT-04 trial showed that the risk of experiencing such exacerbations is reduced by 34% when patients were treated with the SQ HDM SLIT-tablet, it did not report exacerbation rates which would be required to include exacerbations in a health economic model (19). Therefore, this was not captured in the model, potentially underestimating HRQoL and cost benefits in these markets. Data to support the assumption of reduced exacerbations should be considered for future clinical and health economic research.

Conclusion

SQ HDM SLIT-tablet is a cost-effective treatment for patients with HDM AA not well controlled by pharmacotherapy in Czech Republic, Poland and Slovakia. It can therefore be considered a relevant treatment option, addressing an unmet need for improved asthma control and HRQoL in these countries.

Conflict of Interests

William Green and Jessica McMaster work at York Health Economics Consortium (YHEC). YHEC received funding from ALK-Abelló to complete the manuscript. At the time when research was conducted, Robert Babela was a salaried employee of ALK-Abelló. He has also received salary from the St. Elizabeth University, Bratislava, Slovakia, as lecturer. Sarah Buchs is a salaried employee at ALK-Abelló.

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