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ORIGINAL RESEARCH

A Cost-Utility Analysis of SQ® Tree SLIT-Tablet versus Placebo in the Treatment of Birch Pollen Allergic Rhinitis from a Swedish Societal Perspective

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Background and Aims: Allergic rhinitis (AR) is an immunoglobulin E antibody-mediated inflammatory condition that arises in response to inhaled allergens such as pollen. Pollens from trees in the birch homologous group are the most common allergenic tree pollens in Northern and Central Europe and North America. SQ® Tree SLIT-Tablet (ITULAZAX®) is a sublingual immunotherapy tablet indicated for moderate-to-severe AR and/or conjunctivitis induced by pollen from the birch homologous group. The present analysis evaluated the cost-utility of treating adults with AR with SQ Tree SLIT-Tablet versus placebo, both in combination with symptom-relieving medications, from a Swedish societal perspective.

Methods: A model was developed to evaluate changes in cost and quality of life associated with using SQ Tree SLIT-Tablet relative to placebo in an adult population of individuals with AR. The model captured costs associated with symptom-relieving medications, healthcare professional interactions, SQ Tree SLIT-Tablet, and indirect costs arising from absenteeism and reduced workplace productivity. The analysis was conducted over 10 years with costs captured in 2021 Swedish Krona (SEK) and future costs and effects discounted at 3% per annum. One-way and probabilistic sensitivity analyses were conducted.

Results: Treatment with SQ Tree SLIT-Tablet resulted in an improvement of 0.041 quality-adjusted life years (QALYs) over 10 years versus placebo. From a Swedish societal perspective, costs increased by SEK 9077 over the same period, resulting in an incremental cost-utility ratio of SEK 223,445 per QALY gained. One-way sensitivity analysis showed that the model was most sensitive to assumptions around the disease-modifying effect of SQ Tree SLIT-Tablet.

Conclusion: SQ Tree SLIT-Tablet improved quality of life in moderate-to-severe AR and/or conjunctivitis induced by pollen from the birch homologous group in Sweden, with only a modest increase in societal costs over a medium-term time horizon, representing good value for money at a willingness-to-pay threshold of SEK 700,000 per QALY.

Keywords: rhinitis, allergic, desensitization, immunologic, administration, oral, costs and cost analysis, quality of life, Sweden

Introduction

Allergic rhinitis (AR) is an inflammatory condition caused by an immunoglobulin E (IgE)-mediated immunological response to inhaled allergens such as pollen.[1] Local symptoms that arise from the immune cascade in the nasal mucosa can include nasal congestion or obstruction, rhinorrhea, an itchy nose, sneezing, and conjunctivitis. Conjunctivitis manifests as ocular symptoms such as hyperemia, chemosis, periorbital edema, and itchy or watery eyes. In addition to these localized symptoms, individuals with AR also commonly suffer from systemic symptoms such as fatigue, reduced productivity, sleep impairment, and impaired concentration.[1,2] AR also shares elements of pathology and pathophysiology with allergic asthma, which often co-exists with AR in the same individual;[3,4] up to 30% of patients with AR have concomitant asthma, and more than 70% of patients with asthma have concomitant AR.[5,6] The incidence of comorbid AR and asthma likely arises from the common systemic IgE-mediated response to inhaled allergens,[2,7] and AR has been identified as a key risk factor for developing asthma.[8–10]

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AR is most commonly caused by inhaled molds, dust mites, insects, dander, and pollens from weeds, grasses, and trees.[1,11] Of the tree pollens, birch is the most common allergenic pollen in Northern and Central Europe, and among the key pollen allergens in North America.[11–13] In Sweden specifically, the self-reported prevalence of AR was 28.0% according to a 2012 study by Eriksson et al with the highest prevalence of 33.6% reported amongst people aged 30–40.[14] The primary allergenic component of birch pollen is the allergen *Bet v 1*, a homolog of allergens from other trees in the *Fagales* order. Based on a 2008 proposal for allergen homologous groups put forward by Lorenz et al, the European Medicines Agency (EMA) has defined the birch homologous group as including birch, alder, beech, hazel, hop/hornbeam, oak, and chestnut.[15,16] The cross-reactive nature of allergens in the birch homologous group combined with the sequential flowering of trees in the group can result in individuals with birch pollen-induced AR experiencing symptoms for a prolonged period, extending beyond the birch pollen season.[17] The geographical area in which an allergic reaction may be triggered may also be substantially widened thanks to the cross-reactivity between allergens in the group.

The long duration of exposure to pollen from the birch homologous group (birch and cross-reactive allergens) and the diverse range of AR symptoms combine to make birch pollen-induced AR a serious disease that can have a substantial negative effect on patient quality of life. The exact duration of the birch homologous group pollen season varies by year, but a 2019 randomized controlled trial reported the birch pollen season to last for 24 days (range: 10–42 days), while the full tree pollen season (including birch, alder, and hazel) was reported to last for 50 days (range: 14–68 days).[18,19]

The symptoms of AR can be reduced either by allergen avoidance or by one of the two forms of AR treatment recommended by clinical guidelines: symptom-relieving medications or allergy immunotherapy (AIT). Since allergen avoidance is difficult to achieve for tree pollen allergies, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend the use of second-generation (non-sedating) oral or intranasal H_1-antihistamines to treat the symptoms of pollen-induced AR, in combination with an intranasal corticosteroid or leukotriene receptor antagonist in cases where the symptoms are moderate/severe.[20] AIT is then recommended in patients with moderate/severe AR who have a diagnosis of IgE-mediated allergy and have symptoms despite the use of symptom-relieving medications.[20]

SQ® Tree SLIT-Tablet (ITULAZAX®; ALK-Abelló, Hørsholm, Denmark) is a sublingual immunotherapy (SLIT) tablet indicated for the treatment of moderate-to-severe AR and/or conjunctivitis (with or without asthma) induced by pollen from the birch homologous group, indicated in adults with a clinical history of symptoms despite use of allergy pharmacotherapy and a positive test of sensitization to a member of the birch homologous group (skin prick test and/or specific IgE).[21] The SQ Tree SLIT-Tablet is a standardized allergen extract of pollen from white birch (*Betula verrucosa)* per oral lyophilisate and has been investigated in a pan-European clinical development program comprising four randomized controlled trials (RCTs) in patients with AR due to birch pollen. The TT-04 trial was a Phase III, randomized, parallel-group, double-blind, placebo-controlled, multi-site study investigating the efficacy and safety of SQ Tree SLIT-Tablet in 634 subjects with moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group.[18,19] The primary endpoint was the average daily allergic rhinoconjunctivitis total combined score—a sum of the daily symptom score and the allergic rhinoconjunctivitis daily medication score—during the birch pollen season. TT-04 showed that the SQ Tree SLIT-Tablet reduced AR symptoms and symptom-relieving medication use by 39.6% during the birch pollen season and by 36.5% throughout the long tree pollen season (TPS; alder, hazel and birch) ($p < 0.0001$ versus placebo) while significantly improving quality of life versus placebo during both the birch and the long TPS ($p < 0.05$).[18,19]

In 2016, a systematic review of costs arising from AR in five European countries (Sweden, France, Germany, Italy, and Denmark) concluded that AR is associated with a considerable economic burden, driven primarily by indirect costs arising from high levels of absenteeism and reduced workplace productivity.[22,23] Given this economic burden and the increasing pressure to optimize healthcare expenditure, the objective of the present study was to evaluate the cost-utility of the SQ Tree SLIT-Tablet and symptom-relieving medications relative to placebo and symptom-relieving medications, based on a combination of local data from the Swedish setting and the findings of the TT-04 trial.

Methods

Cost-Utility Analysis and Model

A cost-utility analysis was considered to be the most appropriate health economic analysis modality based on the findings of the TT-04 RCT, which, through mapping of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) data to the EQ-5D health state utility values, provided evidence of a significant improvement in quality of life with the SQ Tree SLIT-Tablet relative to placebo.[24,25] A discrete-time, cohort-level, cost-utility model was developed in Microsoft Excel 2016 to evaluate the cost and quality of life outcomes associated with the SQ Tree SLIT-Tablet versus placebo, both in combination with symptom-relieving medications, capturing changes in health-related quality of life, all relevant costs associated with treatment, and indirect costs arising from absenteeism and reduced workplace productivity. The model captured survival using two states: alive with AR, and dead, with time-dependent transitions governed by annual probabilities (to align with the annual cycle length) derived from Swedish life tables. All modeling of costs and quality-adjusted life expectancy, including differences between the SQ Tree SLIT-Tablet and placebo occurred within the "alive with AR" state.

Patient Population

The simulated patient population was in line with the approved indication for the SQ Tree SLIT-Tablet, consisting of individuals ≥18 years of age with moderate-to-severe allergic rhinoconjunctivitis (with or without asthma) induced by birch pollen, with a clinical history of symptoms despite use of symptom-relieving medications and a positive test of sensitization to a member of the birch homologous group (skin prick test and/or specific immunoglobulin E). The cost-utility analysis was conducted in individuals initiating treatment with AIT in the SQ Tree SLIT-Tablet arm (with access to symptom-relieving medications as required) or starting to take symptom-relieving medications only in the placebo arm. Population characteristics were derived from the TT-04 trial population, which was 47% male with a mean baseline age of 36.1 years (standard deviation 13.6 years).[19] As the present study was based exclusively on computer simulation modeling, no human or animal subjects or samples were involved and no Institutional Review Board/Ethics Committee review was sought.

Life Expectancy and Quality of Life

In the base case analysis, age and sex-indexed all-cause mortality was captured based on Swedish life tables using cohort characteristics from the TT-04 trial.

The effect of the SQ Tree SLIT-Tablet on quality of life was evaluated as a secondary endpoint in the TT-04 RCT; using the RQLQ, the SQ Tree SLIT-Tablet significantly reduced the overall RQLQ score by 31.7% relative to placebo during the birch pollen season (24 days) and by 28.0% during the TPS (50 days), reflecting significantly improved quality of life. The RQLQ scores showed that quality of life was better with the SQ Tree SLIT-Tablet versus placebo at all time points assessed during the birch pollen season and the TPS ($p < 0.05$ for all time points except for week 10 [$p = 0.2$] during the TPS).

A utility increase of 0.0047 was modeled with the SQ Tree SLIT-Tablet in year 1 in line with a mapping analysis that estimated EQ-5D health state utility values directly from the TT-04 symptom and medication score data, and RQLQ scores.[25] The quality of life difference was assumed to be maintained over the whole model time horizon. As the mapping analysis only evaluated the difference between the SQ Tree SLIT-Tablet and placebo, the baseline quality of life health state utility was assumed to be 0.92 based on reference values for patients with hay fever (n = 416) from Ara and Brazier.[26] No change in quality of life from this baseline value was modeled in the placebo arm.

Perspective, Time Horizon, and Discounting

The analysis was conducted from a societal perspective, capturing the direct costs borne by the Swedish healthcare system, and indirect costs borne by Swedish society associated with absenteeism and reduced workplace productivity. The base case analysis was conducted over a 10-year time horizon, representing a one-year extension relative to a number of previous cost-utility analyses of AIT in Europe.[27–30] The time horizon was selected based on the assumed

duration of a disease-modifying effect with the SQ Tree SLIT-Tablet. In line with the European Academy of Allergy and Clinical Immunology (EAACI) recommendation of 3 years of AIT treatment, sustained treatment effects have been demonstrated over 6–7 years after treatment cessation with subcutaneous immunotherapy (SCIT).[31,32] A structured review of the literature on disease modification arising from the use of AIT in the treatment of AR identified 14 relevant studies. All but one of the studies reported either a measurable improvement in AR symptoms versus control 1 to 10 years after cessation of AIT or no significant difference in AR symptom scores between treatment cessation and end of study, across grass, house dust mite-induced AR (Table 1).[32–45]

A 3% annual discount rate was applied to all future cost and effectiveness outcomes in line with recommendations from the Swedish Dental and Pharmaceutical Benefits Agency.[46] A maximum willingness-to-pay (WTP) threshold of SEK 700,000 per quality-adjusted life year (QALY) gained was adopted using a "revealed preferences" approach as the highest acceptable incremental cost-utility ratio (ICUR) from the Swedish societal perspective based on the lowest cost per QALY of a declined reimbursement submission in Sweden in the period 2005–2011, as reported in a study by Svensson et al.[47] The same study reported a median WTP threshold of SEK 350,000 across 86 reimbursement decisions in the same period. An alternative WTP threshold of the Swedish per capita gross domestic product (GDP) of SEK 523,000 was also used for comparison, with Swedish GDP obtained from the 2021 Statistiska centralbyrån.[48]

Direct Costs and Resource Use

The base case analysis captured direct costs associated with AIT, healthcare professional (HCP) interactions, and symptom-relieving medications. AIT costs were only captured in the SQ Tree SLIT-Tablet arm, based on a pack price of SEK 2948.81 for 90 SQ Tree SLIT-Tablets. It was assumed that the SQ Tree SLIT-Tablet would be taken perennially, taking one tablet per day for the first three years of the analysis covering the first three pollen seasons falling in the analysis period.[31] On cessation of SQ Tree SLIT-Tablet treatment, no further AIT or HCP interaction costs were captured, but the effect of treatment was assumed to persist based on the established disease-modifying effect of AIT.

It was assumed that patients in the placebo arm would not attend any HCP appointments for AR, while two allergist visits were modeled in the first year of SQ Tree SLIT-Tablet treatment, followed by one allergist visit in subsequent years in line with AIT practice parameters published by the Joint Task Force on Practice Parameters from the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology. The general AIT guidelines recommend patients "should have follow-up visits at least every 6 to 12 months".[49] The 2017 SLIT-specific practice parameter update made no more specific recommendations in terms of routine follow-up for patients using SLIT.[50] A cost of SEK 1878 was assumed for each HCP interaction based on the "Sjv beh Lung och Allergi exkl lungmott (LAPSS1)" (medical treatment for lung and allergy excluding pulmonary embolism) price from the 2021 Prislista Västra Sjukvårdsregionen.

In the base case analysis, the costs of antihistamine tablets (desloratadine), eyedrops (olopatadine), and corticosteroid nasal spray (mometasone) were captured. Symptom-relieving medication resource use was based on data from the TT-04 trial (Table 2), and costs of symptom-relieving medications were taken from fass.se in November 2021 (Table 3). It was assumed that the cost of the nearest integer multiple of symptom-relieving medication packs sufficient to cover the required dose would be incurred in each modeled allergy season.

Indirect Costs

Indirect costs were modeled using a human capital approach based on absenteeism and reduced workplace productivity data from the TT-04 trial. In the base case analysis, the levels of absenteeism and reduced workplace productivity were based on data covering the TPS, with a duration of 50 days in line with the TPS duration in the TT-04 trial. In TT-04, 1.29% of days were taken as sick days with placebo, with the SQ Tree SLIT-Tablet reducing the risk of needing a sick day by 42% (corresponding to a relative risk of 0.58). Mean productivity with placebo in the TT-04 trial was 89.3%, which increased by 3.39%-points (in absolute terms) with the SQ Tree SLIT-Tablet. Reductions in productivity loss were captured for the TPS duration only. Workforce characteristics were derived from a combination of the TT-04 trial population (age and proportion male) and Sweden-specific data from the Statistiska centralbyrån and Eurostat (Table 4).

Table 1 Evidence on the Disease-Modifying Effect of Allergy Immunotherapy Products for Allergic Rhinitis

Study	Year	N	N at Last Follow-Up	Allergy	Treatment Arms	Initial Treatment Duration	Post-Treatment Follow-Up	Outcome Measures	Key Findings at Last Follow-Up
Mosbech[33]	1988	40	32	Grass	• Alutard SQ 20-component extract (SCIT) • Purified 2-component extract (SCIT)	2 years 4 months	6 years	Hay fever symptom questionnaire, diary cards, pollen counts, total IgE, allergen-specific IgE	• Symptoms stabilized or further decreased in nearly all patients • Total serum IgE significantly lower than pre-treatment • Allergen-specific IgE not significantly different from pre-treatment
Des Roches[34]	1996	40		House dust mite	• Standardized Der p extract (SCIT) for 12–35 months • Standardized Der p extract (SCIT) for >36 months	12–35 mths >36 mths	3 years	Skin prick test result, size of skin prick test reaction, symptom-medication scores, peak flow, occurrence of asthma symptoms	• Rate of relapse after cessation of SCIT was significantly higher in the group who received SIT for under 35 months ($p < 0.04$) • Three years after stopping SCIT, there was no relapse in 52% of patients who had received SCIT for >36 months compared with 38% in the group who had received SCIT for 12–35 months
Durham[35]	1999	55	39	Grass	• Alutard SQ grass maintenance (SCIT) (M) • Alutard SQ grass discontinuation (SCIT) (D) • No AIT (no placebo administered) (C)	3 years	3 years	Presence of symptoms, need for rescue medication, VAS (0 indicating minimal symptoms and 10 indicating maximal symptoms)	• No significant differences in scores for total hay fever symptoms, rescue medication, or VAS between M and D groups 3 years after initial treatment period • Symptom and rescue medication scores in M and D groups markedly lower than those in patients in the C group
Jacobsen[32]	2007	205	147	Grass and/or birch	• Alutard SQ grass and/or birch (SCIT) • No AIT (no placebo administered) • Pharmacotherapy as needed	3 years	2 years 7 years	Skin prick test, conjunctival provocation test, methacholine bronchial provocation test, VAS (symptoms of conjunctivitis, rhinitis and asthma), asthma diagnosis	• 2.5x higher odds of developing asthma in no AIT group than Alutard SQ group • Conjunctival sensitivity significantly reduced in Alutard SQ group • Conjunctivitis and rhinitis VAS scores significantly improved in Alutard SQ group

(*Continued*)

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Table 1 (Continued).

Study	Year	N	N at Last Follow-Up	Allergy	Treatment Arms	Initial Treatment Duration	Post-Treatment Follow-Up	Outcome Measures	Key Findings at Last Follow-Up
Ott[36]	2009	213	145	Grass	• Staloral 300 SR (SLIT drops) precoseasonal • Placebo • Pharmacotherapy as needed	3 pollen seasons	1 pollen season	Baseline-adjusted sum score of combined symptom and rescue medication score, specific IgE and IgG_4, adverse event incidence and severity	• SLIT group had sequentially lower combined symptom and medication scores relative to placebo over seasons 2, 3 and the follow-up season • Mean serum concentrations of all immunological parameters returned to baseline values in the follow-up season
Marogna[37]	2010	78	59	House dust mite	• Der p 1/Der p 2 for 3 years (SLIT3), 4 years (SLIT4) or 5 years (SLIT5) • Placebo • Pharmacotherapy as needed	3 years 4 years 5 years	12 years 11 years 10 years	Symptoms plus medications score (SMS) diary card, new skin sensitizations, methacholine provocative dose causing a 20% decrease in FEV_1 (PD_{20}), the percentage of nasal eosinophils	• Difference between control group after SLIT discontinuation remained significant for 6 years in the SLIT3 group and for 7 years in the SLIT4 and SLIT5 groups • At end of study, new sensitizations had appeared in 100% of the control group, 21.4% of the SLIT3 group, 12.5% of the SLIT4 group, and 11.7% of the SLIT5 group
Tabar[38]	2011	239	111+27	House dust mite	• Der p 1 and Der p 2 (Pangramin Depot UM) (SCIT) for 3 years (IT3) and 5 years (IT5) • No AIT (no placebo administered) • Pharmacotherapy as needed	3 years 5 years	2 years	Rhinitis severity scale, asthma symptom scale, quality of life by RQLQ and AQLQ, proportion of patients free of asthma, forced spirometry with bronchodilation, *D pteronyssinus*–specific IgG, IgG_4, and IgE, *D pteronyssinus* skin prick tests	• Rhinitis score at 5 years not significantly different between IT3 and IT5 groups ($p = 0.146$) • Asthma score at 5 years not significantly different between IT3 and IT5 groups ($p = 0.330$) • Clinically relevant increases in AQLQ and RQLQ scores from baseline with no differences observed between IT3 and IT5 groups at 5 years

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Durham[39]	2012	634	238	Grass	• Grazax (P pratense 75,000 SQ-T/2800 BAU) (SLIT tablets) precoseasonal • Placebo • Pharmacotherapy as needed	3 years	2 years	Grass pollen counts, average rhinoconjunctivitis DSS and DMS, weighted RCS calculated on the basis of primary end points, rhinoconjunctivitis quality of life, days with severe symptoms (%), change from baseline in specific IgG_4 levels and IgE-blocking factor, change from baseline in facilitated allergen presentation inhibition, safety and tolerability	• RCS was reduced by between 27% and 41% with Grazax relative to placebo across all 5 pollen seasons • The RCS treatment effect was significant for all 5 years of the trial ($p < 0.01$ for all years) • Differences between Grazax and placebo groups in specific IgG_4, specific IgE-blocking factor, and facilitated allergen presentation inhibition were significant at all assessments ($p < 0.05$) • Quality of life by RQLQ was significantly improved with Grazax relative to placebo across all 5 pollen seasons
Bergmann[40]	2014	509	397	House dust mite	• 1:1 mixture of Der p 1 and Der p 2 (300IR) (SLIT tablets) • 1:1 mixture of Der p 1 and Der p 2 (500IR) (SLIT tablets) • Placebo • Pharmacotherapy as needed	1 year	1 year	Four individual rhinoconjunctivitis symptom scores, individually and summed to give RTSS (0–12), RMS (0–3), AAdSS (0–12), average RTSS, individual ARTSS, average RMS	• Maintenance of the significant reduction in AAdSSs observed in the active treatment groups compared with placebo group in the year 2 period • Similar reductions were observed in ARTSSs in the active groups relative to placebo over the year 2 period

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Table 1 (Continued).

Study	Year	N	N at Last Follow-Up	Allergy	Treatment Arms	Initial Treatment Duration	Post-Treatment Follow-Up	Outcome Measures	Key Findings at Last Follow-Up
Didier[41]	2015	633	372	Grass	• 300IR 5-grass pollen extract (SLIT tablet) precoseasonal starting 2 months preseason (2M) • 300IR 5-grass pollen extract (SLIT tablet) precoseasonal starting 4 months preseason (4M) • Placebo • Pharmacotherapy as needed	3 years	2 years	Six individual rhinoconjunctivitis symptom scores, individually and summed to give RTSS (0–18), use of rescue medication on the RMS (0–3), daily RMS (DRMS), AAdSS, DCS	• DCS, DRTSS and DRMS were similar from years 2 to 5 in the active-treatment groups, whereas they decreased consistently in the placebo group • The DRMS remained stable with the transition from active treatment into treatment-free years 4 and 5 • Safety profiles in treatment-free years 4 and 5 were consistent across the placebo and both active treatment groups
Bozek[43]	2017	108	95	House dust mite	• Staloral 300 SR (SLIT drops) • Placebo • Pharmacotherapy as needed	3 years	3 years	Average adjusted symptom score (AAdSS), serum level of IgG_4 to *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, Der p 1, and Der p 2, and quality of life, and total combined rhinitis score (TCRS), assessed immediately after SLIT and 3 years later	• AAdSS remained at a low level and significantly lower than that in the placebo group • TCRS remained constant at a low value in the active group (post hoc analysis) • Serum-specific IgE levels remained at the same post-treatment level
Scadding[42]	2017	106	92	Grass	• Grazax (SLIT tablets) • Alutard SQ (SCIT) • Placebo	2 years	1 year	Nasal response to allergen challenge defined as average of TNSS at 0–1 hours and 1–10 hours after challenge, change in PNIF after challenge, seasonal weekly VAS, seasonal weekly MiniRQLQ, end-of-season global rhinitis severity scores, seasonal medication use, early and late skin responses to intradermal allergen	• Nasal allergen–induced TNSS in the SLIT group did not differ from placebo • Allergen-induced reduction from prechallenge PNIF baseline did not differ from placebo with either form of immunotherapy • No benefit from either form of immunotherapy was observed in seasonal weekly MiniRQLQ or VAS symptom scores

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Valovirta[44]	2018	812	608	Grass	• Grazax (P pratense 75,000 SQ-T/2800 BAU) (SLIT tablets) • Placebo • Pharmacotherapy as needed	3 years	2 years	Time to onset of asthma in days from randomization, ARC symptoms VAS score, ARC medication score, IgE and IgG_4, safety	• Fewer children on Grazax compared with placebo-treated children experienced asthma symptoms or used asthma medication; odds ratio (OR) = 0.66; p = 0.036, corresponding to a relative risk reduction of 29.4% • ARC symptoms VAS score was statistically significantly lower in the Grazax group • Adjusted mean of the daily ARC medication score in the pollen season was significantly lower in the Grazax group than in the placebo group (relative reduction of 27%)
Yonekura[45]	2021	1042	412	Japanese cedar	• Japanese cedar pollen (Cry j 1) SLIT tablets at 2000, 5000, or 10,000 Japanese allergy units (dose finding) • Placebo–placebo (PP) • Placebo-5000 JAU (PA) • 5000 JAU-placebo (AP) • 5000 JAU-5000 JAU (AA) • Pharmacotherapy as needed	3 years (15 months dose finding and 18 months treatment)	2 years	TNSMS, TOSMS, well days, severe symptom days, proportion of participants who did not use rescue medication, cumulative frequency of rescue medication use, and QoL assessment using the JRQLQ	• Least squares mean TNSMS in the AA group was significantly different from the PP group during peak symptom periods of all years (p < 0.001). • Rate of TNSMS decrease in the AA group varied between 32.1% (first season) and 46.3% (third season) and remained high in the fifth season (34.0%). • TNSMS in the AP group was significantly lower than the PP group in all seasons except the fifth. • TNSMS in the AA group was significantly lower than that of the AP group in the fourth and fifth seasons.

Abbreviations: AAdSS, average adjusted symptom score; AIT, allergy immunotherapy; AQLQ, Asthma Quality of Life Questionnaire; ARC, allergic rhinitis and conjunctivitis; ARTSS, average rhinitis symptom score; DCS, daily combined score; DMS, daily medication score; DSS, daily symptom score; IgE, immunoglobulin E; IgG_4, immunoglobulin G4; JAU, Japanese allergy unit; JRQLQ, Japanese Rhinoconjunctivitis Quality of Life Questionnaire; MiniRQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire; PD20, Provocative dose causing a 20% decrease in FEV_1; PNIF, peak nasal inspiratory flow; RCS, rhinoconjunctivitis combined score; RMS, rescue medication score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, rhinoconjunctivitis total symptom score, SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; TCRS, total combined rhinitis score; TNSS, total nasal symptom score; TNSMS, total nasal symptom and medication score; TOSMS, total ocular symptom and medication score; VAS, visual analog scale.

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Table 2 Symptom-Relieving Medication Resource Use Based on the TT-04 Trial

	Symptom-Relieving Medication Dosing		Proportion of Patients Requiring Symptom-Relieving Medication (%)	
	SQ Tree SLIT-Tablet	Placebo	SQ Tree SLIT-Tablet	Placebo
Desloratadine tablets	17.3	21.7	66.8%	76.70%
Olopatadine eyedrops	29.8	38.0	39.6%	54.80%
Mometasone nasal spray	28.9	38.4	47.9%	61.60%

Table 3 Symptom-Relieving Medication Costs

Symptom-Relieving Medication	Price (SEK)	Pack Size	Reference
Desloratadine tablets	157.48	100	Fass.se Desloratadine Sandoz (ATC: R06AX27; Filmdragerad tablett 5 mg Ljusblå, rund, bikonvex tablett, märkt med "5" på ena sidan. Diameter 6.50±0,10 mm; SEK 157.48 for 100 tablets)
Olopatadine eyedrops	252.38	300	Fass.se Opatanol Novartis (ATC: S01GX09; Ögondroppar, lösning 1 mg/mL klar, färglös lösning; SEK 252.38 for 15 mL) Assuming 20 drops per millilitre
Mometasone nasal spray	70.69	140	Fass.se Mometasone Teva (ATC: R01AD09; Näs别spray, suspension 50 mikrog/dos vit till benvit, ogenomskinlig; SEK 70.69 for 140 doses)

Table 4 Workforce Characteristics Utilized in the Human Capital Approach to Modeling Costs of Absenteeism and Reduced Workplace Productivity

Human Capital Model Input	Base Case Value	Reference
Mean age (SD), years	36.1 (13.6)	TT-04
Proportional male, %	47.0	TT-04
Average male salary, SEK	565,767	[51,52]*
Average female salary, SEK	499,353	[51,52]*
Average age at entry into the workforce, years	18	Assumption
Average age at retirement, years	65	Assumption
Unemployment rate, %	8.9	[51]**
Number of working days per year, days	220	Assumption ***

Notes: *Mean monthly salary of SEK 44,380 was adjusted using the 2016 Eurostat unadjusted gender pay gap estimate for Sweden of 13.3%. **Based on the arithmetic mean of the first 11 months of 2021 for which data were available from Eurostat. ***Based on 261 working days per year, minus 30 days of paid leave and 11 national holidays in Sweden.

In addition to the TT-04 based productivity losses, the base case analysis associated one hour of absenteeism with each HCP interaction in the SQ Tree SLIT-Tablet arm. Based on the assumption of no AR-related HCP interactions in the placebo arm, no excess absenteeism (beyond that based on the rates of absence in the TT-04 trial) was captured in the placebo arm.

One-Way Sensitivity Analyses

A series of one-way sensitivity analyses were conducted to establish the magnitude of the effect of changing various model parameters on outcomes. Annual discount rates were varied from 3% in the base case to 0% *per annum* (undiscounted) and 5% *per annum* to reflect different valuations of costs incurred and QALYs gained in the future. The time horizon was changed from 10 years in the base case analysis to 5 years and 15 years to establish if the cost-utility of the SQ Tree SLIT-Tablet increases or decreases over different time periods. An analysis was conducted in which no mortality was captured over the model time horizon. While no mortality *differences* were assumed in the base case analysis, the "no mortality" sensitivity analysis quantified the effect of 100% of patients surviving for the analysis time

horizon in both arms of the analysis. Given that the assumption of individuals in the placebo arm not attending any allergy-related HCP appointments was likely to underestimate costs in the placebo arm, this was explored in two analyses. In the first, HCP interactions were set to be identical in both arms, and in the second, the HCP interaction *frequency* was set to be identical but individuals in the placebo arm were assumed to attend an appointment with a general practitioner (GP) rather than an allergy specialist.

A series of six analyses were then conducted in which key model options were changed from the base case settings. Productivity loss was modeled over the birch pollen season (24 days) rather than the TPS (50 days) in the base case, resulting in higher productivity loss but over a shorter time period. Indirect costs were excluded from the analysis, no productivity loss was associated with HCP interactions, symptom-relieving medication costs were omitted from the analysis, and the disease-modifying effect of the SQ Tree SLIT-Tablet was omitted using two different modeling assumptions.

In considering the disease-modifying effect, one analysis was conducted in which SQ Tree SLIT-Tablet treatment was continued over 10 years; costs were captured over the full 10-year time horizon (rather than 3 years in the base case analysis), while no changes were made to the effects of treatment relative to the base case analysis. A second analysis was conducted in which the effects of SQ Tree SLIT-Tablet on absenteeism, productivity loss, symptom-relieving medication use, and quality of life were abolished after 3 years to coincide with completion of a 3-year course of treatment. Notably, in the analysis in which SLIT treatment is continued for 10 years, the treatment duration far exceeds the SLIT treatment duration specified in the EAACI Guidelines, which note that "for patients with AR a minimum of three years of AIT is recommended in order to achieve long-term efficacy after treatment discontinuation".[31]

Finally, an analysis was conducted around the rates of persistence with AIT treatment. Persistence rates were aligned with those reported for SLIT tablet use in Allam et al at 41% in year 2 and 31% in year 3.[53] Costs, quality of life improvements, changes in absenteeism and productivity loss, and reductions in the use of symptom-relieving medications were assumed to decline proportionately with the rate of non-persistence across the cohort. After the end of SLIT treatment in year 3, all further cost and effectiveness outcomes were modeled at 30% of those modeled in the base case, in line with the proportion of patients ultimately deemed to be persistent in Allam et al.[53]

Probabilistic Sensitivity Analyses

In addition to the one-way sensitivity analyses, a probabilistic sensitivity analysis (PSA) was conducted in which uncertainty around multiple parameters was captured. In the analysis, 1000 Monte Carlo simulations were conducted, simultaneously drawing from seven distributions around key model parameters. The modeled estimates of cost and quality of life were recorded for each iteration and used to generate a cost-effectiveness scatterplot, cost-effectiveness acceptability curve (CEAC), and an estimate of the expected value of perfect information (EVPI) over a range of WTP thresholds.

EVPI is a theoretical measure commonly used in cost-utility analyses to quantify the value associated with eliminating uncertainty around model parameters. If the actual cost of obtaining that "perfect" information (eg, by means of conducting a larger clinical trial) were higher than the EVPI, then the additional data collection would not be worthwhile. Conversely, if the expected cost of obtaining the additional information were lower than the EVPI, additional research might be warranted. In all cases, the EVPI (and hence the decision to conduct additional research) is dependent on WTP. In the present analysis, the EVPI represents the value to the healthcare decision-maker of removing all uncertainty from the cost-effectiveness analysis. The value can therefore be thought of as the maximum acceptable cost of conducting additional research to obtain perfect information on all model parameters included in the PSA, which would thereby guarantee that the decision on the cost-effectiveness of the SQ Tree SLIT-Tablet versus placebo would be correct in the target population and at the specified WTP threshold.

Results

In the base case analysis, the SQ Tree SLIT-Tablet was associated with an improvement in quality-adjusted life expectancy of 0.041 QALYs relative to placebo over a 10-year time horizon, from 7.951 QALYs to 7.992 QALYs. The increase in quality-adjusted life expectancy was accompanied by an increase in costs of SEK 9077 per patient, from SEK 103,981 to SEK 113,057 over 10 years (Figure 1). The increases in costs and quality-adjusted life expectancy resulted in an ICUR of SEK 223,445 per QALY gained (Table 5).

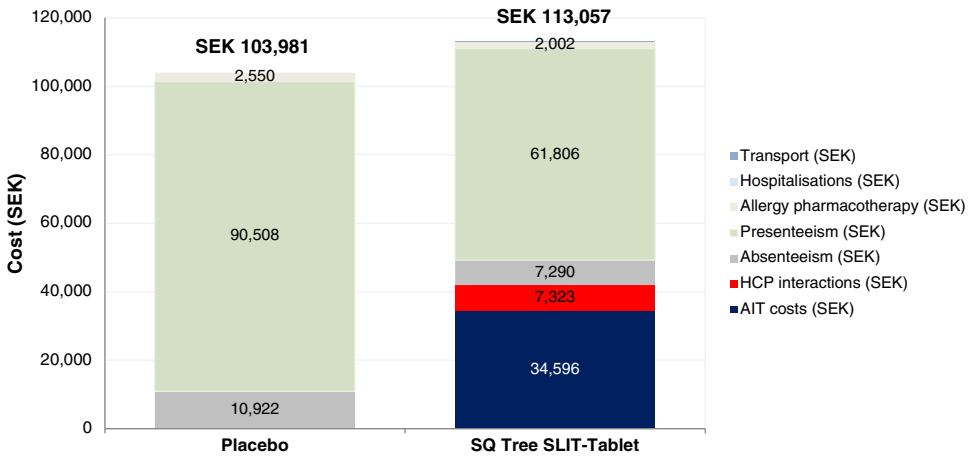

Figure 1 Cost breakdown in the deterministic base case analysis.

One-way sensitivity analyses showed that incremental model outcomes were insensitive to changes in many of the model's individual input parameters, with the notable exceptions of the disease-modifying effect of the SQ Tree SLIT-Tablet, the inclusion of indirect costs (absenteeism and reduced workplace productivity), and assumptions around HCP interactions in individuals in the placebo arm (Table 6). Excluding the disease-modifying effect of the SQ Tree SLIT-Tablet (thereby incurring AIT costs in every year of the analysis) increased the ICUR to SEK 2,210,793 per QALY gained, falling over the WTP threshold. Excluding all indirect costs from the analysis increased the incremental costs of the SQ Tree SLIT-Tablet relative to placebo to SEK 41,371 (from SEK 9077 in the base case), increasing the ICUR to 1,018,468 per QALY gained, which was similarly above the WTP threshold. Including the same frequency and nature of HCP interaction costs in the placebo arm as in the SQ Tree SLIT-Tablet arm resulted in SQ Tree SLIT-Tablet dominating placebo, with improved life expectancy and cost savings of SEK 11,489 per patient over 10 years. Assuming the same frequency of HCP interactions in the placebo arm but with a GP rather than an allergy specialist reduced the ICUR to SEK 77,461 per QALY gained. The analysis in which cost and effectiveness outcomes were reduced proportionately with a modeled rate of persistence to SQ Tree SLIT-Tablet treatment showed reductions in the incremental cost and QALY outcomes relative to the base case, but the assumption of proportionality resulted in an ICUR identical to that in the base case analysis.

Running 1000 PSA iterations showed that the SQ Tree SLIT-Tablet would be more costly than placebo in 84.7% of iterations, and more effective than placebo in 56.6% of iterations (Figure 2). The mean incremental quality-adjusted life expectancy was 0.047 QALYs higher (median 0.039 QALYs) with the SQ Tree SLIT-Tablet than placebo, in agreement with the increase of 0.041 QALYs in the deterministic base case analysis. The mean incremental cost was SEK 9518 higher with the SQ Tree SLIT-Tablet compared to SEK 9077 higher in the deterministic base case (ie, a difference of SEK 441 or 4.8% indicating that parameter uncertainty in the model had a relatively small effect on mean incremental outcomes).

The incremental outcomes from the PSA were then used to plot a cost-effectiveness acceptability curve over a range of WTP thresholds from SEK 0 per QALY gained to SEK 700,000 per QALY gained (Figure 3). At a WTP threshold of

Table 5 Summary of Results from the Base Case Analysis of the Cost-Utility of SQ the Tree SLIT-Tablet Relative to Placebo Over a 10-Year Time Horizon from a Swedish Societal Perspective

	Life Expectancy (Years)	Quality-Adjusted Life Expectancy (QALYs)	Cost (SEK)	Incremental Cost-Utility Ratio (SEK Per QALY Gained)
Placebo	8.643	7.992	113,057	
SQ Tree SLIT-Tablet	8.643	7.951	103,981	
Difference	**0.000**	**0.041**	**9077**	**223,445**

Table 6 One-Way Sensitivity Analysis Results

	Quality-Adjusted Life Expectancy (QALYs)			Cost (SEK)			ICUR (SEK Per QALY Gained)
	Placebo	SQ Tree SLIT-Tablet	Δ	Placebo	SQ Tree SLIT-Tablet	Δ	
Base case	**7.951**	**7.992**	**+0.041**	**103,981**	**113,057**	**+9077**	**223,445**
0% discount rate	9.041	9.087	+0.046	118,233	123,880	+5647	122,266
5% discount rate	7.342	7.380	+0.038	96,012	106,927	+10,914	290,985
5 year time horizon	4.308	4.330	+0.022	56,338	80,918	+24,580	1,116,840
15 year time horizon	11.003	11.060	+0.056	143,892	139,981	−3911	Dominant
No mortality	8.083	8.125	+0.041	105,705	114,402	+8696	210,592
Same HCP interactions in placebo arm as the SQ Tree SLIT-Tablet arm	7.951	7.992	+0.041	124,546	113,057	−11,489	Dominant
Same HCP interaction frequency in placebo and SQ Tree SLIT-Tablet arms, GP only	7.951	7.992	+0.041	109,911	113,057	+3147	77,461
Productivity loss based on birch pollen season	7.951	7.992	+0.041	64,526	84,955	+20,429	502,920
No indirect costs	7.951	7.992	+0.041	2550	43,921	+41,371	1,018,468
No productivity loss for HCP interactions	7.951	7.992	+0.041	103,981	112,062	+8082	198,960
No symptom-relieving medication costs	7.951	7.992	+0.041	101,430	111,055	+9624	236,930
No disease-modifying effect with SQ Tree SLIT-Tablet (10 years of SLIT)	7.951	7.992	+0.041	103,981	193,785	+89,804	2,210,793
No disease-modifying effect with SQ Tree SLIT-Tablet (no effects on productivity loss, absenteeism, symptom-relieving medication use, or QoL after treatment)	7.951	7.965	+0.014	103,981	135,537	+31,557	2,314,583
Persistence in line with Allam et al	7.951	7.964	+0.012	103,981	106,703	+2723	223,445

Abbreviations: GP, general practitioner; HCP, healthcare professional; ICUR, incremental cost-utility ratio; SEK, 2021 Swedish Krona; QALY, quality-adjusted life year; QoL, quality of life.

SEK 350,000 per QALY gained, there would be a 52.1% likelihood that the SQ Tree SLIT-Tablet would be cost-effective relative to placebo (Figure 3); this increased to 53.4% at a WTP threshold of SEK 523,000 per QALY corresponding to Swedish GDP per capita in 2021 and to 53.6% at a WTP threshold of SEK 700,000 per QALY.

Finally, an EVPI curve was generated from the PSA iteration data, showing that, at a WTP threshold of SEK 350,000 per QALY gained, the EVPI would be SEK 52,657 (Figure 4), increasing to SEK 77,436 at a WTP threshold of

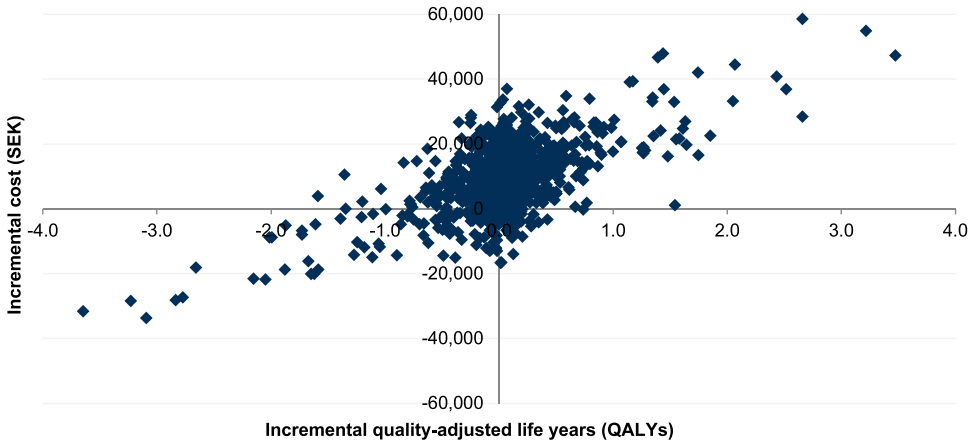

Figure 2 Cost-utility scatterplot based on 1000 probabilistic sensitivity analysis iterations.

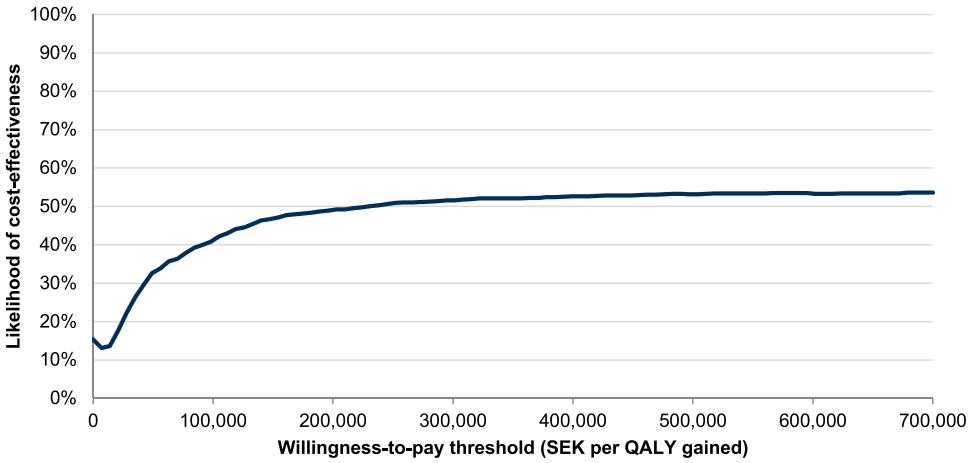

Figure 3 Cost-utility acceptability curve generated from 1000 probabilistic sensitivity analysis iterations.

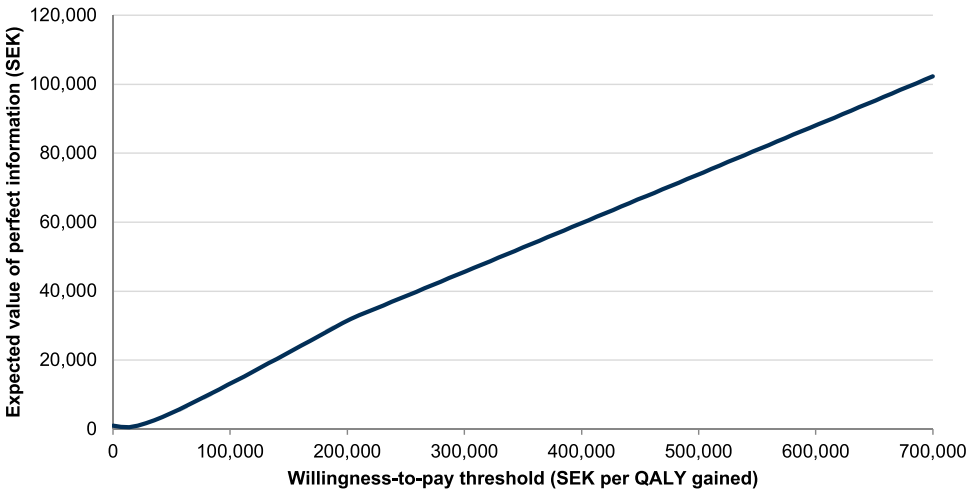

Figure 4 Expected value of perfect information curve based on 1000 probabilistic sensitivity analysis iterations.

SEK 523,000 per QALY gained, and to SEK 102,277 at a WTP threshold of SEK 700,000 per QALY gained. Investment in the collection of additional information to reduce uncertainty in the decision-making around adoption of the SQ Tree SLIT-Tablet should therefore only be considered if the cost of the research fell below SEK 102,277 per patient (assuming a WTP threshold of SEK 700,000).

Discussion

The present analysis showed that the SQ Tree SLIT-Tablet is likely to be cost-effective relative to placebo in the treatment of individuals ≥18 years of age with moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group in Sweden. Over a 10-year time horizon, the SQ Tree SLIT-Tablet was projected to increase quality-adjusted life expectancy by 0.041 QALYs relative to placebo, and incur an additional SEK 9077 in costs, translating to an ICUR of SEK 223,445 per QALY gained. This falls well below the SEK 700,000 per QALY maximum WTP threshold identified using a "revealed preferences" approach in Sweden, and below the median value of SEK 350,000 per QALY across 86 Swedish reimbursement decisions evaluated by Svensson et al.[47]

The key drivers of cost-effectiveness identified through one-way sensitivity analyses were the analysis time horizon, the disease-modifying effect of the SQ Tree SLIT-Tablet and the inclusion of indirect costs borne by Swedish society in addition to direct medical costs. The inclusion of the disease-modifying effect in the base case analysis was based on the

recommendation from the EAACI Guidelines, which note that "for patients with AR a minimum of three years of AIT is recommended in order to achieve long-term efficacy after treatment discontinuation".[31] Notably, in sensitivity analysis, when the cost of the SQ Tree SLIT-Tablet treatment was captured over the full 10-year duration of the analysis, the ICUR increased to SEK 2,210,793 per QALY gained, illustrating that continuous AIT treatment over 10 years would not be cost-effective relative to placebo.

Indirect costs were the biggest driver of cost offsets in the analysis, with the direct cost savings for symptom-relieving medications contributing only SEK 548 to the total SEK 32,882 of cost offsets brought about by the use of the SQ Tree SLIT-Tablet. The remaining cost offsets of SEK 3632 and SEK 28,702 were associated with reduced absenteeism and increased workplace productivity brought about by the SQ Tree SLIT-Tablet, respectively. Excluding these costs resulted in an ICUR of SEK 1,018,468 per QALY gained, which would not be considered cost-effective, but this analysis highlights the conservatism of the base case, particularly the exclusion of HCP interactions for individuals using symptom-relieving medications only; total costs in the placebo arm were only SEK 2550 over 10 years when indirect costs were excluded.

The analysis included numerous assumptions that may have underestimated the costs of placebo and overestimated the costs of SQ Tree SLIT-Tablet, for instance, assuming that individuals receiving no AIT would not have any allergy-related interactions with HCPs over the duration of the analysis. Given the moderate-to-severe nature of the allergic rhinitis and/or conjunctivitis experienced in the target population, this would be unlikely over a period of 10 years. Conversely, the analysis captured the fullest possible costs of HCP interactions with SQ Tree SLIT-Tablet, assuming an allergy specialist would be seen at every appointment and that each appointment would be associated with 1 hour of absenteeism and 10 km of travel. Furthermore, in the base case analysis, it was assumed that individuals would be 100% adherent to the prescribed treatment with SQ Tree SLIT-Tablet, with the likely effect of increasing both cost and efficacy relative to routine clinical practice.

Considering the duration of the AIT treatment course, persistence and adherence are worthy of some further consideration; a 2018 analysis of 2429 patients receiving SLIT and 2109 patients receiving SCIT in Germany reported 3-year persistence rates of 30% and 31% for SLIT tablet and SCIT patients, respectively.[53] Within the persistent patients, adherence rates of 81% and 83%, respectively, were observed in patients treated with SLIT tablet and SCIT, again respectively.[53] While these persistence rates are substantially lower than 100%, the balance of cost and utility (and hence the ICUR) would only be affected substantively if the relationship between adherence/persistence and cost was meaningfully different from the relationship between adherence/persistence and quality-adjusted life expectancy.

The analysis omitted comorbid conditions that commonly occur concomitantly with AR. For instance, the *Bet v 1* allergen is cross-reactive with the major allergens of certain foods, which can result in individuals experiencing pollen-food syndrome (PFS). PFS symptoms include itching of the lips, tongue and throat, sometimes accompanied by swelling.[54] The prevalence of PFS in individuals with AR is high, with 73.3% of individuals with birch-related AR experiencing symptoms associated with eating certain types of food, 86% of whom experienced PFS perennially.[54] Costs of asthma were also not captured in the present analysis. Although the asthma symptom scores recorded in the TT-04 RCT were low (~1 on a scale from 0 to 12) in subjects with a medical history of asthma and in general for all subjects, an analysis of the average asthma daily symptom scores showed a reduction in asthma symptoms in the SQ Tree SLIT-Tablet group compared to placebo during both the birch pollen season ($p = 0.0089$) and the full TPS ($p = 0.0239$). However, an analysis of the proportion of days on which individuals required asthma medication showed no differences between the SQ Tree SLIT-Tablet and placebo during either the birch or tree pollen seasons.

One final potential limitation of the study pertains to the assumptions around the extent and duration of disease modification with the SQ Tree SLIT-Tablet. The assumption of 3 years of treatment with the SQ Tree SLIT-Tablet resulting in modification of the underlying disease is consistent with AIT treatment recommendations made by the EAACI, but the duration and extent of disease modification has not yet been demonstrated in individuals taking the SQ Tree SLIT-Tablet.[31] The disease-modifying effect has been conclusively demonstrated in SQ SLIT tablets indicated for grass pollen-induced allergic rhinitis. Given that the mechanism of action for the birch homologous group is driven by the same immunological processes, it is likely that disease modification would also be observed in this patient group.

To our knowledge, the present study presents the first cost-utility analysis comparing SLIT tablets with placebo in patients with moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group in Sweden; however, a 2008 analysis evaluated the cost-utility of the SQ Grass SLIT-Tablet (SLIT tablets for the treatment of allergic rhinitis induced by polled from Timothy grass) versus symptom-relieving medication over a 9-year time horizon in seven European countries including Sweden.[55] The most notable difference from the present analysis was the use of health state utility values elicited directly from a clinical trial using the EQ-5D, which yielded an estimated 0.0287 QALY improvement per season with the SQ Grass SLIT-Tablet versus symptom-relieving medication. This compares with an estimate of 0.0047 QALY improvement per season in the present analysis, based on mapping symptom and medication score and RQLQ data from the TT-04 trial to health state utility values. Despite this substantial difference in the estimated difference in quality of life with SLIT versus placebo, the 2008 analysis reported a range of ICURs from approximately EUR 23,000 to EUR 50,000 per QALY gained depending on the assumed annual cost of the SQ Grass SLIT-Tablet. While there are numerous methodological differences between these studies which focus on different allergens, the lower end of the estimate from the 2008 study is closely aligned with the ICUR of EUR 21,330 per QALY gained in the present analysis (based on a 90-day trailing average EUR: SEK exchange rate as of May 2022).

Conclusion

The TT-04 RCT demonstrated that SQ Tree SLIT-Tablet is a safe and efficacious AIT product, with a simple mode of administration, and resulting in marked improvements in quality of life in individuals with moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group. The present analysis showed that these quality of life benefits would be associated with only a modest increase in societal costs over a 10-year time horizon, therefore representing a cost-effective treatment option from the Swedish societal perspective based on a WTP threshold of SEK 700,000 per QALY gained.

Ethics Approval and Informed Consent

As the present study was based exclusively on computer simulation modeling, no human or animal subjects or samples were involved and no Institutional Review Board/Ethics Committee review was sought.

Data Sharing Statement

Additional data are available upon reasonable request to the corresponding author.

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Disclosure

RFP is a director, shareholder, and full-time employee of Covalence Research Ltd, which received consultancy fees from ALK-Abelló A/S to develop the cost-utility model, formulate and execute the Swedish analyses, and prepare the manuscript draft. AKS, HB, and TSG were full-time employees of ALK-Abelló A/S at the time of the study. The authors report no other conflicts of interest in this work.

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