NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Betula verrucosa for treating moderate to severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen [ID6462]

Committee Papers

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from ALK Abello:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Association of Respiratory Nurse Specialists
   b. British Society of Allergy and Clinical Immunology (BSACI)
   c. British Society for Immunology – Clinical Immunology Professional Network (BSI-CIPN)
   d. The Royal College of Pathologists

4. **Summary of responses from clinical experts to questions from NICE**

5. **External Assessment Report** prepared by Kleijnen Systematic Reviews

6. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Betula verrucosa (ITULAZAX 12 SQ-Bet) for treating moderate to severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen [ID6462]

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6462_ 12 SQ-Bet company submission	Final	Yes	13.03.25

Contents

Tables and figures

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Table of abbreviations

AA	Allergic asthma
ACT	Asthma control test
AE	Adverse events
AH	Antihistamine
AHPS	Alder and hazel pollen season
AIC	Akaike information criterion
AIT	Allergen immunotherapy
AM	Alveolar macrophage
AR	Allergic rhinitis
AR/C	Allergic rhinitis with, or without conjunctivitis
ARD	Allergic respiratory disease
ARIA	Allergic Rhinitis and its Impact on Asthma
ATC	Anatomical Therapeutic Chemical
AZE	Azelastine hydrochloride
BAT	By basophil activation
BMI	Body mass index
BNF	British National Formulary
BPS	Birch pollen season
BSACI	British Society for Allergy and Clinical Immunology
CAD	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
DMS	Daily medication score
DSA	Deterministic sensitivity analyses
DSS	Daily symptom score
EAACI	European Academy of Allergy and Clinical Immunology
EBM	Evidence Based Medicine
EEC	Environmental exposure chamber
EMA	European Medicines Agency
EMIT	Drugs and pharmaceutical electronic market information tool
ENT	Ear, nose and throat
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAIM	Food allergy independent measure
FAQLQ	Food Allergy Quality of Life Questionnaire
FAS	Full analysis set
FASBPS	Subjects in FAS with observations in the birch pollen season
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FP	Fluticasone propionate
GEE	Generalised estimating equation
GINA	Global Initiative for Asthma
GP	General practitioner
HCP	Healthcare professional

HDM	House dust mite
HES	Hospital Episode Statistics
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG4	Immunoglobulin G subtype 4
IgM	Immunoglobin M
IL	Interleukin
IMP	Investigational medicinal product
INAH	Intranasal antihistamine
INCS	Intranasal corticosteroids
INMB	Incremental net monetary benefit
INS	Intranasal steroids
IQR	Interquartile range
ITT	Intent to treat
ISPOR	The Professional Society for Health Economics and Outcomes Research
IWLM	Important worsening of larger magnitude
LC	Langerhan cell
LME	Linear mixed effect
LN	Lymph node
LTRA	Leukotriene receptor antagonist
MC	Mast cell
MCID	Minimum clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
MIW	Minimally important worsening
N/A	Not applicable
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NR	Not reported
OC	Oral corticosteroids
ONS	Office for National Statistics
OPS	Oak pollen season
OR	Odds Ratio
PBM	Preference-based measure
PFS	Pollen food syndrome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRQLQ	Paediatric Rhinoconjunctivitis Quality of Life Questionnaire
PSA	Probabilistic sensitivity analysis
PSM	Propensity score-matched
PSS	Personal social services
PSSRU	Personal Social Services Research Unit

PT	Preferred term
QALD	Quality-adjusted life days
QALH	Quality-adjusted life hour
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised control trial
REACT	Real-world effectiveness in allergy immunotherapy
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RWE	Real-world evidence
SAE	Serious adverse event
SAR	Seasonal allergic rhinitis
SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SE	Standard error
SGAS	Second generation antihistamines
SLIT	Sublingual immunotherapy
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System Organ Class
SPT	Skin prick test
TA	Technology appraisal
TCS	Total combined score
TPS	Tree pollen season
TRAE	Treatment-related adverse events
TSLP	Thymic stromal lymphopoietin
TH_2	T Helper Cell Type 2
VAS	Visual analogue scale
WAO	World Allergy Organisation
WTP	Willingness-to-pay

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

This submission covers the full marketing authorisation for 12 SQ-Bet SLIT-tablet (ITULAZAX) (containing a highly standardised allergen extract of pollen from white birch (*Betula verrucosa*)).

12 SQ-Bet is indicated for the treatment of adult patients (aged 18-65 years) with a confirmed diagnosis of moderate to severe allergic rhinitis (AR) and/or conjunctivitis induced by pollen from the birch homologous group (*Betula verrucosa* (birch), *Alnus glutinosa* (alder), *Carpinus betulus* (hornbeam), *Corylus avellana* (hazel), *Quercus alba* (oak) and *Fagus sylvatica* (beech)) despite the use of symptom-relieving medication.

The decision problem addressed in this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe AR or allergic conjunctivitis or both caused by pollen from the birch homologous group despite the use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (skin prick test and/or specific IgE).	Adults with moderate to severe AR or allergic conjunctivitis or both caused by pollen from the birch homologous group despite the use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (skin prick test and/or specific IgE).	N/A
Intervention	ITULAZAX 12 SQ-Bet SLIT as an add-on to standard therapy	ITULAZAX 12 SQ-Bet SLIT as an add-on to standard therapy	N/A
Comparator(s)	Established clinical management without ITULAZAX 12 SQ-Bet SLIT, such as Pollinex trees	Established clinical management without ITULAZAX 12 SQ-Bet SLIT	Established clinical management consists of symptomatic pharmacotherapy
Outcomes	The outcome measures to be considered include: • combined symptom and medication score • rhinoconjunctivitis symptom scores • complications of allergic rhinoconjunctivitis • medication usage • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • combined symptom and medication score • rhinoconjunctivitis symptom scores • complications of allergic rhinoconjunctivitis • medication usage • adverse effects of treatment • health-related quality of life	N/A
Special considerations including issues related to equity or equality	None stated	None stated	N/A

Abbreviations: AR, allergic rhinitis; IgE, immunoglobin E; N/A, not applicable; NHS, National Health Service.

1.2 Description of the technology being evaluated

Table 2 presents an overview of the technology being appraised (containing a highly standardised allergen extract of pollen from white birch (Betula verrucosa)), herein referred to as 12 SQ-Bet. Please see Appendix A1.1 for the Summary of Product Characteristics (SmPC) and Appendix A1.2 for the UK Assessment Report.

Table 2: Summary of the technology being evaluated

UK approved name and brand name	ITULAZAX 12 SQ-Bet* sublingual lyophilisate.
Mechanism of action	12 SQ-Bet is an allergen immunotherapy (AIT) containing a highly standardised concentration of allergen extract from birch tree (Betula verrucosa) pollen for the treatment of tree (birch homologous group**) pollen-induced AR and/or conjunctivitis. (Appendix A1.1) Unlike symptomatic pharmacotherapy, AIT modifies the patient's immune response towards allergens (in this instance to tree pollen from the birch homologous group), inducing immune tolerance, and preventing disease progression. (Appendix A1.1) (1-5) Several studies have shown that the immunological response to AIT is characterised by an induction of allergen-specific Immunoglobulin subtype 4 (IgG4). AIT is thought to induce immunological tolerance in two ways: (6) • Immune deviation: T helper 1 cells are mobilised and produce interferon Gamma, triggering B cells to produce immunoglobin G (IgG), instead of immunoglobin E (IgE) (which may trigger an allergic reaction) antibodies. IgG antibodies, which are not capable of inducing an allergic reaction, bind to allergen molecules and block the binding of IgE antibodies. • Induction of regulatory T cells: these cells release cytokines that suppress local effector T-cell responses and stimulate a shift in the production of antibodies from IgE towards IgG4. Allergen-specific IgG4 antibodies interrupt the interaction of the allergen with the immune system. The resultant effect of AIT is that allergic reactions no longer occur or, if they do, they are fewer in number and are less severe. A reduction in the binding of IgE to birch allergens has been confirmed for subjects treated with 12 SQ-Bet and this was accompanied by an induction of a treatment-induced systemic IgG4 response specific for birch. The increase in IgG4 levels is observed after approximately 1 month of treatment and is maintained throughout the treatment period. (Appendix A1.1) Before treatment initiation with 12 SQ-Bet, a high degree of homology and IgE cross-reactivity has been observed between the birch homologous group. This group comprises six cross-reactive species: *Betula verrucosa (birch), Alnus glutinosa (alder), Carpinus*

	betulus (hornbeam), Corylus avellana (hazel), Quercus alba (oak) and Fagus sylvatica (beech). This indicates that allergic sensitisation occurs to all trees within this group, extending the sensitisation period to encompass the pollen seasons of all six tree species. (Appendix A1.1) (7) A comparable level of IgG4 cross-reactivity towards the birch homologous trees was also observed after treatment with 12-SQ-Bet, indicating that 12 SQ-Bet may be able to affect allergic response to a number of trees within this group. (Appendix A1.1)
Marketing authorisation/CE mark status	12 SQ-Bet sublingual lyophilisate (PL 10085/0059) was approved by the MHRA on 9th June for the treatment of moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group in adult patients. (Appendix A1.1 and A1.2)
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	12 SQ-Bet is indicated in adult patients for the treatment of moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group**. 12 SQ-Bet is indicated in patients with a clinical history of symptoms despite use of symptom-relieving medication, and with a positive test of sensitisation to a member of the birch homologous group such as a skin prick test and/or specific IgE test. (Appendix A1.1)
Method of administration and dosage	12 SQ-Bet treatment should be initiated by physicians with experience in the treatment of allergic diseases. Following this, patients can perform daily self-administration at home. 12 SQ-Bet is provided as an oral lyophilisate. Once 12 SQ-Bet is placed under the tongue, swallowing should be avoided for approximately one minute. (Appendix A1.1) The recommended dose for adult patients is one sublingual lyophilisate (12 SQ-Bet) daily. Treatment with 12 SQ-Bet should be initiated outside the pollen season (at least 16 weeks prior to the expected start of the birch homologous group pollen season) and continued during the tree pollen season. If no improvement is observed during the first year of treatment, there is no indication for continuing treatment. International treatment guidelines and consensus statements refer to a treatment period of three years for AIT to achieve disease modification and thereby long-term treatment benefit even after treatment cessation. (8)
Additional tests or investigations	A diagnosis of AR and/or conjunctivitis by clinical history and a positive test of sensitisation to a member of the birch homologous group (skin prick test and/or specific IgE) is required before treatment initiation. (Appendix A1.1)
List price and average cost of a course of treatment	£80.12 per pack of 30 tablets of 12 SQ-Bet.
Patient access scheme (if applicable)	N/A

*Notes: * SQ-Bet is the dose unit for ITULAZAX. SQ is a method for standardisation on biological potency, major allergen content, and complexity of the allergen extract.*
*** Birch homologous group: Betula verrucosa (birch), Alnus glutinosa (alder), Carpinus betulus (hornbeam), Corylus avellana (hazel), Quercus alba (oak) and Fagus sylvatica (beech).*
Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; EMA, European Medicines Agency; IgE, immunoglobin E; IgG, Immunoglobulin G; IgG4, Immunoglobulin subtype 4; N/A, not applicable.
Reference: ITULAZAX SmPC (Appendix A1.1); EAACI., 2014 (1); Jutel et al., 2015 (2); Jutel et al., 2016 (3); Licari et al., 2014 (4); Licari et al., 2016 (5); Larsen et al., 2016 (5); Lorenz et al., 2009 (7); Roberts et al., 2017 (8).

Company evidence submission template for Betula verrucosa (ITULAZAX 12 SQ-Bet) for treating moderate to severe allergic rhinitis and/or conjunctivitis from tree pollen [ID6462]

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

Disease description

Allergic rhinitis

AR is an immunoglobulin class E (IgE)-mediated inflammatory condition of the nasal passage that occurs in the nasal mucosa. It is triggered by an allergic immune response to an inhaled allergen in individuals who have become sensitised to that allergen. The most common inhalant allergens causing AR include house dust mites, pollen and spores from trees, grasses and weeds, and flakes of animal skin. (9-11)

The inflammatory cascade that is triggered upon allergen exposure can affect the upper and/or lower airways. Inflammation in the lower airways affects airflow in the lungs, and results in allergic asthma symptoms such as breathlessness, a tight chest, and coughing. When the upper airways are affected, the inflammatory cascade results in the characteristic nasal symptoms of AR – congestion/obstruction, rhinorrhoea (runny nose), itchy nose, and/or sneezing. Conjunctivitis describes ocular symptoms such as itchy eyes, watery eyes, hyperaemia (congestion of the blood vessels in the eye), chemosis (swelling of the conjunctiva), and periorbital oedema (puffy eyes). (6, 10) The term ‘allergic rhinoconjunctivitis’ captures the nasal and eye symptoms of an allergic reaction and is often used interchangeably with AR. In this appraisal, the term AR is used throughout and assumed to encompass symptoms associated with allergic rhinoconjunctivitis.

Birch pollen-induced AR

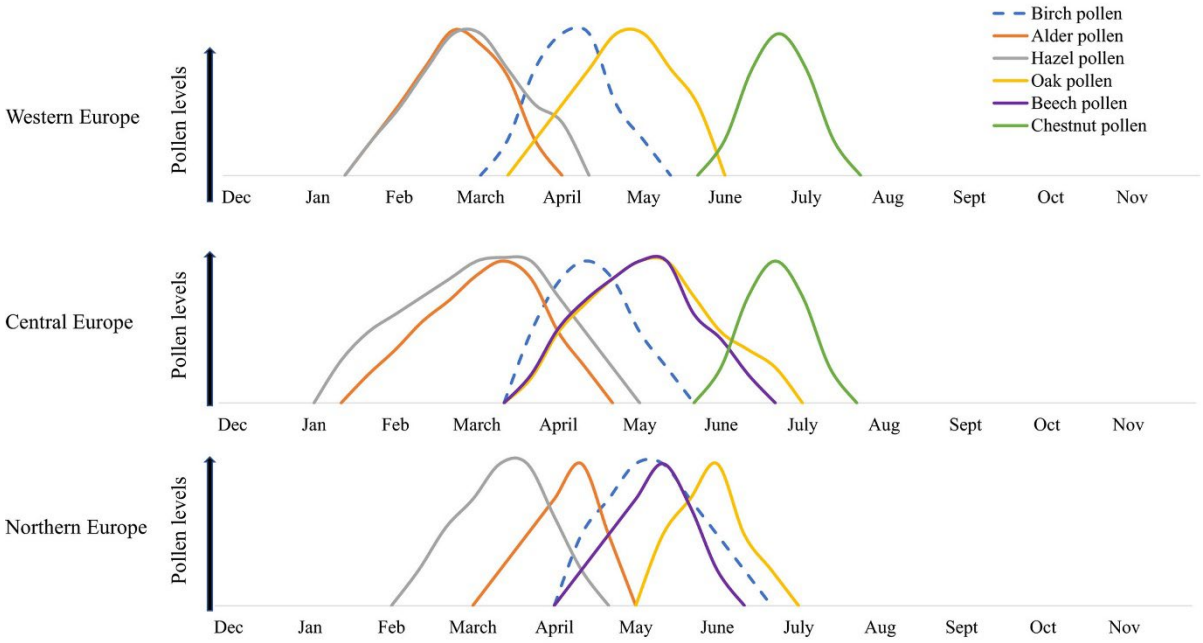
This appraisal is concerned with AR induced by pollen from the birch homologous group (*Betula verrucosa* (birch), *Alnus glutinosa* (alder), *Carpinus betulus* (hornbeam), *Corylus avellana* (hazel), *Quercus alba* (oak) and *Fagus sylvatica* (beech)), (12) referred to herein as birch pollen-induced AR. The birch homologous

group is characterised by the homology of Bet v 1, the major allergen of birch pollen, with the allergens of pollen from other trees in the order *Fagales* – Aln g 1 for alder, Fag s 1 for beech, Cor a 1 for hazel, Car b 1 for hornbeam, Que a 1 for oak, and Cas s 1 for chestnut. Clinical data has shown that a high proportion of birch sensitised individuals were also sensitised to alder (92–98%) and hazel (88–97%). (1, 7, 10, 13-16)

Notably, the European Medicines Agency (EMA) definition for the birch homologous group also includes chestnut trees. However, immunological evidence for 12 SQ-Bet showed no correlation between birch and chestnut in IgE reactivity pre-treatment, or in immunoglobulin subtype 4 (IgG4) reactivity post-treatment. Therefore, chestnut is not considered in this submission. (17)

Pollen from the birch homologous group is the most prevalent allergenic tree pollen across most parts of Europe. (9, 18) During the tree pollen season, sensitised individuals who have developed allergies will experience the debilitating symptoms of AR. The timing of the birch homologous group pollen seasons in Europe can vary from year to year and between countries. (19) Figure 1 presents an overview of the potential length of pollen season over time in Western, Central, and Northern Europe for the trees within the birch homologous group.

Figure 1: Pollen season maps for trees within the birch homologous group (Western, Central, and Northern Europe; 2011–2016)

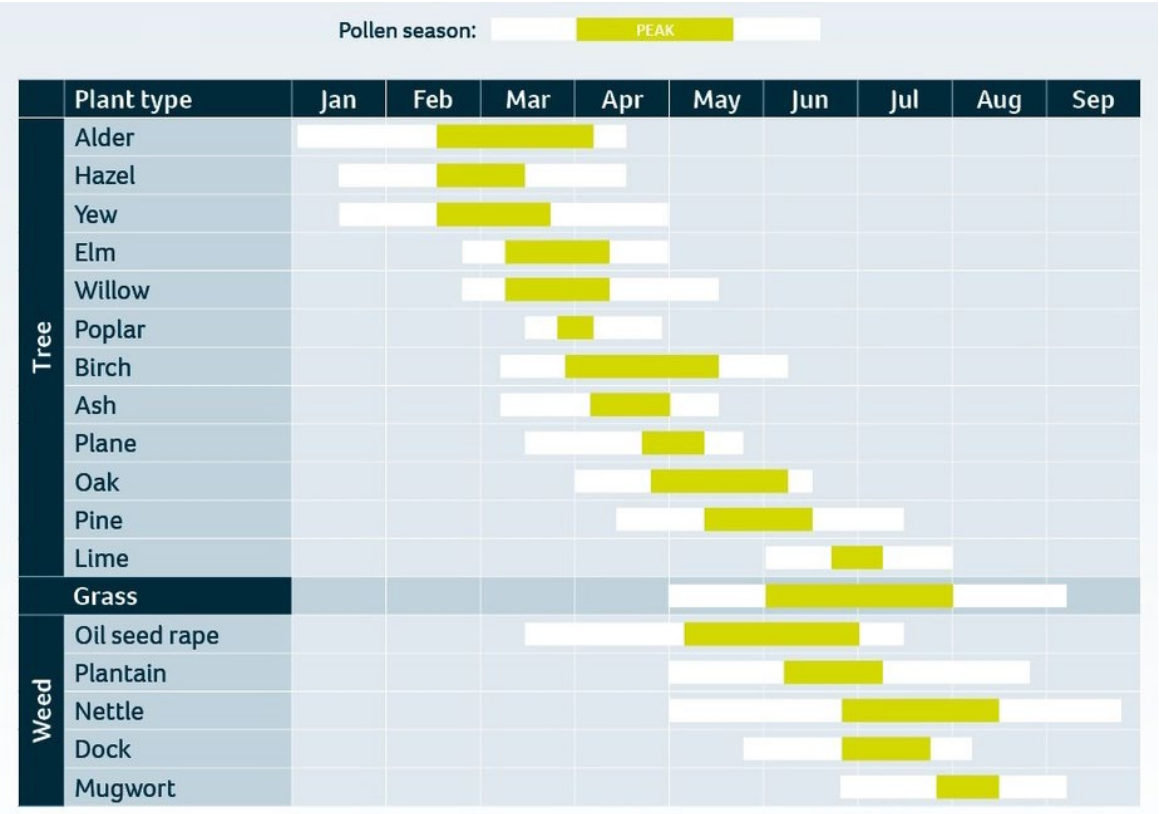


Note: The curves do not represent the relative pollen levels of different tree species but rather provide an approximate indication of the potential duration of their pollen seasons over time.
Reference: Figure taken from Biedermann et al., 2019. (20)

The tree pollen season can commence as early as December in Europe, with hazel and alder trees pollinating from December to April. (18, 21, 22) Following on from the alder season are the ash, birch, and oak pollen seasons, which finish in June. The sequential flowering of trees in the birch homologous group leads to consecutive and often overlapping pollen seasons among these trees. Combined with the high levels of allergenic cross-reactivity between species within the Fagales order, this extends the duration of AR symptoms for birch pollen allergic individuals. As a result, symptoms can potentially last for six months of the year, from January-June. (18, 20, 22, 23)

Individuals can experience AR symptoms induced by both tree and grass pollens. These co-sensitised individuals will experience AR symptoms for a significant portion of the year, as shown in Figure 2. (24, 25)

Figure 2: Allergy UK pollen calendar for tree and grass pollens in the UK (1991 to 2021)



Note: The figure is based on data from Worcester University.
Reference: Figure taken from Allergy UK. (24)

Co-morbidities and multi-morbidities associated with AR

AR has an association with a variety of burdensome multi-morbid and co-morbid conditions. As an allergic disease, it often coexists with other conditions within the spectrum of allergic diseases, including allergic asthma (AA), atopic dermatitis, food allergies, and anaphylaxis. AR and conjunctivitis primarily affect the nasal passages, frequently triggering or occurring alongside other nasal and respiratory-related disorders such as sinusitis, otitis media, rhinosinusitis, nasal polyposis, olfactory disorders, adenoid hypertrophy, and eosinophilic esophagitis. (26)

AR can be associated with food allergy; more specifically, birch pollen-induced AR is often associated with pollen food syndrome (PFS). PFS is a common IgE-mediated allergic disease caused by a cross-reaction between pollen and plant food allergens. This causes allergy symptoms to food that are linked to pollen allergy that occurs in

the mouth and throat. (27, 28) Similar to the cross-reactivity among pollen from trees within the birch homologous group, Bet v 1 (the major allergen of birch pollen) is also cross-reactive with major allergens of certain foods. Consequently, individuals with birch pollen-induced AR are more likely to develop allergic symptoms after ingesting various types of fruits, nuts, and vegetables. (10) Characteristic symptoms of PFS include itching of the lips, tongue, and throat, often accompanied by swelling. Approximately 73% of individuals with birch pollen-induced AR experience symptoms associated with eating certain types of food. The symptoms of PFS persist throughout the year with individuals having to remove specific fruits and vegetables from their diet permanently due to the fear of potential impacts on their overall health. (10, 29, 30)

AA is the most prominent co-morbidity of AR, with studies consistently finding significant overlap between the two. (31-35) AR and AA share pathological and pathophysiological mechanisms, frequently co-existing within individuals. (36) While AR involves upper airway inflammation, similar processes in the lower airways lead to asthma symptoms such as wheezing, coughing, and breathing difficulties. (37) Over 80% of asthmatics have co-morbid AR, and vice versa, AR is a strong risk factor for asthma development. (38-40) Effective AR treatment can improve asthma control, whereas poor AR management can increase the risk of asthma exacerbations. (38, 41)

1.3.2 Epidemiology

Published prevalence and diagnosis data is often inaccurate due to the range of diagnosis codes that GPs use for AR (such as hay fever or rhinosinusitis). A Delphi panel was conducted with four general practitioners with an interest in allergy, and three specialist consultant allergists to gain consensus on the treatment landscape and management of allergic respiratory disease (ARD) in the UK. The term ‘ARD’ describes a group of respiratory conditions triggered or exacerbated by allergies and refers to inflammation manifestations in the upper and lower airways known as AR and AA, respectively. (42-44)

As part of this Delphi process, participants were asked a series of survey questions to estimate the proportion of people in the UK with birch pollen-induced AR, and the size of the patient population with uncontrolled moderate to severe disease despite compliant use of symptomatic treatments. Overall, it was estimated that ARD affects approximately 29% of the UK population, with 26% sensitised to tree pollen. Among this population, two-thirds were estimated to have AR. It was further estimated that 35% of AR patients have moderate to severe disease, with 38% of these patients having uncontrolled disease despite compliant use of symptomatic treatments. These figures were used to estimate the prevalence of uncontrolled moderate to severe birch pollen-induced AR in the UK, with approximately 47 in 100,000 people affected, relating to around 26,800 people in England. The full report of all the key findings is presented in Appendix J1. (45)

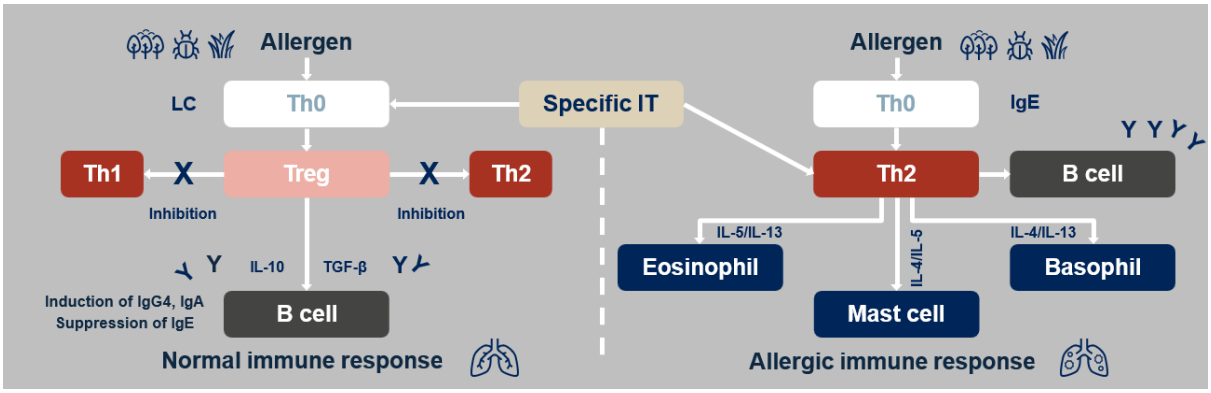
1.3.3 Pathophysiology

Birch pollen-induced AR is driven by the generation of IgE antibodies to airborne allergens from the birch homologous group. These IgE antibodies bind to receptors on the surface of mast cells (46) and, upon subsequent exposure, induce an allergic immune response. (6)

Airborne allergens infiltrate the respiratory system of the sensitised individual and discharge their allergenic contents onto the mucosal barrier. Upon invading the respiratory tract, these allergens are engulfed and phagocytosed by dendritic cells residing within the mucosal tissue before subsequently being presented on the surface as antigens. This induces the activation and differentiation of naïve CD4 T cells into T Helper Cell Type 2 (TH_2) cells. These TH_2 cells secrete several cytokines, including interleukin (IL)-4, and IL-13. IL-4 triggers B cells to transition from producing immunoglobin M (IgM) to IgE. (42-44, 46) IgE antibodies then bind to and activate basophils and mast cells, triggering the release of various inflammatory mediators such as histamine, leukotrienes, and prostaglandins. Pre-formed mediators, such as histamine, stimulate sensory nerve endings within seconds, causing itch and sneezing, and promote dilatation of local vasculature and glandular

secretion, causing obstruction and rhinorrhoea, respectively. Newly synthesised mediators, including leukotrienes, as well as chemokines, and cytokines contribute to a delayed eosinophil and TH_2 predominant inflammation, the late-phase response, characterised by nasal obstruction and hyperreactivity. (42-44, 46) A comparison of a normal immune response compared to the response to allergens in a sensitised individual is presented in Figure 3.

Figure 3: The immunological mechanisms of AR compared to a normal immune response



Abbreviations: B cell, B lymphocyte; EC, endothelial cell; IgA, Immunoglobulin A; IgE, Immunoglobulin E; IL, interleukin; IgG4, Immunoglobulin G subtype 4 ; IT, immunotherapy; LN, lymph node; MC, mast cell; OX40L, OX40 ligand (OX40, tumour necrosis factor receptor superfamily, member 4); PC, plasma cell; TGF- β; Transforming growth factor- β; Th1, T helper 1; TH2, T helper 2; Treg, Regulatory T cells ; TLRs, toll-like receptors; TSLP, thymic stromal lymphopoietin; LC, Langerhan cell.
Reference: Figure adapted from Akdis et al., 2006 (47)

1.3.4 Current management

The only management guidance for AR is from the British Society for Allergy and Clinical Immunology (BSACI). The NICE Clinical Knowledge Summary on AR (48) incorporates recommendations from the BSACI and the Allergic Rhinitis and its impact on Asthma (ARIA) international guidelines (2016 revision) for the diagnosis and management of patients with AR. (46, 49)

1.3.5 Diagnosis

Approximately half of patients with birch pollen-induced AR in the UK are seen in primary care. Patients are primarily diagnosed with an ARD in primary care, using clinical history (48) and a skin prick test or a blood sample for specific IgE. If a patient has chronic AR symptoms and is not responding to symptomatic treatment

options, a GP can refer the patient to secondary care, specifically an allergy, immunology, or ear, nose and throat (ENT) department, where further investigations take place before a confirmed diagnosis of birch pollen sensitivity and the type of rhinitis, as GPs do not routinely make such diagnoses. (Appendix J1) Approximately 16% of patients are referred from primary to secondary care.

As noted earlier, published prevalence/diagnosis data on ARD is often inaccurate due to the range of diagnosis codes which GPs may use for AR (including 'hayfever' or 'rhinosinusitis'). Minimal data is available on the prevalence/diagnosis of ARD at the community pharmacy level, meaning that a group of patients may not be captured in existing prevalence/diagnosis estimates.

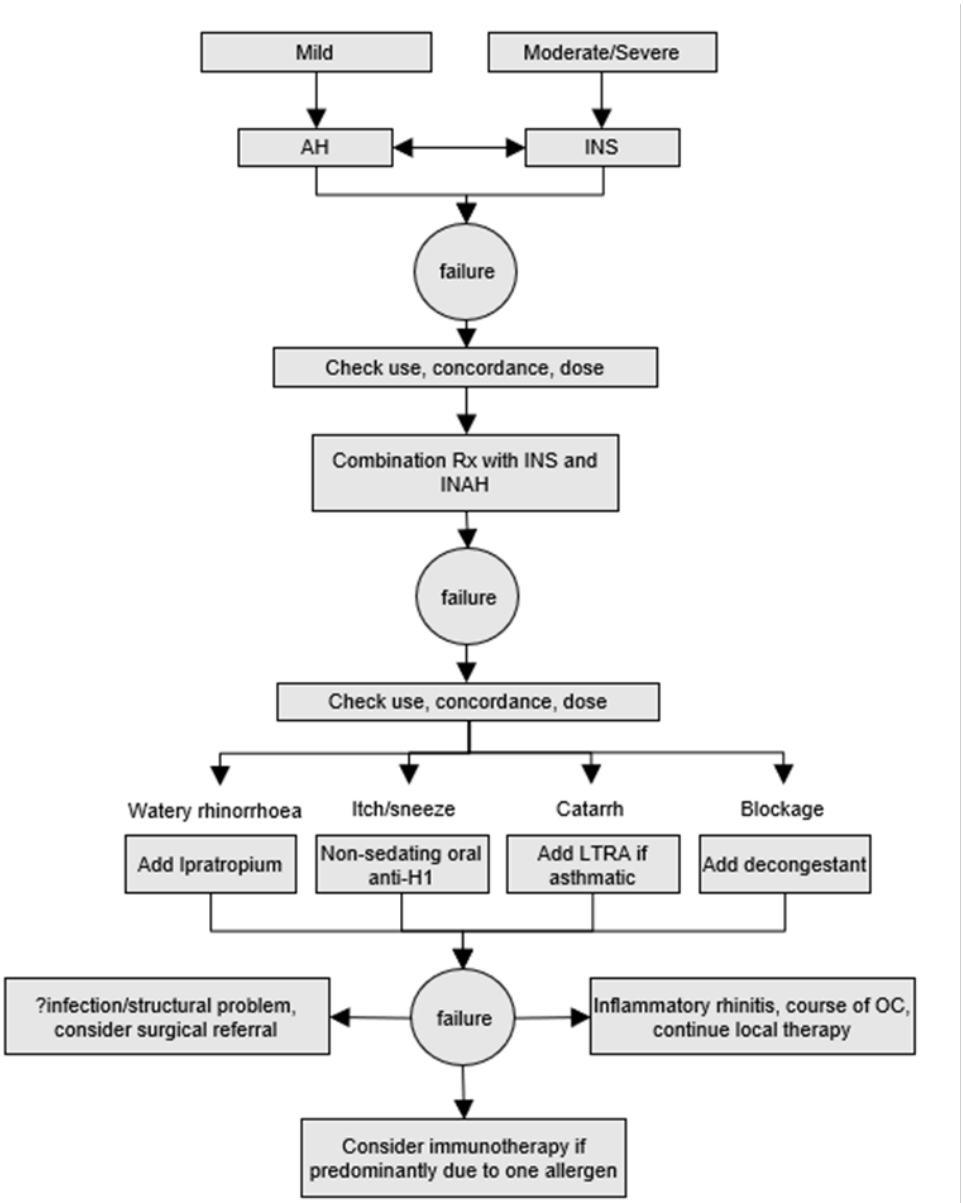
1.3.6 Setting of care

Mild AR is usually self-managed with over-the-counter medications, and the majority of patients whose symptoms cannot be self-managed are seen in primary care. (Appendix J1) However, referral to secondary care is required if the diagnosis is uncertain, patients have moderate to severe disease, or ongoing chronic symptoms that persist despite optimal management in primary care. (Appendix J1) (48, 50)

1.3.7 Clinical pathway of care

AR patients are typically treated in UK clinical practice with a range of symptomatic therapies in line with NICE guidelines in primary care (48), and BSACI and ARIA guidelines in secondary care. (46, 49) The overall treatment pathway for AR in the UK is based on the BSACI rhinitis treatment algorithm, summarised in Figure 4. (46)

Figure 4: BSACI rhinitis treatment algorithm



Abbreviations: AH, antihistamine; Anti-H1, H1-antihistamine; IN, intranasal; INS, intranasal steroids; INAH, intranasal antihistamine; LTRA, leukotriene receptor agonist; OC, oral corticosteroids.
Reference: Scadding, et al., 2017. ***(46)***

If a person has a diagnosis of AR, advice on allergen avoidance is usually recommended; in the context of pollen allergy, this can include significant lifestyle modifications such as avoiding walking in grassy, open areas, staying inside during the early morning, early evening, and whenever the pollen count is high, keeping windows closed, planning holidays to avoid the pollen season, and washing hair

every night. (46, 48) Additional recommended preventive physical measures for patients include wearing sunglasses and nasal barriers. (46, 48)

For patients with mild to moderate, intermittent, or mild persistent symptoms, oral, or intranasal antihistamines are the first line of therapy. (46, 48) For patients with moderate to severe persistent symptoms, or those for whom initial treatment is ineffective, intranasal corticosteroids are recommended. (46, 48) If symptoms persist despite these treatments, combination therapies can be explored, including combinations of oral antihistamines and intranasal corticosteroids or combined preparations of intranasal corticosteroids and intranasal antihistamines. If these treatments are ineffective despite compliance and proper technique, clinicians can consider add-on therapies, depending on the persistent/refractory symptoms. (46, 48) These are summarised in Table 3. Systemic corticosteroids are rarely prescribed for the management of AR due to their side effect portfolio, except as short-term rescue medication to treat severe nasal obstruction. (46, 51)

Table 3: Add-on AR therapies

Persistent/refractory symptoms	Treatment
Watery rhinorrhoea	Intranasal anticholinergics e.g., ipratropium bromide
Itching/sneezing	Regular non-sedating oral H1-antihistamines
Nasal congestion	Intranasal decongestants e.g., xylometazoline
Persistent symptoms with history of asthma	Leukotriene receptor antagonist (LTRA) e.g., montelukast alongside oral, or intranasal antihistamines

Abbreviations: AR, allergic rhinitis; H1, histamine type 1; LTRA, leukotriene receptor antagonist.
References: NICE, 2023 ***(48)*** *and Scadding, et al., 2017.* ***(46)***

As presented in Figure 4, the BSACI guidelines recommend the consideration of allergy immunotherapy (AIT) for AR in patients with a seasonal allergy to pollen whose symptoms persist despite maximal symptomatic pharmacotherapy, including a combination of intranasal corticosteroids and antihistamines taken regularly. (46) Additionally, the current ARIA guidelines recommend the consideration of AIT for patients with AR/conjunctivitis and/or AA caused predominantly by allergen exposure, with poor symptom reduction despite adequate pharmacotherapy during the allergy season and/or change in natural allergy history. (49)

Current established clinical management options do not provide adequate relief from all symptoms of AR, leaving patients dissatisfied with their treatment, particularly moderate to severe patients whose symptoms are persistent and/or recurrent, and whose disease has a drastic impact on their daily lives and quality of life. (52-54)

Furthermore, symptomatic medications for AR are associated with risks of adverse events, as supported by the findings of an advisory board conducted in 2024 to investigate the use of sublingual immunotherapy (SLIT) in UK clinical practice (see Appendix J2 for full details). The panel included nine UK clinical experts in allergy management, comprising allergy clinical leads, consultant allergists, primary care physicians with a special interest in allergy, and allergy consultant nurses with experience in using AIT. Clinicians commented that intranasal decongestants, LTRAs, ipratropium, and systemic corticosteroids are regarded as ineffective with undesirable side effects, leading to their avoidance in clinical practice. One of the main disadvantages of symptomatic pharmacotherapy is its inability to address the underlying pathophysiology of AR, resulting in no lasting effect, in contrast to AIT treatment, which modifies the course of allergic disease. (6)

Furthermore, in a separate Delphi panel conducted with three consultant allergists and immunologists and two GPs with a specialist interest in allergy, several clinicians commented that the treatment algorithm depicted in Figure 4 does not accurately reflect current clinical practice. Notably, ipratropium bromide is not widely recognised among allergists, and patients who do not respond to antihistamines (AH) and intranasal steroids (INS) are more likely to be offered immunotherapy rather than an additional INS. Furthermore, decongestants play a limited role and are generally not recommended by ENT specialists for use beyond a few days. (Appendix J6)

1.3.8 Disease burden

The burden of AR on an individual is considerable and can affect many aspects of a person’s life. Due to the sequential flowering of trees and strong cross-reactivity of allergens within the birch homologous group, individuals with birch pollen-induced

AR are likely to experience symptoms for a prolonged period, extending beyond the birch pollen season. (55) According to the ARIA guidelines, AR can be classified as mild or moderate to severe, depending on the severity of symptoms and their impact on the patient's daily life. (39) AR is classified as moderate to severe when one or more of the following items are present: troublesome symptoms, sleep disturbance, impairment of school or work, or impairment of daily activities, leisure, and/or sport. (39) Consequently, AR patients with persistent moderate to severe disease have reduced quality of life (QoL), frequently experience challenges with their mental well-being, and require frequent visits to a healthcare provider, placing a considerable economic burden on society. (56-59)

The ARIA guidelines categorise the symptoms of AR as 'intermittent' and 'persistent'. Intermittent symptoms are defined as symptoms present for <4 days per week or for <4 consecutive weeks. Persistent symptoms are defined as symptoms present for >4 days per week and for >4 consecutive weeks. Intermittent or persistent symptoms are then assigned a severity grading that takes into account the resulting impairments in everyday function. Consequently, the symptoms of AR can be classified in one of four ways: intermittent mild; intermittent moderate to severe; persistent mild; persistent moderate to severe. (60)

Clinical burden

Troublesome symptoms

The morbidity associated with AR is significant, with the troublesome symptoms of the disease imposing an impactful burden on patients. As outlined in Section 1.3.1, patients with AR are likely to experience troublesome symptoms for a duration that extends well beyond the birch pollen season. A panel comprising three consultant allergists and immunologists, along with two general practitioners specialising in allergy, concurred that, based on their clinical experience, due to the sequential flowering of trees and strong cross-reactivity of allergens within the birch homologous group, individuals with AR induced by pollen from the birch homologous

group are likely to experience symptoms for a prolonged time period, extending beyond the specific birch pollen season. (Appendix J6)

These troublesome symptoms are most commonly sinusitis (67% of AR patients), congestion/obstruction, rhinorrhoea, sneezing, and itchy and watery eyes. (61) Patients with persistent moderate to severe AR symptoms have affected sleep, hampered normal daily functioning, and emotional distress. (61) There is a high proportion of patients who are polyallergic and experience allergy symptoms on exposure to multiple allergens including both seasonal and perennial allergens e.g., tree pollen, grass pollen, and house dust mites. These patients will experience symptoms for extended periods of the year. (62)

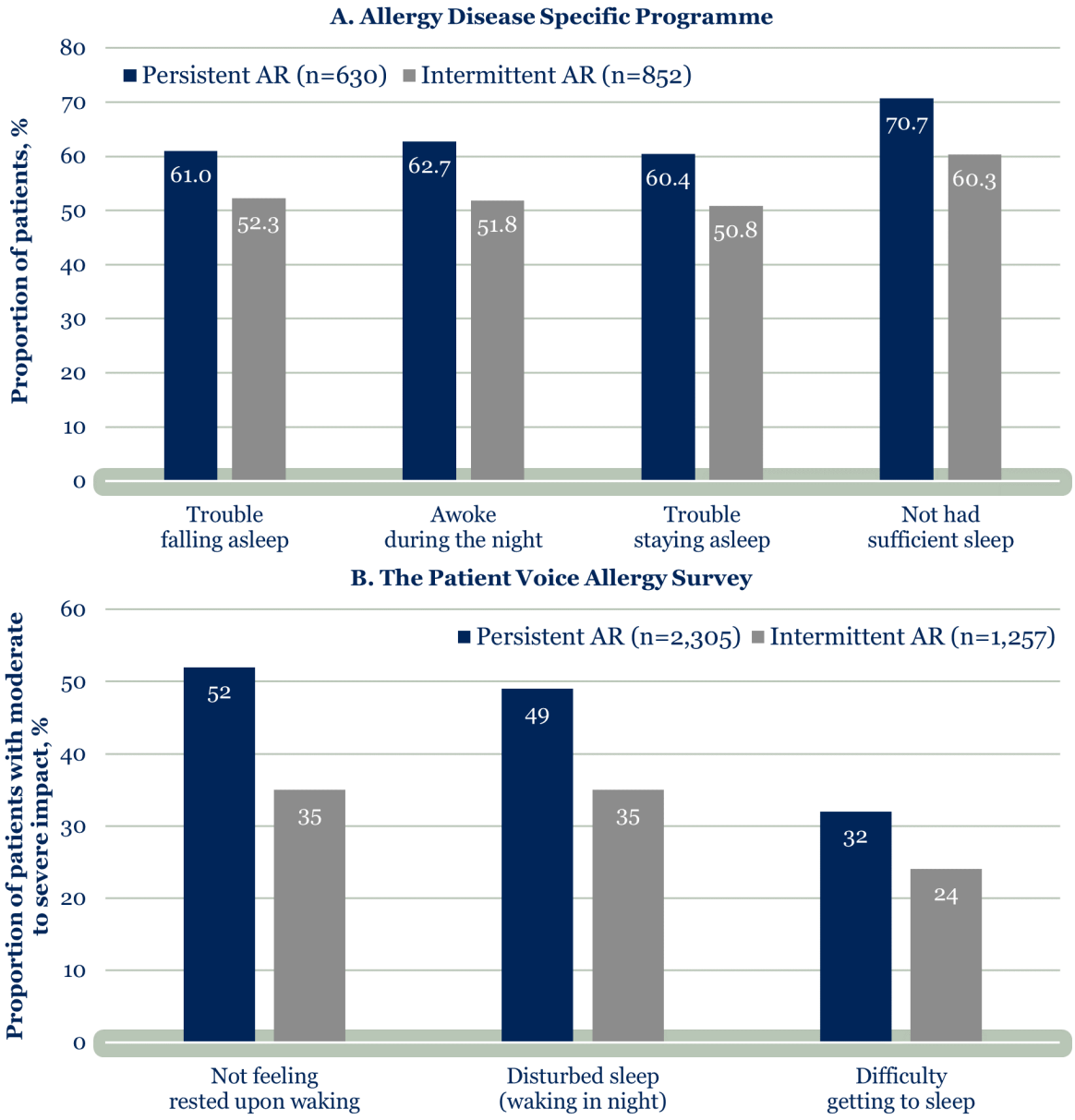
Further adding to the symptomatic burden, AR is a key risk factor for asthma. Up to 30% of patients with AR have concomitant asthma, with symptoms including coughing, dyspnoea, chest tightness, and wheezing. (31, 36, 38) In addition, PFS is a common co-morbidity of the AR condition, with approximately 73% of patients suffering from the syndrome all-year round. PFS interferes with activities of daily living, as patients will experience local oral symptoms such as itching, tingling, swelling in the mouth or oral angioedema after intake of a number of common food items, including fruits, vegetables, and nuts, with apples found to be the main trigger of food hypersensitivity. (20, 29, 61, 63) Although generally regarded as non-severe, the burden of PFS is understated as it is highly prevalent and often perennial. (64) Furthermore, reactions such as urticaria, asthma, or severe systemic reactions such as anaphylactic shock may occur. (64)

Sleep disturbance

The impact of AR symptoms on sleep is a major consideration for allergy patients. Two surveys conducted in Europe describe the negative impact of AR on sleep. AR patients often report trouble getting to sleep, disturbed sleep, and not feeling rested upon wakening (Figure 5). (65, 66)

In both surveys, persistent symptoms caused more sleep disturbances than intermittent symptoms; the majority of patients reported that they had not had sufficient sleep or did not feel rested upon waking. (65, 66) These findings are supported by a cross-sectional study conducted in the US to evaluate the association between AR and poor sleep parameters. (67) The study reported that individuals with AR were more likely to experience poor sleep quality than those without AR, often having difficulty getting to sleep or experiencing insomnia, sleep apnoea, or sleep disturbances requiring the use of sleep medication. (67) Individuals with AR also reported waking up too early, not getting enough sleep, and feeling unrested/overly sleepy during the day, which impacted their daytime functioning. (67)

Figure 5: Impact of AR on sleep – European patient surveys



Notes: A. Data was collected from patients with AR in France, Germany, Italy, and the UK.
B. Data was collected from patients with AR in Belgium, Czechia, Finland, France, Germany, Greece, Italy, the Netherlands, Spain, Switzerland, and the UK.
Abbreviations: AR, allergic rhinitis.
References: Valovirta, et al., 2008; Caninica, et al., 2007. ***(65, 66)***

Additionally, a large Spanish cohort study evaluated the quality of sleep using the Medical Outcomes Study sleep scale. (68) The quality of sleep was found to be significantly worse during the pollen season than outside of the pollen season. (68) Individuals experienced significantly more sleep disturbances, snoring, and

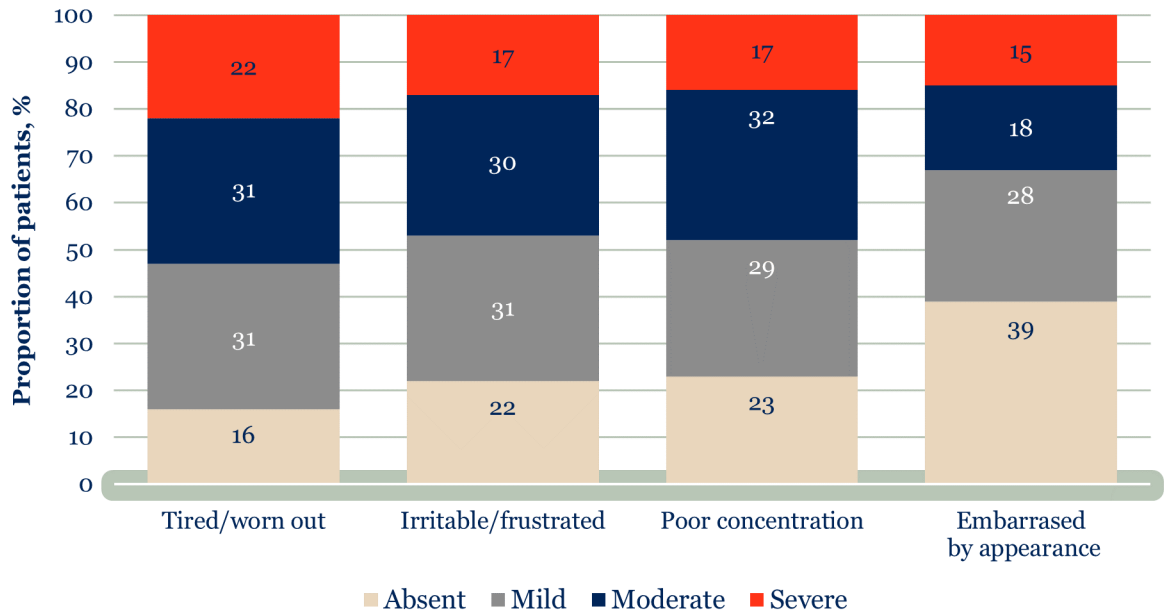
somnolence and were short of breath (on awakening) during the pollen season ($p<0.05$). (68) In addition, the study also found that increasing severity of symptoms was associated with a poorer quality of sleep. (68)

Humanistic burden

Emotional Impact

AR can have a moderate to severe emotional impact, driven by feelings of tiredness, irritability, and poor concentration (Figure 6). (65, 66, 69) For example, 31% of patients with AR reported that tiredness/feelings of being worn out had a moderate impact on their life, and 22% felt that the impact was severe. (65) Other emotional manifestations of AR include nervousness/anxiety, sadness/depression, discomfort, stress, and a loss of motivation. (65, 66, 70)

Figure 6: Emotional impact of AR across Europe



Notes: Data were analysed from 3,562 questionnaires to collate background information on AR.
Abbreviations: AR, allergic rhinitis.
Reference: Valovirta, et al., 2008. ***(65)***

A considerable proportion of individuals report that AR has also had a moderate to severe impact on aspects of their social life, such as going out with friends and visiting friends' houses. AR can also influence an individuals' choice of daily activity;

32.8% of AR patients report that their condition impacts their ability to take part in outdoor activities. (58, 65)

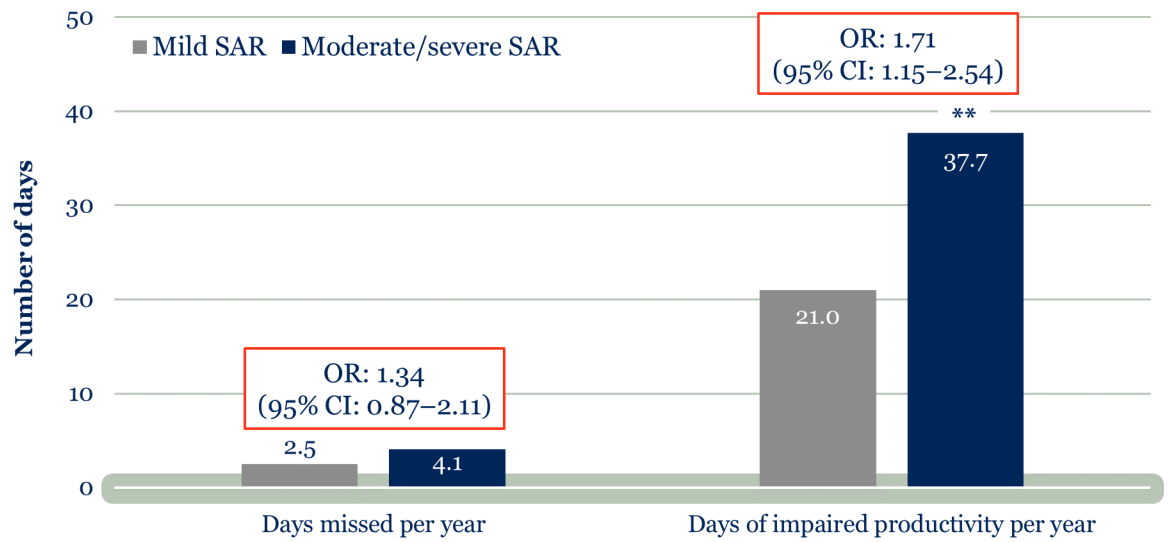
The combined effect of impairments in physical, emotional (psychological), and social aspects of daily life, induced by AR, results in a lower QoL for individuals with AR versus those without AR. (71, 72) Indeed, there is a wealth of evidence to show that AR is associated with a reduced QoL, which worsens as the disease increases in severity. (73-77)

Impact of AR symptoms on functioning in the workplace

The troublesome symptoms of AR can have a negative effect on work activities and productivity, as supported by various patient surveys. (66, 69) In the European Allergy Disease-Specific Programme a high proportion of individuals with AR (79%) reported that their symptoms had a considerable impact on work/school performance during a 7-day retrospective period. (66) This finding is supported by data from a Spanish survey in which 72.7% of respondents reported a considerable impact of AR symptoms on their work/school performance. (69)

As previously mentioned, AR is associated with significant sleep disturbances which can affect learning, as a consequence of the resulting daytime tiredness. (78) Furthermore, for working individuals, symptomatic AR can hamper future professional development, through days missed from the workplace, or as a result of performing with a reduced work capacity. (65, 66, 69, 70) A cross-sectional questionnaire-based study conducted in the UK among patients with seasonal allergic rhinitis (SAR) (61.9% of whom had moderate to severe symptoms triggered by tree pollen) revealed that those with moderate to severe SAR were more likely to miss workdays due to their condition compared to patients with mild SAR (Figure 7). (79). Furthermore, they had significantly higher odds of experiencing reduced workplace performance as a result of SAR symptoms (Odds Ratio [OR]: 1.71, 95% CI: 1.15–2.54; p=0.0048). (79)

Figure 7: Impact of SAR on workplace productivity



*Notes: **p<0.01 versus mild SAR.*
Mild SAR, n=254; moderate/severe SAR, n=746.
Abbreviations: CI, confidence interval; OR, Odds Ratio; SAR, seasonal allergic rhinitis.
Sources: Prince, et al., 2015. ***(79)***

In a survey, AR patients were asked directly how their disease impacts their life and ability to work. In both the Netherlands and Sweden, over 50% of respondents said that AR impacts their sleep, and 42% and 25%, respectively, said it limited their participation at school or work. When the number of missed hours was calculated, AR was estimated to cost society up to €673 per person due to less productive workers as a result of their disease. (80)

A US cross-sectional study has shown that individuals with AR had double the odds of experiencing difficulties working than those without AR ([OR]: 2.16 [95% CI: 1.45, 3.22]; p<0.01). (67) The European Patient Voice Allergy Survey found that 36% of working respondents felt their work activities were frequently impacted by AR, while 13% reported that their work was affected all of the time by their disease. (65) A large online survey conducted in the US showed that nasal congestion affected 59% of respondents at work through issues with concentration (42%) or poor productivity (36%). (70)

Economic burden

AR has a significant impact on the NHS, as patients with moderate to severe disease tend to have a higher number of visits to both primary and secondary care services. The total number of visits to primary care associated with moderate to severe birch pollen-induced AR is estimated to be 1.93 per patient per year, equating to over 51,800 visits in England. This is estimated to cost the NHS approximately £2.2 million. (45, 50, 81) (Appendix J1 and J6) The estimated total number of visits to secondary care is estimated to be 2.61 visits per patient per year, equating to over 70,000 visits in England. This is estimated to cost the NHS approximately £14 million. (45, 50, 82) (Appendix J1 and J6)

There are also significant indirect costs associated with AR due to lost productivity with missed days at work and performing with a reduced work capacity. (74) A UK study estimated that individuals with moderate to severe AR miss four days per year on average due to SAR. The cost of this absenteeism was estimated to amount to £1.14 billion per year. Notably, this figure does not account for presenteeism, which affected 38 days of the year for each individual with moderate/severe AR. (79)

Extensive evidence is available across Europe on the costs associated with allergic diseases, the majority of which are indirect costs. An analysis of the socioeconomic costs of allergic diseases in the European Union, based on published literature and online statistical data, found that avoidable indirect costs per patient with insufficiently treated allergies (both airways and skin allergies) range between €55 and €151 billion annually due to absenteeism and presenteeism. (83) A Swedish study estimated the total cost of AR to Swedish society to be €1.3 billion per year (€961 per person with AR per year, based on a prevalence rate of 24%). Direct costs, including the cost of medication and healthcare contacts such as physician visits, amounted to €210.30 per individual per year. Lost productivity (absenteeism and presenteeism) was the main indirect cost associated with AR estimated to cost €750.80 per individual per year with presenteeism, alone, accounting for 70% of the total cost of AR in Sweden. (84) The findings of this study on the ratio of indirect to

direct costs for AR were supported by results from a Spanish study, FERIN, that estimated the total cost of AR to be €2,326.70 (SD: €3,013.93) per patient per year. Again, indirect costs were the main cost driver, accounting for €1,772.90 (SD: €2,906.20) per patient per year. (85)

A pooled analysis of eight studies evaluating presenteeism using the Work Productivity and Activity Impairment questionnaire estimated that AR impairs work performance by 35.9% (95% CI: 29.7, 42.1). (86) This study analysed data from six studies to investigate the economic cost of lost productivity (absenteeism and presenteeism).(86) With worsening disease severity, there was a significant increase in the indirect costs of AR, driven mainly by worsening presenteeism – 85.15 (standard deviation [SD]: 162.07) hours for individuals with mild disease, 125.85 (SD: 204.14) hours for moderate disease, and 179.71 (SD: 276.63) hours for severe disease. (85)

1.3.9 12 SQ-Bet reimbursement in other countries

12 SQ-Bet has received national reimbursement in the following countries on the following dates: Austria (1st July 2020), Czechia (1st July 2024), Denmark (4th November 2019), Finland (1st February 2020), France (25th October 2022), Germany (1st September 2019), Luxembourg (April 2020), the Netherlands (1st July 2020), Norway (1st April 2020), Slovakia (1st February 2021), Slovenia (28th January 2021) Sweden (13th December 2019), and Switzerland (1st August 2020).

1.3.10 Therapeutic need

Despite appropriate administration and compliance with optimised symptomatic pharmacotherapy, a subset of moderate to severe AR patients have uncontrolled disease, and as such, their treatment satisfaction is low. (Appendix J1) 59-66% of ARD patients are unsatisfied with their symptom control despite maximum use of pharmacotherapy. (52) This displays a clear unmet need for a better treatment option for these patients.

Established clinical management for AR is limited to symptomatic pharmacotherapy and allergy avoidance. Symptomatic pharmacotherapy does not provide adequate relief from all symptoms of AR, such that some individuals become dissatisfied with treatment due to persistent or recurrent symptoms. Symptomatic medications carry the risk of adverse effects, which also contributes to patient dissatisfaction. In particular, long-term steroid use is well known to cause significant side effects, with intranasal corticosteroids associated with local side effects and oral corticosteroids causing systemic side effects. (39) Long-term high-dose corticosteroid use is associated with osteoporosis, fractures, adrenal suppression, hyperglycemia, diabetes, cardiovascular disease, dyslipidemia, dermatological and gastrointestinal events, psychiatric disturbances, and immunosuppression. (87) In addition, the use of intranasal spray devices and eye drops for AR are prone to high error rates, which can impact patient adherence and treatment effectiveness. In a cross-sectional study conducted from June to September 2020, the majority of patients with AR reported using INS. However, their understanding, adherence, and perceptions of the treatment were found to be inadequate. Concerns about safety, along with factors such as age, gender, education level, socioeconomic status, and smoking, significantly influenced their adherence to the prescribed treatment. (88)

One of the key drawbacks of symptomatic pharmacotherapy is its inability to target the underlying allergy, meaning that there is no lasting effect and that patients must continue to take their medication for as long as the symptoms are present.

In contrast, AIT modifies the course of allergic disease by causing desensitisation to the allergen, such that allergic reactions no longer occur, are fewer in number, and/or are less severe. By inducing immune tolerance, the clinical effect persists beyond the end of treatment. Clinical guidelines recommend treatment for a minimum duration of 3 years to achieve long-term efficacy after treatment discontinuation. (8, 12)

AIT, as presented in Section 1.3.4, can be considered for the treatment of AR. AIT can be administered by injection, termed subcutaneous immunotherapy (SCIT), or

by the oral route as sublingual immunotherapy (SLIT) tablets or SLIT-drops. SLIT treatments are considered safer than SCIT. (89) While some SCIT products have shown efficacy in the treatment of AR, this evidence largely stems from clinical experience, as clinical trial data is limited in comparison to SLIT-tablets. The administration of SCIT involves numerous injections and frequent clinic visits, as treatment should be initiated in a medical clinic with physician supervision. This schedule is not only inconvenient but also imposes a considerable economic burden on the NHS and patients due to the higher healthcare resource utilisation compared to the at-home administration of SLIT-tablets. (90, 91) Additionally, patient needle phobia further limits the practicality of SCIT for managing AR. (Appendix J6) In addition, there is little to no evidence supporting the use of SLIT-drops for AR. Overall, the SCIT and SLIT-drops treatment options are currently used infrequently and inconsistently across the UK, are less preferred by patients compared to SLIT-tablets, and are not considered part of established clinical management for birch pollen-induced AR. (90, 92)

In a Delphi panel consisting of three consultant allergists and two general practitioners with a specialist interest in allergy, unanimous agreement was reached that the primary unmet need for patients with moderate to severe AR induced by pollen from the birch homologous group is the limited access to sublingual immunotherapy (SLIT). This finding further underscores the importance of making SLIT more widely available as a therapeutic option for these patients. (Appendix J6)

The BSACI position statement published in June 2023 lists 12 SQ-Bet and Pollinex tree as the only two medications licensed for specific allergen immunotherapy for tree pollen allergy. (93) However, Pollinex has recently failed to meet its primary endpoint in Phase 3 trials. (94) Besides 12 SQ-Bet, the main treatment strategies for birch pollen-induced AR are restricted to unlicensed treatments, general antihistamines, corticosteroids, and avoidance practices.

1.3.11 Introduction to 12 SQ-Bet

12 SQ-Bet is an AIT in the form of a SLIT lyophilisate tablet that provides a new treatment option for birch pollen-induced AR in the UK, by targeting the underlying cause of birch pollen-induced AR, as opposed to current pharmacotherapy options that provide only symptomatic relief for moderate to severe patients.

Each 12 SQ-Bet tablet contains a highly standardised allergen extract of pollen from the European white birch (*Betula verrucosa*) (12). 12 SQ-Bet is an oral lyophilisate made with Zydis technology and a rigorous SQ standardisation process, which rapidly disintegrates under the tongue, releasing the allergen extract on the oral mucosa.

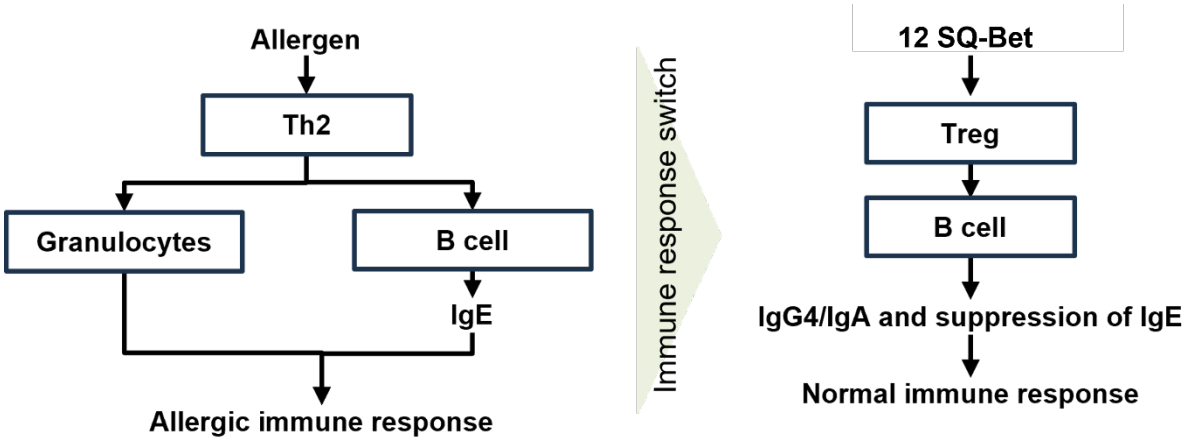
12 SQ-Bet is indicated for the treatment of moderate to severe AR and/or conjunctivitis induced by pollen from birch, alder, hazel, hornbeam, oak, and beech, i.e., the birch homologous group for 12 SQ-Bet; with this cross-reactivity providing relief of AR symptoms throughout the tree pollen season, not just during the specific birch pollen season. (95) 12 SQ-Bet is indicated in patients with a clinical history of symptoms despite use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group by either a skin prick test and/or specific IgE. (Appendix A1.1)

The efficacy and safety of 12 SQ-Bet has been demonstrated in the Phase 3 TT-04 trial (Section 2.6). Additionally, throughout the clinical development programme, 12 SQ-Bet has been shown to be well tolerated and suitable for home treatment. (23, 96-99)

Several studies have shown that the immunological response to AIT, and 12 SQ-Bet more specifically, is characterised by an induction of allergen-specific IgG4, which reduces the activation of immune cells on exposure to an allergen. This induces a switch from an allergic response to a tolerance-building immune response upon allergen exposure.

Mechanistically, 12 SQ-Bet is an aetiological treatment, addressing the underlying mechanism of birch pollen-induced AR, aiming to modify the patient's immunologic response to birch pollen allergens. This averts the allergic symptoms by preventing the 'inflammatory cascade': T and B cell activation, cytokine secretion, and the induction of IgE production, which leads to the binding of mast cells and basophils and the release of histamine and leukotrienes. (100-102) Treatment with 12 SQ-Bet has been demonstrated to induce an increase in birch pollen-specific IgG4 and to induce a systemic antibody response which can compete with IgE in the binding of birch pollen allergens (Figure 8). The increase in IgG4 occurs through two main mechanisms: immune deviation and through the induction of regulatory T cells. Immune deviation refers to the mobilisation of T helper type 1 cells, which produce interferon Gamma, stimulating B cells to produce IgG instead of IgE. The induction of regulatory T cells leads to an increase in interleukin-10 and transforming growth factor beta, which suppress local effector T-cell responses and promote antibody class switching in favour of IgG4. (6)

Figure 8: The mechanism of action for 12 SQ-Bet



Abbreviations: Bet, Betula verrucosa; Th2, T helper cell type 2; IgA, immunoglobulin A; IgE, Immunoglobulin E; IgG4, Immunoglobulin G4.
Reference: Figure adapted from Akdis et al., 2006. **(47)**

Inducing immunological tolerance through either or both of the two proposed mechanisms, immune deviation and induction of regulatory T cells, results in a reduction, or even elimination, of an allergic reaction in response to allergen

exposure. (6) It is the unique disease modifying ability of AIT that makes it such a powerful therapy for the treatment of allergic conditions. (6)

Treatment should be initiated ≥4 months prior to the expected start of the tree pollen season (for the birch homologous group) and continued throughout the season. The first tablet should be taken under medical supervision (12) and, thereafter, patients can perform daily self-administration at home, and follow-up can be conducted in primary or secondary care. Onset of the clinical effect is to be expected 8-14 weeks after initiation of treatment. (103)

Overall, 12 SQ-Bet is a fast-dissolving, once daily SLIT-tablet that provides clinically relevant relief from the symptoms of birch pollen-induced AR and, ultimately, improves patient QoL providing an alternative treatment option for patients whose symptoms are inadequately controlled despite compliant use of symptomatic treatments. 12 SQ-Bet has demonstrated good tolerability and clinically meaningful efficacy throughout the clinical development programme. (23, 96-99) Due to the cross-reactivity between the major allergens of pollen from trees in the birch homologous group, 12 SQ-Bet provides relief of AR symptoms throughout the tree pollen season, not just during the specific birch pollen season. (99, 104)

1.3.12 Proposed place in therapy for 12 SQ-Bet

12 SQ-Bet is indicated in adult patients for the treatment of moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group. Further, 12 SQ-Bet is indicated in patients with a clinical history of symptoms despite use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (skin prick test and/or specific IgE). (12) In this regard, 12 SQ-Bet is intended to be a second-line treatment, used as an add-on to standard therapy for AR rather than a replacement for an existing symptom-relieving medication in the treatment pathway.

Wider access to AIT, especially SLIT, has been demonstrated to provide long-term symptom control, reduce the need for symptomatic treatments, and provide a

treatment option for AR patients, especially for those with moderate to severe disease who have uncontrolled disease despite compliant use of current treatments, or those who have tolerability issues. (12) The potential disease modifying effect of AIT may reduce the progression of the AR disease and, therefore reduce the number and severity of co-morbidities associated with the condition, as described in Section 1.3.1. (99, 104)

1.4 Equality considerations

There are no known equality issues relating to the use of 12 SQ-Bet for the treatment of adult patients (aged 18-65 years) with a confirmed diagnosis of moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group despite the use of symptomatic treatment.

2 Clinical effectiveness

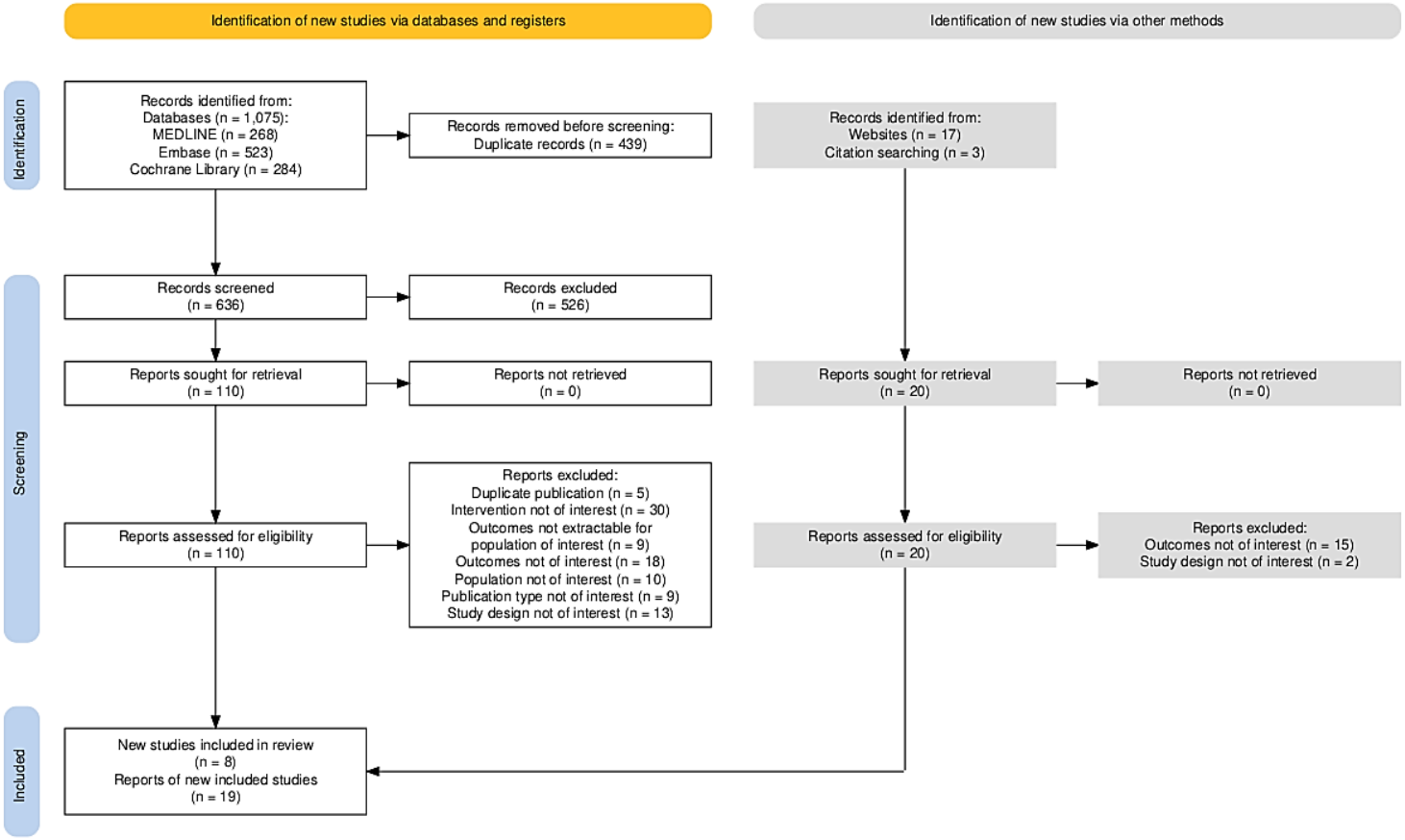
2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify and synthesise randomised control trial (RCT) evidence reporting on the efficacy and safety of birch sublingual immunotherapy tablets for treating and/or managing SAR in people with birch homologous group-induced sensitivity, compared to standard of care (SoC) interventions of interest. This SLR was conducted following the standards set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (105) and the Cochrane Handbook for Systematic Reviews of Interventions, (106) and followed the high-quality standards required by the National Institute for Health and Care Excellence (NICE) for SLRs. (107) Full details of the SLR search strategy, study selection process and results are presented in Appendix B.

The following electronic databases were searched on 27th May 2024: Embase; MEDLINE® incorporating MEDLINE® In-Process & Other Non-Indexed Citations, MEDLINE® ePub Ahead of Print, and MEDLINE® Daily; and the Cochrane Library incorporating Evidence Based Medicine (EBM) Reviews – Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. Additional hand searching of conference proceedings from the last 3 years, health technology assessment (HTA) websites, clinical trial registries, and other supplementary sources was conducted to identify further relevant evidence.

The electronic database search identified 1,075 citations. After removing 439 duplicates, 636 citations were screened based on title and abstract, with 110 publications considered potentially relevant and obtained for full publication review. Upon review, 16 articles from the database search were identified as eligible for inclusion in the SLR. Three additional records were identified via the grey literature search or supplementary sources (see Appendix B for searching details). The PRISMA diagram is represented in Figure 9.

Figure 9: PRISMA flow diagram



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Reference: Page et al., 2021 ***(105)***

Company evidence submission template for Betula verrucosa (ITULAZAX 12 SQ-Bet) for treating moderate to severe allergic rhinitis and/or conjunctivitis from tree pollen [ID6462]

In total, 19 articles were found to report on the review questions; however, 7 of these were pooled analyses and/or literature reviews which were only used for citation tracking. (108-114) Therefore, of the records identified, 12 publications (96, 97, 99, 115-123) reporting on 8 unique RCTs were eligible for further discussion in this SLR.

The reported trials were as follows:

- 12 SQ-Bet SLIT-tablets (n=4 studies), TT-01 Birk *et al.*, 2017, (97) TT-02 (EudraCT-2012-000031-59), (117, 122) TT-03 (NCT02481856), (96) and TT-04 (EudraCT-2015-004821-15) (99, 116, 121)
- Birch/alder allergoid (1,000 units of allergen [AU]) tablets (n=2 studies), EudraCT-2013-002129-43 (119, 123) and Frati *et al.*, 2023 (115)
- Recombinant Bet v1 (rBet v 1) SLIT-tablets (50 µg, 25 µg and 12.5 µg doses) (n=1 study), Rak *et al.*, 2010 (120)
- Unspecified SLIT (n=1 study), Smith *et al.*, 2002 (118)

As specified in the decision problem, the primary trials of interest for this appraisal were those of 12 SQ-Bet. As such, in preparing for this appraisal, included studies were filtered once again to exclude trials where no comparisons were made with 12 SQ-Bet. Consequently, these studies are not included in this appraisal, and only those investigating or including 12 SQ-Bet therapy are recorded in this submission.

Table 4 provides an overview of the clinical trial programme of 12 SQ-Bet. TT-04 is the pivotal trial, but TT-03, TT-02, and TT-01 have been included to clarify the overall clinical trial programme for 12 SQ-Bet SLIT-tablet for AR.

Table 4: Overview of 12 SQ-Bet SLIT Studies

Study name	Reference	Publication type	Intervention(s)	Study design	Included in economic model?	Rationale for study being included/excluded from the model
TT-04 (EudraCT-2015-004821-15)	Biedermann et. al, 2019 (99)	Journal article	N=634 12 SQ-Bet SLIT, n=320 Placebo, n=314	Pivotal trial, demonstrating the efficacy and safety of 12 SQ-Bet SLIT Phase 3 randomised double-blind placebo-controlled (See Section 2.3.1 for full details)	Yes	TT-04 is the pivotal trial for 12 SQ-Bet SLIT assessing the efficacy and safety in adolescents and adults (12-65 years) with persistent, moderate to severe AR induced by birch pollen.
TT-04 (EudraCT-2015-004821-15)	Nolte *et al.*, 2021 (116)	Journal article	N=634 12 SQ-Bet SLIT, n=320 Placebo, n=314	Post-hoc analysis of Birch 12 SQ-Bet SLIT during birch-free oak pollen season. Phase 3 randomised double-blind placebo-controlled	No	A post-hoc analysis outside of birch pollen season.
TT-03 (NCT02481856)	Couroux *et al.*, 2019(96)	Journal article	N=219 12 SQ-Bet SLIT, trial arms: 2 DU, n=55 7 DU, n=54 12 SQ-Bet, n=54 Placebo, n=56	Optimal dosage study of 12 SQ-Bet SLIT with clinical sessions using environmental exposure chambers (EECs) not performed	No	Phase 2, dose optimising using EEC chambers, no exposure during BPS.

Study name	Reference	Publication type	Intervention (s)	Study design	Included in economic model?	Rationale for study being included/excluded from the model
				in birch pollen season (BPS) Phase 2 randomised double-blind placebo-controlled		
TT-02 (EudraCT-2012-000031-59)	Makela *et al.*, 2018 (117, 122)	Journal article	N=637 12 SQ-Bet SLIT, trial arms: 0.5 DU, n=93 1 DU, n=90 2 DU, n=89 4 DU, n=92 7 DU, n=88 12 SQ-Bet, n=97 Placebo: n=88	Dose-related efficacy and safety study of 12 SQ-Bet SLIT Phase 2 randomised double-blind placebo-controlled	No	Phase 2, conducted during a BPS with unusually low pollen counts.
TT-01 (EudraCT-2007-003234-42)	Birk *et al.*, 2017 (97)	Journal article	N=65 12 SQ-Bet SLIT: 1 DU, n=9 2 DU, n=9 4 DU, n=9 8 DU, n=8 12 SQ-Bet, n=9 24 DU, n=8 Placebo, n =18	Dose escalation study of 12 SQ-Bet SLIT Phase 1 randomised double-blind placebo-controlled	No	Phase 1, dose escalation study only investigating the tolerability and acceptable dose range of the SQ tree 12 SQ-Bet SLIT in adults with AR.

Abbreviations: 12 SQ-Bet SLIT, 12 SQ-Bet sublingual lyophilisate; AR, allergic rhinitis; BPS, birch pollen season; EEC, environmental exposure chamber.
Reference: Appendix B.

2.2 List of relevant clinical effectiveness evidence

The key clinical study evidencing the efficacy and safety of 12 SQ-Bet as a treatment for adult birch pollen-induced AR is detailed in Table 5.

Table 5: An overview of the clinical effectiveness evidence for 12 SQ-Bet

Study	Efficacy and safety of the SQ tree SLIT-tablet in subjects with moderate to severe AR and/or conjunctivitis induced by pollen from the birch group. Trial ID: TT-04 EudraCT no.: 2015-004821-15.
Study design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multi-site field trial.
Population	Subjects with clinically relevant history of moderate to severe AR and/or conjunctivitis induced by birch pollen despite having received treatment with symptom-relieving medication during the two previous TPS.
Intervention(s)	SQ tree SLIT-tablet (N=320).
Comparator(s)	Placebo (N=314).
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	The outcome measures to be considered include*: • Combined symptom and medication score • Rhinoconjunctivitis symptom scores • Complications of allergic rhinoconjuctivitis • Medication usage • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	Pharmacodynamic endpoints were also captured in the TT-04 trial, see Section 2.6.5.

*Notes: *The medication usage and adverse effects of treatment outcomes were applied directly in the economic model. Combined symptom and medication score, rhinoconjunctivitis symptom scores, and health-related quality of life outcomes from TT-04 were captured indirectly as they were included as covariates in the mapping analysis by Dick et al., 2019 (124) (see Section 3.3.1).*
Abbreviations: AR, allergic rhinitis; SLIT, sublingual immunotherapy; SQ, standardised quality; TCS, Total Combined Score; TPS, tree pollen season.
Reference: TT-04 CSR. (104)

2.3 Summary of methodology of the relevant clinical effectiveness evidence

A summary of the methodology of the TT-04 trial is included in Table 6.

Table 6: Summary of methodology of the TT-04 study

Methodology	Description
Trial design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multi-site field trial including 634 subjects with a clinically relevant history of moderate to severe AR and/or conjunctivitis induced by birch pollen despite having received treatment with symptom-relieving medication during the two previous TPS.
Duration of study and follow-up	Subjects were randomised in September and October 2016. All subjects received at least 16 weeks of treatment before the start of the TPS 2017. The treatment duration with the investigational medicinal product was between 6½ months and 9½ months for subjects completing the trial. Mean duration: 224 days Median duration: 239 days P5%-P95%: 31-267 days Range: 1-282 days
Eligibility criteria	• Male or female aged 18 to 65 years at time of consent (in Poland adolescents aged 12-17 were also included) • A documented clinically relevant history of moderate to severe AR and/or conjunctivitis induced by birch pollen (with or without controlled/partly controlled asthma) despite having received treatment with symptom-relieving medication during the two previous TPS • An appropriate minimum level of allergic rhinoconjunctivitis symptoms induced by birch pollen during the BPS 2016 and a minimum use of antihistamines and/or nasal steroids during the screening period (i.e. an average daily symptom score (DSS) ≥6 with at least two moderate or one severe symptom and use of antihistamines and/or nasal steroids on at least 4 of the 7 days of the screening period) • Presence of one or more of the following ARIA QoL items due to AR and/or conjunctivitis during the previous BPS: a) Sleep disturbance b) Impairment of daily activities, leisure, and/or sport c) Impairment of school or work d) Troublesome symptoms • Positive SPT response (wheal diameter ≥ 3 mm) to birch (Betula verrucosa) extract at screening • Positive specific IgE against Bet v 1 (≥IgE Class 2; 0.7 kU/L) at screening • No clinically relevant history of symptomatic (seasonal or perennial) AR and/or conjunctivitis caused by an allergen source, other than tree pollen from the birch homologous group overlapping the TPS • No severe asthma exacerbation within the last 3 months

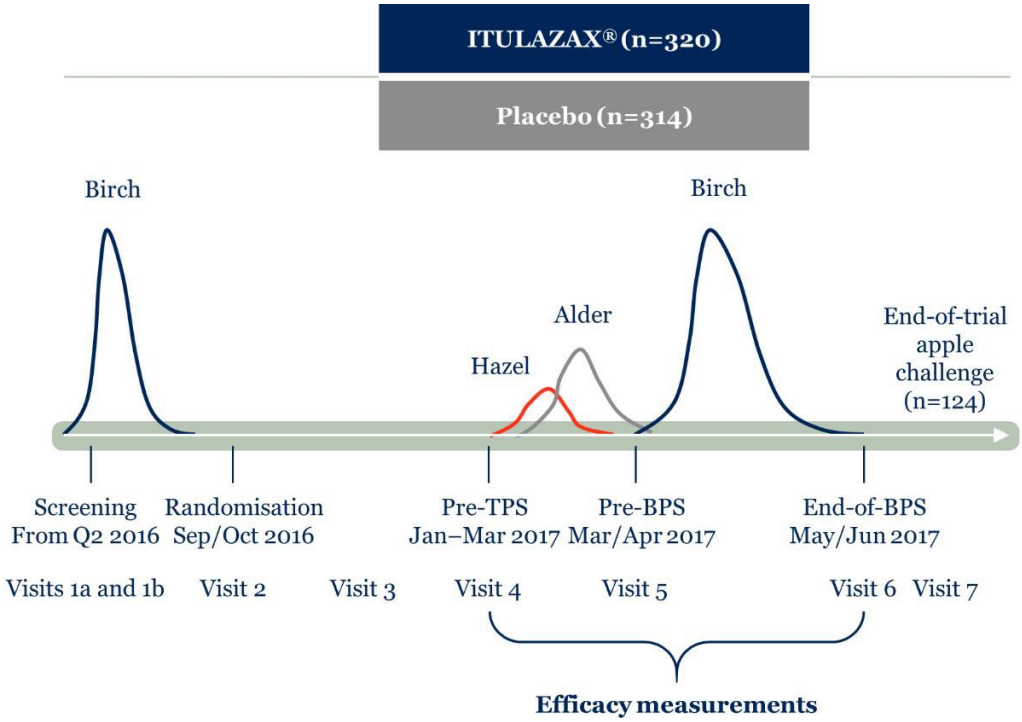
Methodology	Description
	• No clinical history of uncontrolled asthma (by GINA definition) within 3 months prior to screening • FEV1 ≥70% of predicted value after adequate pharmacological treatment
Settings and locations	There was a total of 57 trial sites in EU (Sweden, Finland, Denmark, Poland, Germany, the Czech Republic, France) and Russia.
Trial drugs	SQ tree SLIT-tablet, 12 SQ-Bet, batch numbers 1592975, 1598079. Placebo, batch number 1592017.
Concomitant medications	Symptom-relieving medications for AR and conjunctivitis were provided as open-labelled medication and were used in addition to the IMP to which the subjects had been randomised: • Oral antihistamine tablets (Desloratadine tablets, 5 mg) • Nasal corticosteroid spray (Mometasone, 50 µg/dose) • Antihistamine eye drops (Olopatadine eye drops, 1 mg/mL)
Outcomes	A full list of the outcomes included in the TT-04 trial is provided in Section 2.3.6.
Pre-planned subgroups	No subgroup analysis relevant to the appraisal population was performed in the TT-04 trial.

Abbreviations: AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; Bet, Betula verrucosa; BPS, Birch Pollen Season; DSS, Daily symptom score; EU, European Union; FEV, Forced expiratory volume; GINA, Global Initiative for Asthma; IgE, Immunoglobulin E; IMP, Investigational Medicinal Product; SPT, skin prick test; TPS, tree pollen season.
Reference: TT-04 CSR. (104)

2.3.1 Trial design

TT-04 was a large-scale, prospective Phase 3, randomised, parallel-group, double-blind, placebo-controlled multicentre study to evaluate the efficacy and safety of 12 SQ-Bet in adult and adolescent patients with moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group. (99) The study design of TT-04 is presented in Figure 10.

Figure 10: TT-04 study design

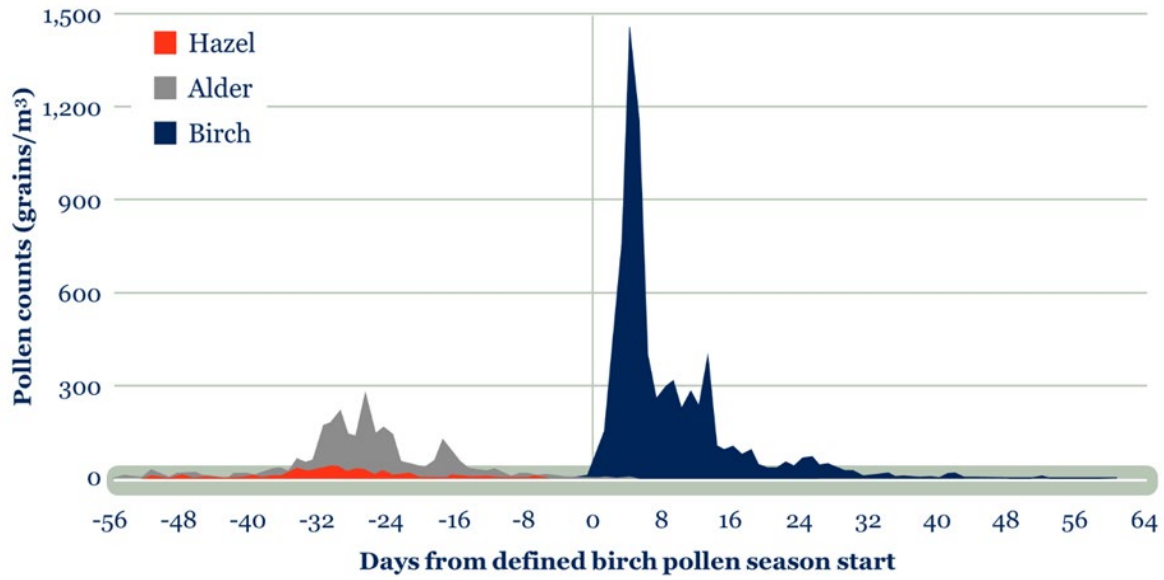


Abbreviations: BPS, birch pollen season; Q2, second quarter; SLIT, sublingual immunotherapy; TPS, tree pollen season.
Reference: TT-04 CSR. ***(104)***

Efficacy measurements in the study included both the tree pollen season (TPS) and birch pollen season (BPS) time frames. (99) The term TPS represents the combined pollen seasons for hazel, alder, and birch that was evaluated in the TT-04 trial. The TPS was defined between the first and last day of three consecutive days with tree pollen count larger than or equal to 10 grains/m^3, excluding the days between the pollen seasons where pollen counts fall below 10 grains/m^3. The BPS, the primary season in the study was defined by the same criteria, though the pollen threshold was 30 grains/m^3. Notably, pollen counts of the oak pollen season were not included in TT-04 trial but were explored in a post-hoc analysis study. (116)

The BPS on average across the trial sites of the TT-04 trial, lasted 24 days (range: 10-42) and the TPS 50 days (range: 14-68). The average daily pollen counts for the 2017 TPS are presented in Figure 11.

Figure 11: Average daily pollen counts for the 2017 TPS



Abbreviations: TPS, tree pollen season.
*References: TT-04 CSR **(104)** and Biedermann et al., 2019. **(99)***

Randomisation was performed in September and October 2016; patients were randomly allocated to one of two treatment arms – 12 SQ-Bet or placebo. All subjects received ≥16 weeks of treatment before the start of the 2017 TPS (mean treatment duration 224 days), which included hazel, alder, and birch seasons. Treatment duration with IMP was between 6½ months and 9½ months for subjects completing the trial. (104)

Screening (Visit 1) was planned to take place during, or prior to, the 2016 BPS (April to June). During the screening phase, diary data was entered by the subject in a paper diary. During the 2017 TPS, diary data was entered in an eDiary by the subject. The following items were recorded on a daily basis: rhinitis and/or conjunctivitis symptoms (6 symptoms), use of symptom-relieving medication for treatment of rhinitis and/or conjunctivitis, asthma symptoms (4 symptoms), use of asthma medication, rhinoconjunctivitis visual analogue scale (VAS), overall productivity, sick days due to allergic symptoms induced by pollen from the birch homologous group. The following items were entered on a weekly basis: Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)(S) (adults) and RQLQ +12

(for adolescent). An asthma control test (ACT) was performed every 4 weeks for subjects with asthma.

Prior to the start of the TPS (Visit 4) and the BPS (Visit 5), patients were provided with pre-specified commonly used symptomatic pharmacotherapy (antihistamines: desloratadine tablets, 5 mg and olopatadine eye drops, 1 mg/mL; nasal corticosteroid spray: mometasone, 50 µg/dose) for rhinitis and conjunctivitis. (99) Medications were to be used in addition to the treatment allocated at randomisation, if required, but only once the investigator had confirmed the start of the TPS. (99, 104)

The study also included an apple challenge to explore the effect of 12 SQ-Bet on the symptoms of apple-specific PFS in a subset of 124 subjects from Germany and Poland who were positive for apple-specific PFS at screening, participated in an apple challenge after completion of the main part of the trial (Visit 6). The apple challenge was performed as an open challenge that included five steps with increasing amounts of apple (4, 8, 16, 32 and 64 g apple) in intervals of 15 minutes. (104)

A subgroup of patients (from Germany or Poland) in the TT-04 study, who were positive for apple-specific PFS at screening, participated in an apple challenge after completion of the main part of the trial (Visit 6). (104, 125) Patients were required to eat increasing amounts of apple (4, 8, 16, 32, and 64 g) in 15-minute intervals and were observed for 2 hours. The challenge was terminated if objective symptoms occurred, or at the discretion of the investigator or patient. (104) The apple challenge was conducted to assess the effect on 12 SQ-Bet on PFS as an exploratory endpoint.

2.3.2 Eligibility criteria

A summary of the inclusion and exclusion criteria of the TT-04 trial is provided in Table 7.

Table 7: An overview of the inclusion and exclusion criteria of the TT-04 trial

Inclusion criteria	Exclusion criteria
The study population comprised adults (aged 18–65 years, in Poland adolescents 12-17 years were also included) with moderate to severe AR and/or conjunctivitis induced by tree pollen, with or without asthma (controlled/partly controlled), despite being treated with allergy pharmacotherapy in the previous two pollen seasons	Patients were excluded if they had a clinically relevant history of AR and/or conjunctivitis caused by allergens other than tree pollen from the birch homologous group (including animal hair and dander)
The presence of at least one of the following four ARIA QoL items: sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; troublesome symptoms	Severe asthma exacerbation within the last 3 months
A positive response to a birch extract SPT	A clinical history of uncontrolled asthma within 3 months prior to screening
A positive IgE against Bet v 1 (the major allergen of birch pollen)	Reduced lung function (FEV1 < 70% of predicted value after adequate pharmacological treatment)

Abbreviations: AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; IgE, immunoglobulin E; SPT, skin prick test.
Reference: Biedermann et al., 2019. ***(99)****; TT-04 CSR* ***(104)***

2.3.3 Settings and locations

The trial was conducted at 57 trial sites in the EU (Sweden, Finland, Denmark, Poland, Germany, the Czech Republic, France) and Russia. (104)

2.3.4 Trial drugs

Participants were randomly assigned to receive treatment with either 12 SQ-Bet or placebo. Treatment started at visit 2 (the randomisation visit) where the IMP was dispensed, and hereafter, the IMP was dispensed at visit 4 (pre-TPS visit). IMP treatment for all subjects started at the randomisation visit (visit 2) and last tablet intake was the day of the final visit (visit 6) for subjects not participating in the apple challenge, and the day before visit 6 for subjects participating in the apple challenge. The first dose was administered under medical supervision for 30 minutes after the

tablet intake. Food and beverages were not to be ingested for 5 minutes following intake of IMP. The daily dose of IMP was one 12 SQ-Bet SLIT-tablet, preferably taken in the morning. On average, patients were exposed to treatment (12 SQ-Bet or placebo) for 223.8 days. (104)

2.3.5 Permitted and disallowed concomitant medications

Concomitant and pre-treatment medication

TT-04 participants were free to use specific SoC medications for AR and conjunctivitis, which make up the majority of SoC in clinical practice and were provided to participants as part of the trial. Symptom-relieving medication was provided by ALK before the start of the 2017 TPS as a pre-defined, open-labelled medication and was used in addition to the IMP in both study arms. (104) The following medication was provided in the TT-04 trial:

- Oral antihistamine tablets (desloratadine tablets, 5 mg)
- Nasal corticosteroid spray (mometasone, 50 µg/dose)
- Antihistamine eye drops (olopatadine eye drops, 1 mg/mL)

An adequate initial supply of each of these symptom-relieving medications was dispensed to the subjects at visits 4 and 5, but they were not to be used until the investigator confirmed that, in their opinion, the TPS had started. (104) Notably, the use of oral antihistamine tablets, nasal corticosteroid sprays, and antihistamine eye drops in the trial was considered representative of the typical standard of care medication for patients with AR by nine UK clinical experts in allergy management in an advisory panel conducted in 2024 (see Appendix J2 for further details) and a 2025 Delphi panel comprising three consultant allergists and immunologists, along with two GPs with a specialist interest in allergy (see Appendix J6 for further details).

In the TT-04 trial subjects were instructed to freely initiate treatment with antihistamine tablets and/or eyedrops according to their symptoms and could initiate

additional treatment with nasal corticosteroids if their symptoms persisted. Symptom-relieving medication was dispensed to the subjects at visit 4 and 5 and was used according to the dosage instructions outlined in Table 8.

Table 8: The dosage instructions for symptom-relieving medication provided to subjects in the TT-04 trial

Symptom-relieving medication	Subject dosage instructions
Rhinitis	
Desloratadine tablets, 5 mg	1 tablet once daily as needed for control of allergic rhinoconjunctivitis symptoms
Mometasone, 50 µg/dose	2 spray per nostril once daily as needed for control of AR symptoms
Conjunctivitis	
Olopatadine eye drops, 1 mg/mL	1 drop in the affected eye(s) twice daily, morning, and evening as needed in case of persisting allergic conjunctivitis symptoms

Abbreviations: AR, allergic rhinitis.
*Reference: TT-04 Clinical study report **(104)***

Subjects' use of all concomitant medication, including allergy and asthma medication, was documented in the subject's medical records and in the eCRF (generic name or trade name). Additionally, each change in concomitant medication (e.g. new treatment, discontinuation of treatment, and change in dosage/routine) during the trial was documented. (104)

Relevant previous medication was also recorded. This included allergy and asthma medication taken within the past two years. Medication not provided as part of the trial was kept to a minimum. However, if considered necessary for the subject's well-being and unlikely to interfere with the trial assessments, concomitant medication was given at the discretion of the investigator according to the local SoC. (104)

Prohibited concomitant medication

Restricted and prohibited concomitant medications during the TT-04 trial are outlined in Table 9.

Table 9: Restricted and prohibited concomitant medications are randomisation in the TT-04 trial

Medication		Time window	Reason
An investigational drug		≤30 days or 5 half-lives of the drug (whichever longest) prior to visit 1 and until end of trial	Possible interaction between investigational drugs. Interferes with efficacy and safety evaluations.
Anti-IgE treatment, e.g. omalizumab		<130 days or 5 half-lives of the drug (whichever longest) prior to visit 1 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments
Antihistamine	Oral, intravenous, nasal, or ocular	≤3 days before visit 4 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments. Interferes with safety evaluation
	Long-acting (astemizole)	≤100 days before visit 4 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments. Interferes with safety evaluation
Antidepressant medications	Antidepressant medication with antihistaminic effect (e.g. doxepin, mianserine)	≤14 days before visit 4 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments due to antihistaminic effect
	Tricyclic antidepressants		Tricyclic antidepressants may potentiate the effect of adrenaline. Interferes with safety evaluation.
Antipsychotic medications with antihistaminic effects (e.g. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)		≤7 days before visit 4 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments due to antihistaminic effect. Interferes with safety evaluation

Medication			Time window	Reason
Glucocorticosteroid	Topical (nasal or ocular)		≤30 days before visit 4 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments. Interferes with safety evaluation.
	Systemic	Up to 10 days treatment with doses < 40 mg/day	≤2 weeks before visit 4 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments. Interferes with safety evaluation.
		Up to 10 days treatment with doses ≥ 40 mg/day	≤4 weeks before visit 4 and until end of trial	
		More than 10 days treatment regardless of dose	≤90 days before visit 4 and until end of trial	
		Depot injection, regardless of dose	≤90 days before visit 4 and until end of trial	
Immunosuppressive treatment (ATC code L04 or L01)			≤90 days before visit 1 and until end of trial	Interferes with conjunctivitis and/or asthma efficacy assessments
Immunotherapy with any other allergen(s)			From visit 1 and until end of trial	Interferes with asthma and rhinitis and/or conjunctivitis efficacy assessments. Interferes with safety evaluation.
Inhaled, topical, or oral nedocromil or cromolyn sodium			≤14 days before visit 4 and until end of trial	Interferes with conjunctivitis and/or asthma efficacy assessments

Medication	Time window	Reason
Leukotriene antagonists / synthase inhibitors	≤30 days before visit 4 and until end of trial	Interferes with asthma/rhinoconjunctivitis efficacy assessments
Nasal decongestants	≤3 days before visit 4 and until end of trial	Interferes with rhinitis efficacy assessments
Pizotifene	≤7 days before visit 4 and until end of trial	Interferes with rhinitis and/or conjunctivitis efficacy assessments due to antihistaminic effect

Abbreviations: ATC, Anatomical Therapeutic Chemical; IgE, immunoglobin E.
Source: TT-04 Clinical study report. ***(104)***

These medications were prohibited to improve standardisation between study arms and reduce potential confounding due to differences in SoC medication use. Furthermore, as combined medication use is a key endpoint of AR clinical trials, a standardised set of symptomatic medications is essential in reliably determining treatment efficacy. Importantly, the composition of SoC medication for the TT-04 trial was consistent for both study arms. (104)

Notably, the prohibited elements of SoC in the TT-04 trial are not likely to meaningfully impact patient outcomes. Excluded treatments for AR included leukotriene receptor antagonists (LTRA), which are rarely used in clinical practice; ipratropium bromide, which only alleviates rhinorrhoea; and intranasal decongestants, which do not have a sustained effect in improving patients' symptoms. During the TT-04 trial all subjects were provided with specific rescue medication (oral antihistamine tablets, nasal corticosteroid spray and antihistamine eye drops), which remain the cornerstones of AR management. (Appendix J2 and J6) These medications were freely available for use by participants throughout the TT-04 trial. (104)

2.3.6 All reported outcomes of the TT-04 study

Please see Table 10 for all reported outcomes in the TT-04 study.

Table 10: Efficacy endpoints in the TT-04 trial

Endpoint		Description
Primary	• The primary endpoint of the trial was the average daily allergic rhinoconjunctivitis total combined score (denoted TCS) during the BPS. The TCS is the sum of the average allergic rhino conjunctivitis DSS (DSS) and average allergic rhinoconjunctivitis daily medication score (DMS) during the BPS	• The TCS was the sum of the of DSS and the DMS. For the DSS, participants rated four rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and two conjunctivitis symptoms (red/itchy eyes and watery eyes) daily on a scale of 0 to 3 (0=no symptoms, 1=slight symptoms, 2=moderate symptoms, 3=severe symptoms). For the DMS, each medication was assigned a score per dose (desloratadine=6 per tablet, olopatadine=1.5 per drop, nasal corticosteroids=2 per spray)
Key secondary efficacy endpoints	• The average DSS during the BPS • The average TCS during the TPS • The average DSS during the TPS	
Secondary efficacy endpoints	• The average DMS during the BPS • The average DMS during the TPS	• For the DMS, each medication was assigned a score per dose (desloratadine=6 per tablet, olopatadine=1.5 per drop, nasal corticosteroids=2 per spray)
	• Average number of mild days during the BPS and the TPS • Average number of severe days during the BPS and the TPS	• Mild days were defined as a day without any intake of antihistamines (Desloratadine tablets) or Olopatadine eye drops (Mometasone nasal spray is allowed) and none of the six individual symptoms is scored higher than 1 (mild) • Severe days were defined as a day with a DSS greater than or equal to 6 and at least 2 moderate or 1 severe symptom

Endpoint		Description
	• Average rhinoconjunctivitis symptom VAS during the BPS and the TPS	• The average VAS during the BPS and TPS was calculated for each subject as the average of non-missing VAS during the given pollen season
	• Patient-rated clinical global improvement, by response category, and by aggregation into either improved or not improved during the BPS and the TPS	• For analysis of global evaluation, subjects answering “better” or “much better” to the question “Compared to your rhinitis and/or conjunctivitis symptoms in the previous birch/tree pollen season, how have you felt overall in this birch/TPS?” were categorised as improved, and consequently, subjects answering “much worse”, “worse” or “the same” were categorised as “not improved”
	• RQLQ during the BPS and the TPS	• The RQLQ consists of 28 questions, each on a 7-point (0-6) scale, divided into seven domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). All items within each domain are weighted equally. The weekly domain scores were calculated as the average of all items scores for each domain. The weekly overall RQLQ score was the average of all 28 item scores, with higher scores indicating worse rhinoconjunctivitis health-related quality of life (HRQoL)
Exploratory efficacy endpoints	• Number of sick days caused by allergy symptoms during the BPS and the TPS • Reduction in overall productivity due to allergy symptoms during the BPS and TPS • ACT during the BPS and the TPS in subjects with asthma at randomisation • Average asthma DSS during the BPS and TPS • Proportion of days during the BPS and TPS with use of asthma medication	• Productivity endpoint: The impact on productivity was measured on a VAS scale ranging from "not affected" to "completely affected". The response from the subject was transformed to a scale ranging from 0 mm to 100 mm. Not affected corresponded to 0 mm and completely affected corresponded to 100 mm • ACT endpoint: Each of the five questions in the questionnaire was scored on a scale from 1 to 5. The total ACT score was defined as the sum of the scores from the five questions

Endpoint		Description
	• Proportion of days during the BPS and TPS with asthma DSS ≥1 and use of asthma medication • Average daily TCS with European Academy of Allergy and Clinical Immunology (EAACI) medication scoring during the BPS and during the TPS	The total score for pollen season was calculated as the average of the non-missing scores every 4 weeks during the pollen season • TCS with EAACI scoring endpoint: The TCSEAACI is defined as the sum of the DSS divided by 6 and DMSEEACI (see Section 2.6.4). TCSEAACI will assume values in the range of 0 to 5. The average TCSEAACI during each of the pollen seasons was calculated as the average of all non-missing values of the TCSEAACI score during the given pollen season
Exploratory efficacy endpoints – Apple challenge	• Average PFS symptoms by apple dose step • Average PFS overall VAS by apple dose step • PFS global evaluation • Average amount of apple without any objective symptoms pre-defined in the observer list • Maximum completed dose step in the apple challenge • No observer assessed symptoms pr. apple dose • Change in average total FAQLQ and FAIM scores	• PFS symptoms and VAS endpoints: The symptoms were measured on a VAS scale ranging from no symptoms to severe symptoms. The response from the subject was transformed to a scale ranging from 0 cm to 10 cm. No symptoms corresponded to 0 cm and severe symptoms corresponded to 10 cm • FAQLQ endpoint: The FAQLQ consists of 29 questions. All items were weighted equally. The average scores were calculated as the average of all items scores • FAIM endpoint: Consists of six questions. All items were weighted equally. The average scores were calculated as the average of all items scores

Abbreviations: ACT, asthma control test; BPS, birch pollen season; DSS, daily symptom score; DMS, daily medication score; EAACI, European Academy of Allergy & Clinical Immunology; FAIM; the food allergy independent measure FAQLQ, The Food Allergy Quality of Life Questionnaire; HRQoL, health-related quality of life; PFS, pollen food syndrome; RQLQ, rhinitis quality of life questionnaire; TCS, total combined score; TPS, tree pollen season; VAS, visual analogue scale.
Reference: TT-04 Clinical study report. **(104)**

2.3.7 Subject baseline characteristics

Subject demographics and baseline characteristics of the TT-04 trial are summarised in Table 11. Overall, the treatment groups were generally well balanced with respect to demographics and baseline characteristics. The mean age of the population was 36.1 years, with a range of 12 to 65 years, which is in alignment with the age limits specified in the inclusion criteria. A total of 60 adolescent subjects (9.5%) were included in the trial, of which 57 completed. All subjects had Bet v 1 specific IgE ≥ class 2 (0.7 kU/l), 43.5% reported asthma, and 66.4% had a medical history of PFS. (99) On average, patients reported having birch pollen allergy for 15.9 years. Skin prick tests showed that all patients were sensitised to birch, and 75.7% were polysensitised (defined as sensitisation to birch, alder, hazel, and others). (99)

Table 11: Demographic and baseline characteristics in the TT-04 study (FAS)

Treatment group	Placebo (N=314) n (%)	12 SQ-Bet (N=320) n (%)	Overall (N=634) n (%)
Allergy history			
Birch pollen allergy	314 (100%)	320 (100%)	634 (100%)
Asthma (all causes)	134 (43%)	142 (44%)	276 (44%)
PFS	209 (67%)	212 (66%)	421 (66%)
Sensitisations by skin prick test			
Birch	313 (>99%)*	320 (100%)	633 (>99%)
Alder	288 (92%)	293 (92%)	581 (92%)
Hazel	274 (87%)	270 (84%)	544 (86%)
Mono-sensitised**	72 (23%)	82 (26%)	154 (24%)
Polysensitised	242 (77%)	238 (74%)	480 (76%)
Impact on quality of life during BPS prior to randomisation			
Impairment of daily activities, leisure and or sport	264 (84%)	278 (87%)	542 (85%)
Impairment of school or work	228 (73%)	242 (76%)	470 (74%)
Sleep disturbance	211 (67%)	212 (66%)	423 (67%)
Troublesome symptoms	299 (95%)	307 (96%)	606 (96%)
Gender			
Male	146 (46%)	152 (48%)	298 (47%)
Female	168 (54%)	168 (53%)	336 (53%)
Ethnic origin			
White	304 (97%)	314 (98%)	618 (97%)
Asian	3 (<1%)	4 (1%)	7 (1%)

Treatment group	Placebo (N=314) n (%)	12 SQ-Bet (N=320) n (%)	Overall (N=634) n (%)
Black/African American	1 (<1%)	-	1 (<1%)
Hispanic/latino	2 (<1%)	1 (<1%)	3 (<1%)
Other	2 (<1%)	1 (<1%)	3 (<1%)
Unknown	2 (<1%)	-	2 (<1%)
Age			
Mean (SD)	35.3 (13.5)	36.8 (13.7)	36.1 (13.6)
Median	34.5	36	36
Min-Max	12.0-65.0	12.0-65.0	12.0-65.0
BMI			
Mean (SD)	24.6 (4.1)	25.0 (4.3)	24.8 (4.2)
Median	24.2	24.7	24.5
Min-Max	14.5-41.3	16.2-40.4	14.5-41.3
Smoking history			
Never	253	(81%)	252
Former	35	(11%)	39
Current	26	(8%)	29
Bet v1 specific IgE class			
2-3	134	(43%)	137
4-6	180	(57%)	183

*Notes: * missing for one subject.*
*** mono-sensitised defined as skin prick test positive to birch, alder, or hazel.*
Abbreviations: BMI, body mass index; FAS, full analysis set; HDM, House dust mite; SD, standard deviation; IgE, Immunoglobulin E.
Sources: TT-04 clinical study report. **(104)**

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 Statistical analysis

A summary of the statistical analysis carried out in the TT-04 trial is shown in Table 12. Statistical analyses of the data aimed to determine if 12 SQ-Bet was significantly different to placebo in terms of efficacy and immunology (the safety data were not analysed statistically). All statistical tests were two-sided and were performed using a significance level of 5%. (104)

Table 12: Summary of the statistical analysis carried out in the TT-04 trial

Hypothesis objective	The primary and key secondary endpoints were controlled for multiplicity by means of hierarchical testing to ensure a maximum overall type I error rate of 5% in hypothesis testing. The null hypothesis was the hypothesis of no difference between the two treatments.

Statistical analysis	All statistical tests were two-sided and were performed using a significance level of 5% The primary efficacy endpoint, and key secondary endpoints, were analysed using a linear mixed effect (LME) model, with treatment group as fixed effect and pollen region as a random effect. An LME model was also used to analyse other endpoints (secondary and exploratory): average rhinoconjunctivitis symptom VAS, productivity, asthma DSS, ACT score, and the changes from baseline in IgE and IgG4.(99) Patient-rated clinical global improvement, percentage of mild, or severe days, number of sick days, and asthma medication use, were analysed using a generalised logistic regression model. The RQLQ was analysed using a repeated measurement linear mixed model. Exploratory endpoints related to the apple challenge were summarised using descriptive statistics. The LME model described above was also used to analyse two other sets of data:(99, 104) • *post-hoc* analysis of the average TCS, DSS, and DMS data in the combined alder and hazel pollen season (separate to the BPS) • subgroup analysis of the average TCS during the BPS data for adolescent patients.
Sample size, power calculation	A sample size of 300 per treatment group was needed to have at least 90% power to detect a significant difference between active and placebo treatment in the primary endpoint. The power calculation was based on a 2-sided t test with a 5% significance level assuming use of all observed data, a 20% reduction in TCS in the active compared with placebo groups, a 10% dropout rate, and a coefficient of variation of 0.79 in both treatment groups (based on previous trial with the SQ tree SLIT-tablet (TT-03)). (98) For the post *post-hoc* analysis of the average TCS, DSS, and DMS in in the combined alder and hazel pollen season (separate to the BPS) 34 individuals were randomised (tree SLIT-tablet = 320; placebo = 314) and analysed during the oak pollen season (OPS); 575 participants were in the FASBPS population that was analysed during the continuous TPS. Rubin's multiple imputation strategy was used and missing values in both treatment groups were sampled from the observed data of the end point in the placebo group.
Data management, patient withdrawals	The full analysis set (FAS) was defined as all randomised patients in accordance with the intent to treat (ITT) principle. The FAS was used for baseline demographics. The primary analysis was conducted on patients in the FAS who had at least one diary entry during the BPS – known as the FASBPS. The apple challenge analysis set (FASAPPLE) comprised all patients in the FAS who participated in the apple challenge and for whom data were available. The asthma analysis set (FASASTHMA) included all patients with an asthma diagnosis at randomisation with at least one observation related to an asthma endpoint and was used for the analysis of ACT score. The safety analysis set (SS) represents the 'as treated' population regardless of randomisation and was used for all safety analyses.

Abbreviations: BPS, birch pollen season; FAS, full analysis set; FASASTHMA, Subjects in FAS with a medical history of asthma; FASAPPLE, The apple challenge analysis set; FASBPS, Subjects in FAS with observations in the birch pollen season; IgE, immunoglobulin E;IgG4, immunoglobulin G subtype 4; ITT, intent to treat; LME, linear mixed effect; OPS, oak pollen season; TCS, total combined score.
*References: TT-04 clinical study report **(104)** and Biedermann et al., 2019.* **(99)**

Company evidence submission template for Betula verrucosa (ITULAZAX 12 SQ-Bet) for treating moderate to severe allergic rhinitis and/or conjunctivitis from tree pollen [ID6462]

2.4.2 Description of study populations in TT-04

Please see Table 13 for a description of all the analysis sets in TT-04 and the number of participants included in each set.

Table 13: Description of analysis sets in TT-04

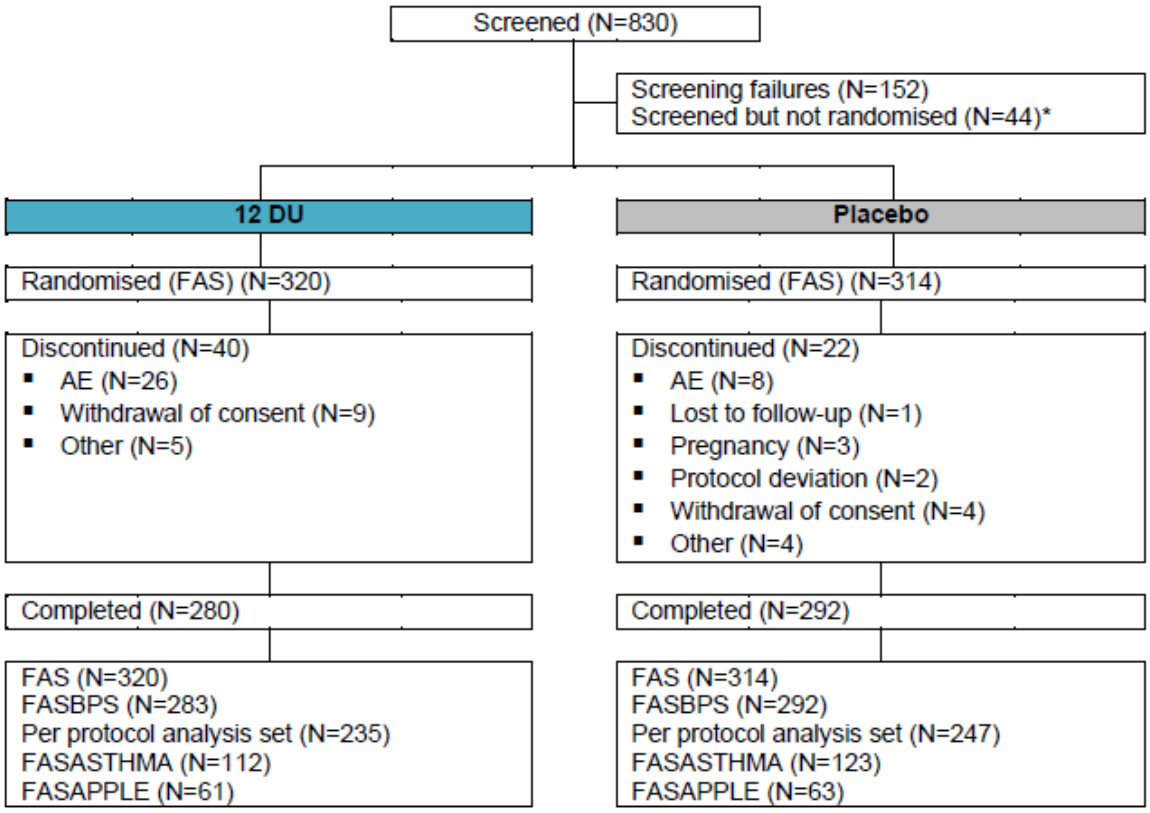
Analysis set	Description	12 SQ-Bet, n	Placebo, n	Overall
Total analysis set	The total analysis set comprises all subjects who signed informed consent. This analysis set includes screening failures. The total population will be used for listing reasons, for screening failures, and AEs before randomisation.	-	-	830
FAS	The FAS is, in accordance with the ICH ITT principle, all randomised subjects according to which treatment the subject was randomised to. The FAS will be used for all baseline/demography tables and sensitivity analysis, and subject listings. All randomised subjects.	320	314	634
FASBPS	All subjects in FAS, with observations during the BPS. This set is used as a primary analysis set for all efficacy analyses.	283	292	575
Per protocol analysis set (PP)	Subjects in FASBPS with at least 70% IMP compliance, no major protocol violations assessed as having an impact on the primary endpoint, at least 50% diary records during the BPS and at least 7 days with pollen counts above 100 and cumulative above 1,000 grains/m^3 during the BPS.	235	247	482
Safety analysis set (SS)	The safety analysis set is “as treated” meaning that each subject is analysed according to the treatment actually received regardless of the randomisation. The safety analysis set is used for all safety tables/listings.	262	175	437
Apple challenge analysis set (FASAPPLE)	FAS subjects with data from an apple challenge.	61	63	124
Asthma analysis set (FASASTHMA)	FAS subjects with an asthma diagnosis at randomisation who have at least one observation related to an asthma endpoint.	112	123	235

Abbreviations: AEs, adverse events; BPS, birch pollen set; FAS, full analysis set; FASASTHMA, Subjects in FAS with a medical history of asthma; FASAPPLE, The apple challenge analysis set; FASBPS, Subjects in FAS with observations in the BPS; SS, safety set; ICH, International Conference on Harmonisation; ITT, Intent to treat; IMP, Investigational medicinal product.
References: TT-04 clinical study report. ***(104)***

2.4.3 Patient disposition in TT-04

Subject disposition for the trial, including the number of subjects randomised, the number who discontinued from the trial, and the reasons for discontinuation are summarised in Figure 12. The most common reason for screening failure (N=66) was failure to meet inclusion criteria I8 concerning specific IgE (Bet v 1) that should be class 2 or above (≥0.7 kU/l). Furthermore, a number of subjects (N=44) were screened but not randomised, mainly due to withdrawal of consent. The rate of discontinuation was higher in the 12 SQ-Bet group (13%) compared to placebo (7%). This difference was mainly driven by a higher number of AE discontinuations in the 12 SQ-Bet group (8%) compared to the placebo group (3%). (104)

Figure 12: Subject disposition in TT-04



*Notes: * primarily subjects who withdrew consent or were lost to follow-up prior to randomisation.*
Abbreviations: AEs, adverse events; FAS, full analysis set; FASAPPLE, The apple challenge analysis set; FASASTHMA, Subjects in FAS with a medical history of asthma; FASBPS, Subjects in FAS with observations in the BPS.
*References: TT-04 Clinical study report **(104)***

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Please see Appendix B for the complete quality assessment for TT-04. Table 14 assesses the relevant clinical effectiveness evidence, using criteria taken from the NICE User Guide. For more details on discontinuations and missing data please see Sections 2.4.1 and 2.11.4.

Table 14: Quality assessment of TT-04

Quality assessment criteria	Response
Was the method used to generate random allocations adequate?	Yes.
Was the allocation adequately concealed?	Yes.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes.
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes (double blinded).
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained, or adjusted for?	No.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate, and were appropriate methods used to account for missing data?	Yes, ITT analyses were included. Appropriate sensitivity analyses were performed (see Appendix B, for full explanation).
Did the study authors declare any conflicts of interest?	Yes.

Abbreviations: *ITT, intention-to-treat.*
Reference: *Appendix B.*

2.6 Clinical effectiveness results of the relevant studies

2.6.1 Primary efficacy endpoint: Average daily allergic rhinoconjunctivitis TCS during the BPS

TCS, is a sum of the allergic rhinoconjunctivitis DSS and allergic rhinoconjunctivitis DMS and has been deemed the optimal endpoint for AIT trials for allergic rhinoconjunctivitis by the European Academy of Allergy and Clinical Immunology

(EAACI) task force. (126) The TCS was measured during the BPS as a primary endpoint of the TT-04 trial. This endpoint was met, as 12 SQ-Bet demonstrated a statistically significant improvement in average TCS during the BPS compared to placebo. The estimated absolute difference between 12 SQ-Bet and placebo was 3.02, corresponding to a difference of 40% relative to placebo (p<0.0001), demonstrating 12 SQ-Bet's superiority over placebo to improve AR symptoms and reduce their medication usage. This reduction met the World Allergy Organisation's (WAO) recommendation of a pre-specified clinically relevant difference of 20% (Table 15). (99, 104, 127) This difference also exceeds the US Food and Drug Administration (FDA) criteria to demonstrate the efficacy of AIT which states a minimum difference of 15% versus placebo must be observed. (128)

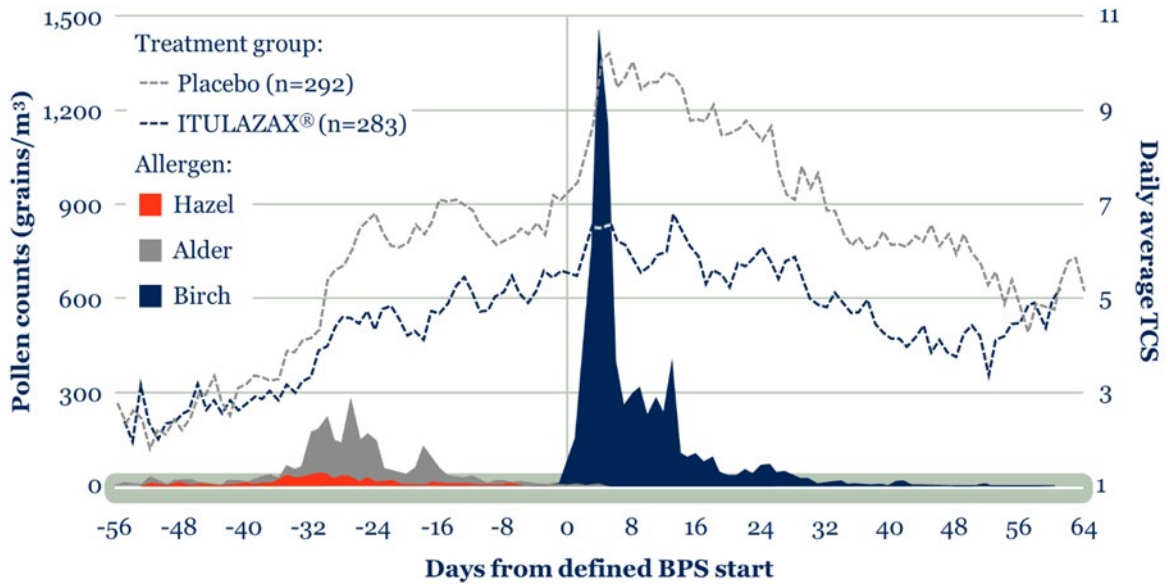
Table 15: Overview of the results for TCS during the BPS in the FASBPS and PP analysis sets of the TT-04 trial

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet)	% Relative to placebo [95% CI]	p-value
TCS during the BPS (FASBPS)					
Placebo	292	7.62	-	-	-
12 SQ-Bet	282	4.61	3.02 [1.99, 4.05]	39.59 [28.24, 49.51]	<0.0001
TCS during the BPS (PP)					
Placebo	247	7.63	-	-	-
12 SQ-Bet	235	4.35	3.27 [2.17, 4.38]	42.90 [31.11, 53.12]	<0.0001

Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
Abbreviations: N, number *of subjects in analysis set*; *FASBPS*, *subjects in FAS with observations during the BPS.*
Reference: *TT-04 CSR.* ***(104)***

The average daily pollen counts alongside the average TCS during the TPS in the TT-04 trial are presented in Figure 13. 12 SQ-Bet separated from placebo on the primary endpoint approximately 4 weeks before the onset of the BPS, coinciding with the earlier hazel and alder pollen seasons. This separation was sustained throughout the BPS, with the most pronounced difference observed during the first 4 weeks. (104)

Figure 13: The average daily pollen counts and average TCS during the TPS in the TT-04 trial



Notes: Data is presented for the FASBPS (all patients with ≥1 observation during the BPS; 12 SQ-Bet, n=283; placebo, n=292).
Abbreviations: BPS, birch pollen season; FAS, full analysis set; FASBPS; subjects in FAS with observations during the BPS; TCS, total combined score.
Reference: TT-04 CSR. ***(104)***

Since the primary analysis focused on subjects within the FASBPS group, sensitivity analyses were conducted as outlined in the Statistical Analysis Plan. These included all randomised subjects (FAS) and utilised two types of multiple imputation. The results from both analyses aligned with the primary analysis, demonstrating a relative difference between 12 SQ-Bet and placebo of 35.69% and 36.55% (p<0.0001 for both), see Table 16 and Table 17. (104)

Table 16: Sensitivity analysis for TCS during the BPS using multiple imputation method 1 (FAS)

Trial arm	N Total	N Observed	N Imputed	Adjusted mean	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
TCS during the BPS (FAS)							
Placebo	314	292	22	7.67	-	-	-
12 SQ-Bet	320	283	37	4.93	2.74 [1.69, 3.78]	35.69 [24.25, 46.20]	<0.0001

Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.

Abbreviations: BPS, birch pollen season; CI, confidence interval; N, number of subjects in analysis set; FAS, all randomised subjects.
Reference: TT-04 CSR. ***(104)***

Table 17: Sensitivity analysis for TCS during the BPS using multiple imputation method 2 (FAS)

Trial arm	N Total	N Observed	N Imputed	Adjusted mean	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
TCS during the BPS (FAS)							
Placebo	314	292	22	7.67	-	-	-
12 SQ-Bet	320	283	37	4.93	2.74 [1.69, 3.78]	35.69 [24.25, 46.20]	<0.0001

Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
Abbreviations: BPS, birch pollen season; N, number of subjects in analysis set; FAS, all randomised subjects.
Reference: TT-04 CSR. ***(104)***

2.6.2 Key secondary endpoints: Average allergic rhinoconjunctivitis DSS during the BPS and TPS; Average allergic rhinoconjunctivitis TCS during the TPS

All analyses of key secondary endpoints showed a statistically significant improvement for the 12 SQ-Bet treatment group compared to placebo, supporting the primary analysis results. Furthermore, the analyses of the key secondary endpoints for the PP population were consistent with those conducted on the FASBPS. (104)

As with the primary analysis, sensitivity analyses were conducted for the key secondary endpoints, including all randomised subjects and employing the same two types of multiple imputation used for the primary endpoint. All of these analyses supported the outcome of the analysis on FASBPS. (104)

Average allergic rhinoconjunctivitis DSS during the BPS and TPS

12 SQ-Bet significantly reduced patient AR symptoms compared to placebo during both the BPS and the extended TPS periods. During the BPS, the estimated

absolute difference was 1.32, equating to a 36.75% reduction relative to placebo (p<0.0001). Similarly, during the TPS, the estimated absolute difference was 0.99, corresponding to a 32.73% reduction relative to placebo (p<0.0001) (Table 18). The efficacy differences in DSS between 12 SQ-Bet and placebo during both timeframes exceeded the pre-specified clinically relevant thresholds of 20% and 15%, as recommended by the WAO and FDA, respectively. (99, 104, 127) (128)

Table 18: Overview of the DSS results during the TPS and BPS in the FASBPS analysis set of the TT-04 trial

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet)	% Relative to placebo [95% CI]	p-value
Average DSS during the BPS (FASBPS)					
Placebo	292	3.60	-	-	<0.0001
12 SQ-Bet	283	2.28	1.32 [0.84, 1.81]	36.75 [25.29, 46.70]	
Average DSS during the TPS (FASBPS)					
Placebo	292	3.02	-	-	<0.0001
12 SQ-Bet	283	2.03	0.99 [0.60, 1.38]	32.73 [21.45, 42.56]	

Notes: FASBPS refers to subjects in FAS with observations during the BPS.
Abbreviations: BPS, birch pollen season; DSS, daily symptom score; FAS, full analysis set; N, number of subjects in analysis set; TPS, tree pollen season.
References: TT-04 CSR. ***(104)***

As demonstrated by the TCS results, there is a separation of the average DSS for 12 SQ-Bet and placebo approximately 4 weeks before the start of the BPS, coinciding with the alder and hazel pollen season; this separation is sustained throughout the BPS.

Average allergic rhinoconjunctivitis TCS during the TPS

The reduction in symptoms and medication use for AR patients improved further with 12 SQ-Bet as the treatment duration extended from the BPS (average of 24 days) to the full TPS (average of 50 days). The difference in the estimated mean TCS during the TPS was statistically significant in favour of 12 SQ-Bet compared to placebo. The estimated absolute difference was 2.27, corresponding to a 36.54% reduction relative to placebo (p<0.0001). Overall, both groups experienced lower average symptom levels and medication use (and consequently, TCS) during the TPS compared to the BPS (see Table 19). (104)

Table 19: Overview of the TCS results during the TPS in the FASBPS analysis set of the TT-04 trial

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet)	% Relative to placebo [95% CI]	p-value
Average TCS during the TPS (FASBPS)					
Placebo	292	6.22	-	-	<0.0001
12 SQ-Bet	283	3.95	2.27 [1.44, 3.11]	36.54 [24.99, 46.62]	

Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
Abbreviations: N, number of subjects in analysis set; FASBPS, subjects in FAS with observations during the BPS.
References: TT-04 CSR. ***(104)***

2.6.3 Other secondary endpoints: average allergic rhinoconjunctivitis DMS; average number of mild and severe days; average rhinoconjunctivitis symptom VAS; global evaluation of efficacy; and RQLQ endpoints during the BPS and TPS

In general, analyses of all other secondary efficacy endpoints showed an improvement for subjects in the 12 SQ-Bet groups compared to placebo.

Average allergic rhinoconjunctivitis DMS during the BPS and TPS

To evaluate the effect of 12 SQ-Bet on patients' use of pharmacotherapy, a daily medication score (DMS) was recorded during both the BPS and TPS periods. Each dose of symptomatic pharmacotherapy was assigned a score, allowing daily tracking of medication usage patients needed to manage their disease. During the BPS, the adjusted mean DMS during the BPS was lower for subjects in the 12 SQ-Bet group compared to placebo, with an estimated absolute difference of 1.58, corresponding to 49.20% reduction in medication usage compared to placebo (p<0.0001). Similarly, when the pollen season was extended to examine the TPS, the adjusted mean for the average DMS was lower for subjects in the 12 SQ-Bet group compared to placebo with an estimated absolute difference of 1.20, corresponding to a 46.71% reduction compared to placebo (p<0.0001) (see Table 20). These results demonstrate the improved control of AR symptoms achieved with 12 SQ-Bet

treatment, significantly reducing the needed for symptomatic pharmacotherapy. (104)

Table 20: Overview of the DMS results during the TPS and BPS in the FASBPS analysis set of the TT-04 trial

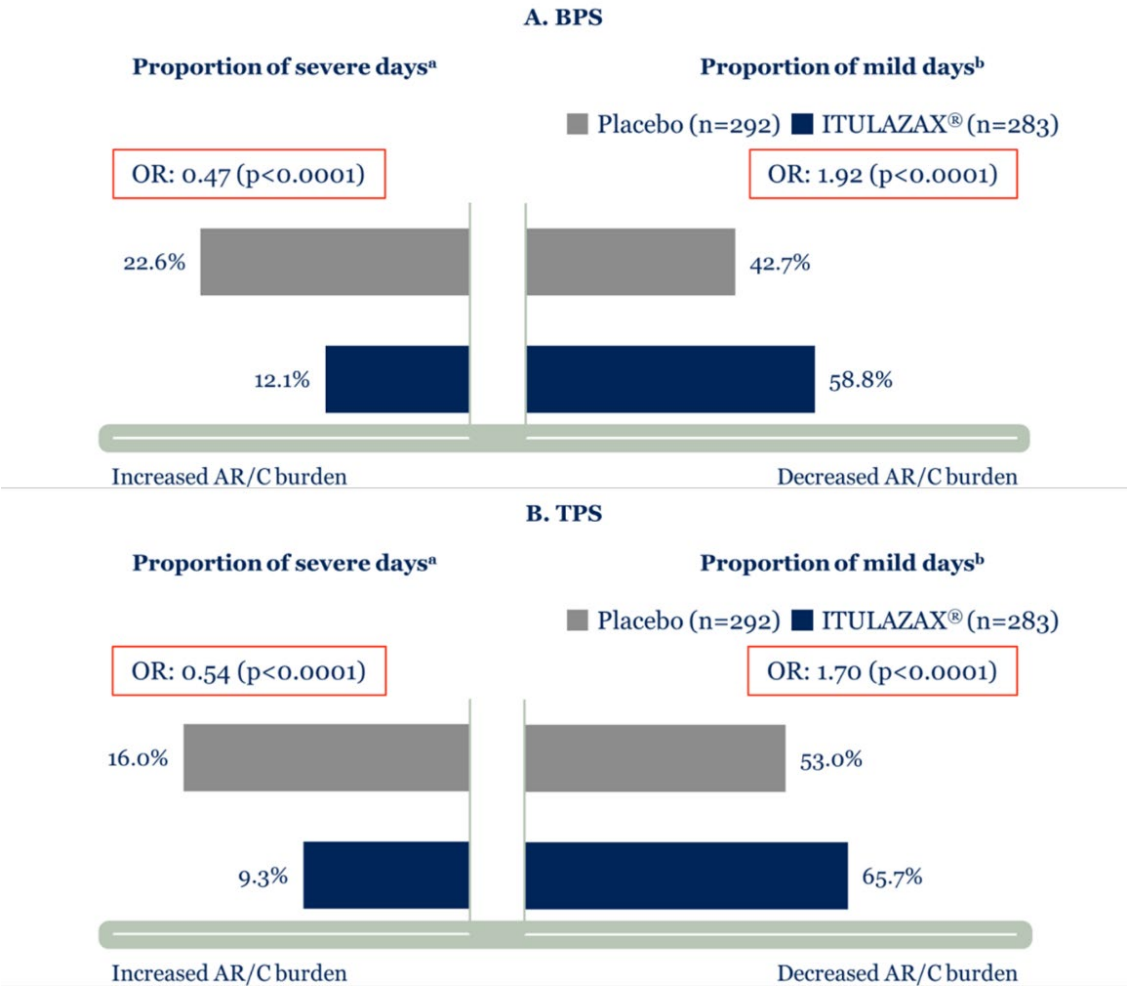
Trial arm	No. observed (no. Imputed)	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo (95% CI)	p-value
Average DMS during the BPS (FASBPS)					
Placebo	292	3.21	-	-	<0.0001
12 SQ-Bet	283	1.63	1.58 (0.94, 2.22)	49.20 (33.38, 62.41)	
Average DMS during the TPS (FASBPS)					
Placebo	292	2.58	-	-	<0.0001
12 SQ-Bet	283	1.37	1.20 (0.69, 1.72)	46.71 (30.47, 60.29)	

Notes: FASBPS refers to subjects in FAS with observations during the BPS.
Abbreviations: CI, confidence interval; TCS, Total combined score; TPS, tree pollen season; N, Number of subjects in analysis set; FASBPS, subjects in FAS with observations during the BPS.
Reference: TT-04 CSR. **(104)**

The proportion of mild and severe days during the BPS and TPS

In the TT-04 trial, alongside the DSS endpoint, the effect of 12 SQ-Bet on symptoms in patients with birch pollen-induced allergic rhinoconjunctivitis was evaluated by measuring the average number of days during the BPS and TPS when patients reported that their symptoms were mild or severe. During a BPS lasting 24 days on average, the number of severe days was reduced from 5.1 days with placebo to 2.7 days with 12 SQ-Bet. During a TPS lasting 50 days on average, the number of severe days was reduced from 7.8 days with placebo to 4.6 days with 12 SQ-Bet. During the BPS, the odds of experiencing a severe day halved with 12 SQ-Bet treatment compared with placebo (OR, 0.47; p<0.0001), whereas the odds for experiencing a mild day doubled (OR, 1.92; p<0.0001). Similar results were seen during the TPS, see Figure 14. This significant reduction in the number of severe symptom days with 12 SQ-Bet during both BPS and TPS further supports the significant reduction observed in these timeframes for the DSS. (104)

Figure 14: Proportion of mild and severe days during the BPS



Notes: Mild days, Days without intake of antihistamine tablet/eyedrops and no single symptom scoring greater than 1; Odds ratio, SQ tree SLIT-tablet/placebo; Severe days, days with DSS of 6 or greater and 2 or more moderate or 1 severe symptom.
Data is presented for the FASBPS (all patients with ≥1 observation during the BPS)
[a] A severe day was defined as a day with a DSS ≥6 points and the presence of at least two moderate symptoms or one severe symptom; [b] a mild day was defined as a day without any intake of antihistamines or olopatadine eye drops and no individual symptom scores >1 point on any of the six individual symptoms – runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, watery eyes.
Abbreviations: AR/C, allergic rhinitis with, or without conjunctivitis; BPS, birch pollen season; DSS, daily symptom score; FAS, full analysis set; OR, Odds Ratio; TPS, tree pollen season.
Reference: ITULAZAX CVD data based on TT-04 CSR. **(104)**

Average rhinoconjunctivitis symptoms VAS during the BPS and TPS

A further measure of symptom reduction with 12 SQ-Bet was conducted using a VAS, which is a tool used to assess the severity of a patient's disease through the assessment of subjective symptoms such as physical and emotional states. The adjusted average rhinoconjunctivitis symptom VAS during the BPS and the TPS was

significantly lower for patients in the 12 SQ-Bet group compared with placebo, indicating a reduced disease severity and hence better symptom control for patients. The estimated absolute difference was 5.77, corresponding to a 32.37% relative reduction compared to placebo (p<0.0001). For the TPS, the estimated absolute difference in rhinoconjunctivitis symptoms VAS for subjects in the 12 SQ-Bet group compared to placebo was 4.25, corresponding to a 29.63% relative reduction compared to placebo (p<0.0001) (see Table 21). (104)

Table 21: Analysis of average rhinoconjunctivitis symptoms VAS during the BPS and TPS of the TT-04 trial (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo [95% CI]	p-value
Average rhinoconjunctivitis VAS during the BPS					
Placebo	292	17.83	-	-	<0.0001
12 SQ-Bet	283	12.06	5.77 [3.25, 8.30]	32.37 [19.69, 43.53]	
Average rhinoconjunctivitis VAS during the TPS					
Placebo	292	14.34	-	-	<0.0001
12 SQ-Bet	283	10.09	4.25 [2.20, 6.30]	29.63 [16.56, 41.18]	

Notes: The response variable in the analysis is: average VAS (0-100 mm). The analysis is based on a linear mixed effect (LME) model with treatment as fixed class effect.
Abbreviations: N, number of subjects with observations; FASBPS, subjects in FAS with observations during the BPS; VAS, visual analogue scale.
Reference: TT-04 CSR. ***(104)***

Global evaluation of efficacy

To further support 12 SQ-Bet's efficacy at reducing AR symptoms, patient assessment of overall clinical improvement with treatment was evaluated using the global evaluation of efficacy endpoint. This endpoint was based on the patients' response to the question, "Compared to your rhinitis and/or conjunctivitis symptoms in the previous birch/TPS, how have you felt overall in this birch/TPS?" Patients were categorised as either "improved" or "not improved". The proportion of subjects with improved global evaluation was high in both treatment groups; however, 12 SQ-Bet was superior compared to placebo (91.06% versus 71.71%, OR=0.25, p<0.0001; Table 22). (104)

Table 22: Analysis of global evaluation of efficacy in the TT-04 trial (FASBPS)

	N	Estimate	Odds ratio (95% CI)	p-value
Estimated proportion of subjects improved (%)				
Placebo	292	71.71	0.25 (0.15, 0.40)	<0.0001
12 SQ-Bet	283	91.06		

Notes: The analysis is based on a logistic regression model. ORs are calculated as placebo/active.
Abbreviations: N, number of subjects with observations; FASBPS, subjects in FAS with observations during the BPS.
Reference: TT-04 CSR. **(104)**

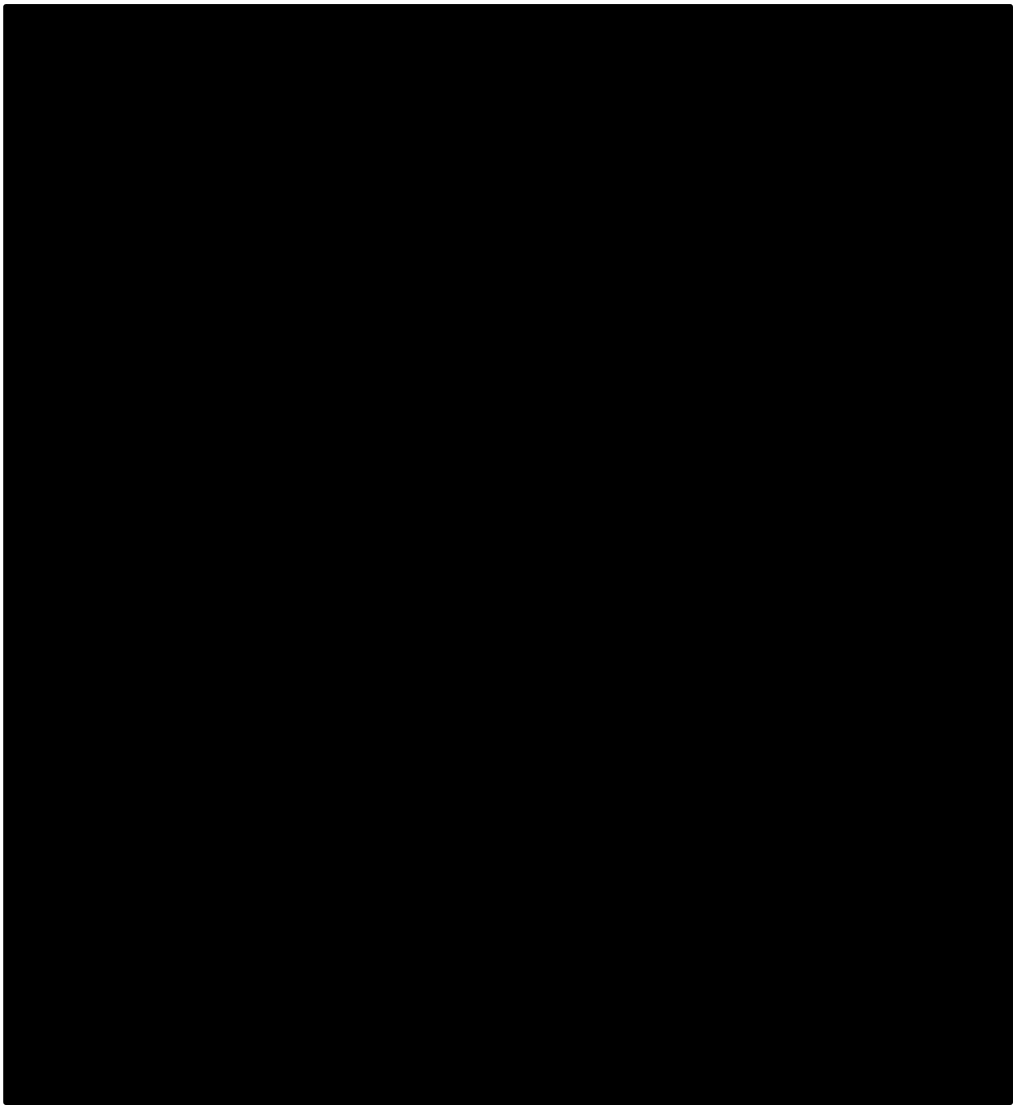
Overall RQLQ score during the BPS and TPS

The RQLQ score is a patient-reported, disease-specific assessment of QoL. 12 SQ-Bet significantly reduced the patients' overall RQLQ score by 31% relative to placebo during the BPS (adjusted mean: 0.99 12 SQ-Bet versus 1.45 placebo; p<0.0001) and by 28% during the TPS (adjusted mean: 0.95 12 SQ-Bet versus 1.32 placebo; p<0.0001), indicating that treatment reduces the impact of the disease on patients' daily activities and overall well-being. The overall RQLQ score was lower for 12 SQ-Bet compared to placebo at all time points during both BPS and TPS with the exception of week 10 during the TPS. The improvement in QoL with 12 SQ-Bet was most pronounced during Weeks 2–5 of the BPS and Weeks 5–8 of the TPS. Additional analysis also demonstrated 12 SQ-Bet's superiority compared to placebo for the scores for the individual domains of the RQLQ score: activity, sleep, nasal symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function (see Figure 15).

[redacted]

[redacted](129)

Figure 15: Results for the individual RQLQ domain scores during the BPS and TPS



*Notes: ***p<0.0001 versus placebo. Data is presented for the FASBPS (all patients with ≥1 observation during the BPS)*
Abbreviations: BPS, birch pollen season; CI, confidence interval; FAS, full analysis set; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TPS, tree pollen season.
Reference: TT-04 RQLQ analysis tables – Data on file. ***(129)***

To further understand the benefit to patients that 12 SQ-Bet provides, a retrospective analysis of data from the TT-04 study set out to estimate the minimum clinically important difference (MCID) for the RQLQ results. Patients are typically asymptomatic before the pollen season due to the absence of allergen exposure, with QoL usually declining during the pollen season when patients are exposed to the allergen. Based on this, 'no clinically meaningful worsening' in health-related

quality of life (HRQoL) was considered a positive outcome for patients with allergies. The analysis estimated that an increase of 0.5 points on the RQLQ total score represents a minimally important worsening (MIW) for an individual patient and an increase of 1.0 points represents important worsening of larger magnitude (IWLM). Notably the MCID values were derived from the same TT-04 dataset. (130)

[redacted] **(130)**

Table 23: The proportion of patients meeting minimally important worsening and important worsening of larger magnitude in RQLQ total score at BPS week 2

	12 SQ-Bet (n= 187)	Placebo (n=193)	p-value
Minimally important worsening, n(%)			
Worsened by ≥0.5 point	[redacted]	[redacted]	[redacted]
Important worsening of larger magnitude, n(%)			
Worsened by ≥1.0 point	[redacted]	[redacted]	[redacted]

Abbreviations: SQ, standardised quality.
Reference: ALK- Abelló., 2019 – Data on file.. ***(130)***

Additional RQLQ data analysis investigated the effect of 12 SQ-Bet when patient QoL was at its worst (i.e., when their RQLQ score was highest).

[redacted] Therefore, 12 SQ-Bet provides clinically meaningful QoL benefits to significantly more patients than placebo. (130)

2.6.4 Exploratory endpoint: Sick days, Productivity, Asthma-related endpoints, Average TCS with EAACI medication score, Pollen food syndrome

The proportion of sick days during the BPS and TPS

Beyond the physical symptoms AR can take a substantial toll on daily activities and as stated in Section 1.3.8, absenteeism caused by AR places a significant burden on

patients. To quantify this burden, the proportion of sick days taken during both the BPS and TPS was recorded in the TT-04 trial. Overall, the proportion of sick days was low for all subjects; however, subjects in the placebo group had a higher proportion of sick days compared to subjects on 12 SQ-Bet during both the BPS (OR: 2.07, p<0.0001) and TPS (OR: 1.72, p<0.0001). (104, 131)

Table 24: Analysis of the proportion of sick days during the BPS and TPS (FASBPS)

	N	Estimate	Odds ratio (95% CI)	p-value
Proportion of sick days during the BPS				
Placebo	292	1.78	-	-
12 SQ-Bet	283	0.87	2.07 (1.63, 2.62)	<0.0001
Proportion of sick days during the TPS				
Placebo	292	1.29	-	-
12 SQ-Bet	283	0.75	1.72 (1.42, 2.08)	<0.0001

Notes: ORs are calculated as placebo/active. The analysis is based on a logistic regression model with treatment as fixed class effect and pollen region as a random class variable
Abbreviations: BPS, birch pollen season; FASBPS, subjects in FAS with observations during the BPS; N, number of subjects with observations; TPS, tree pollen season.
References: TT-04 CSR (104)

Average effect on productivity during the BPS and TPS

The burden of AR in the workplace and on daily activities can also be seen in the reduced productivity associated with the condition. On average, subjects in both treatment groups reported that their productivity was not affected to any major extent in the TT-04 trial; however, subjects in the placebo group reported a higher impact on productivity than subjects in the 12 SQ-Bet group during both the BPS (p=0.0002) and the TPS (p=0.0004). (104)

Table 25: Analysis of the average effect on productivity during the BPS and TPS (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo (95% CI)	p-value
Average effect on productivity during the BPS					
Placebo	292	13.47	-	-	0.0002
12 SQ-Bet	283	8.99	4.49 [2.17, 6.80]	33.31 [17.74, 46.78]	
Average effect on productivity during the TPS					
Placebo	292	10.69	-	-	0.0004
12 SQ-Bet	283	7.31	3.39 [1.51, 5.27]	31.67 [15.49, 45.79]	

Notes: The response variable in the analysis is: the average effect on productivity. The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
Abbreviations: BPS, birch pollen season; CI, confidence interval; N, number of subjects with observations; FASBPS, subjects in FAS with observations during the BPS; TPS, tree pollen season.
Reference: TT-04 CSR. **(104)**

Asthma-related endpoints

As mentioned in Section 1.3.1, uncontrolled AR is a risk factor for asthma exacerbations. To explore this association and assess the beneficial effect of 12 SQ-Bet on asthma, various exploratory endpoints were conducted in the TT-04 trial: average asthma DSS, asthma medication use, and ACT score. All subjects answered questions in relation to asthma symptoms and medication use in the daily diary and therefore asthma symptom score (asthma DSS) and medication use endpoints are reported for FASASTHMA and FASBPS analysis sets. ACT was only answered by subjects with a medical history of asthma and is thus only reported for FASASTHMA. (104)

Overall, the asthma DSS was low (~1 on a scale from 0-12) both in subjects with a medical history of asthma (FASASTHMA) and in general for all subjects in FASBPS. In FASBPS subjects, relative to placebo, 12 SQ-Bet reduced asthma symptoms by 29.3% (p=0.0089) during the BPS and by 24.2% (p=0.0239) during the TPS. The average ACT scores in the trial were high, indicating good asthma control. The average ACT during the BPS was higher in the 12 SQ-Bet group compared to placebo (p=0.0365). No difference between groups could be seen for the TPS (see Table 26). (104)

Table 26: Overview of the asthma endpoints of the TT-04 trial (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo (95% CI)	p-value
Average asthma DSS during the BPS (FASBPS)					
Placebo	292	1.15	-	-	0.0089
12 SQ-Bet	283	0.81	0.34 [0.08, 0.59]	29.32 [8.56, 46.21]	
Average asthma DSS during the TPS (FASBPS)					
Placebo	292	0.96	-	-	0.0239
12 SQ-Bet	283	0.73	0.23 [0.03, 0.44]	24.18 [3.71, 41.30]	

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo (95% CI)	p-value
Average ACT during the BPS (FASASTHMA)					
Placebo	88	21.80	-	-	0.0365
12 SQ-Bet	96	22.24	-1.22 [-2.36, -0.08]	-5.79 [-11.53, -0.39]	
Average ACT during the TPS (FASASTHMA)					
Placebo	111	21.80	-	-	0.5282
12 SQ-Bet	110	22.09	-0.30 [-1.22, 0.63]	-1.35 [-5.66, 2.79]	

Abbreviations: N, *number of subjects with observations*; *FASASTHMA*, *subjects in FAS with asthma*; *FASBPS*, *subjects in FAS with observations during the BPS*.
Reference: TT-04 CSR. **(104)**

The use of asthma medication was low in the trial, with no differences evident between the proportion of asthma medication days during the BPS and TPS for both the 12 SQ-Bet and placebo treatment groups for FASBPS and FASASTHMA. (104)

Average TCS with EAACI medication score during the BPS and TPS

Subjects' use of symptom-relieving medication was also scored using the EAACI medication score, as outlined in Table 27 (132). The EAACI symptom score was calculated by dividing the total symptom score (scale 0-18) by 6, resulting in a scale ranging from 0 to 3, where 0 indicates no symptoms, 1 indicates mild symptoms; 2 indicates moderate symptoms, and 3 indicates severe symptoms. The total combined rhinoconjunctivitis EAACI score was the sum of the EAACI symptom score and the EAACI medication score and assumed values in the range of 0 to 5 (104).

Table 27: EAACI medication score

Symptom-relieving medication for rhinitis/conjunctivitis	
Symptom-relieving medication	EAACI medication score (0 if medication is not used)
Desloratadine tablets, 5 mg	1
Olopatadine eye drops, **1** mg/mL	1
Mometasone nasal spray, 50 µg/dose	2

Notes: The EAACI medication score is defined as the maximum value of either of the 3 above components i.e. the EAACI medication score assumes values of 0, 1, or 2. Note that in Pfaar et al. **(132)** the EAACI medication score may also assume a value of 3 (oral corticosteroids). *This is not possible in the present trial since oral corticosteroids were not allowed.*
Abbreviations: EAACI, European Academy of Allergy & Clinical Immunology.
*References: TT-04 CSR **(104)**; Pfaar et al.2014. **(132)***

The average TCS with EAACI medication score was lower for the 12 SQ-Bet group compared to the placebo group during both the BPS and TPS with relative differences of 37.88% (p<0.0001) and 34.94% (p<0.0001), respectively (Table 28). (104)

Table 28: Analysis of average TCS with EAACI medication score during the BPS and TPS (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo [95% CI]	p-value
Average TCS EAACI during the BPS					
Placebo	292	1.22	-	-	<0.0001
12 SQ-Bet	283	0.76	0.46 [0.30, 0.62]	37.88 [26.67, 47.67]	
Average TCS EAACI during the TPS					
Placebo	292	1.0	-	-	<0.0001
12 SQ-Bet	283	0.65	0.35 [0.22, 0.48]	34.94 [23.66, 44.82]	

Notes: The response variable in the analysis is: the square root of the average TCSEAACI. The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
Abbreviations: BPS, birch pollen season; EAACI, European Academy of Allergy & Clinical Immunology CI, confidence interval; N, number of subjects with observations; FASBPS, subjects in FAS with observations during the BPS; TPS, tree pollen season.
References: TT-04 CSR. **(104)**

Pollen food syndrome assessed in the apple challenge

In addition to the beneficial effect of relieving the symptoms of birch pollen-induced AR, 12 SQ-Bet also improved the oral symptoms of PFS. Subjects from Germany and Poland with PFS associated with oral symptoms after the intake of apples were offered to participate in the apple challenge study (FASAPPLE, N=124) as part of the TT-04 trial to examine the potential treatment effect on PFS by 12 SQ-Bet. 124 subjects participated in the apple challenge. The apple challenge took place on the same day as the end of the trial visit (visit 6) after the visit specific procedures had been finalised. (104)

Around 70 percent of birch allergic individuals develop allergic symptoms against certain foods such as nuts and apples that contain homologous cross-reactive allergens to the major birch allergen Bet v 1. (29, 133) The symptoms are manifested as PFS, and its occurrence typically involves pre-sensitisation to pollen allergens

from the Fagales order. PFS is IgE-mediated and is caused by cross-reactivity between Bet v 1 and other protein family 10 proteins in a number of common food items such as apple, hazelnut, carrot, and peach. (20, 29)

PFS symptoms reported in the PFS questionnaire at screening were similar between treatment groups in FASAPPLE. A higher proportion of subjects in the 12 SQ-Bet group reported that their PFS symptoms had improved after receiving treatment compared to placebo (86.89% versus 63.93%, OR=0.27, p=0.0028). Especially, the increase in symptoms from before the apple challenge to after the first dose of apple (4 g) was more pronounced for participants in the placebo group, suggesting improved tolerance in the active group. This tendency was similar for individual symptoms and the overall PFS VAS score. A global evaluation of efficacy on PFS symptoms showed that more participants in the active group reported improved PFS symptoms after treatment with 12 SQ-Bet compared with placebo (87% versus 64%, OR = 0.27; p=0.0028). The FAQLQ and FAIM scores were generally low in both groups (i.e. low impact of food allergy on QoL), and there were no statistically significant differences between the treatment groups in FAQLQ or FAIM scores at the follow-up 30 days after the apple challenge. (104, 125)

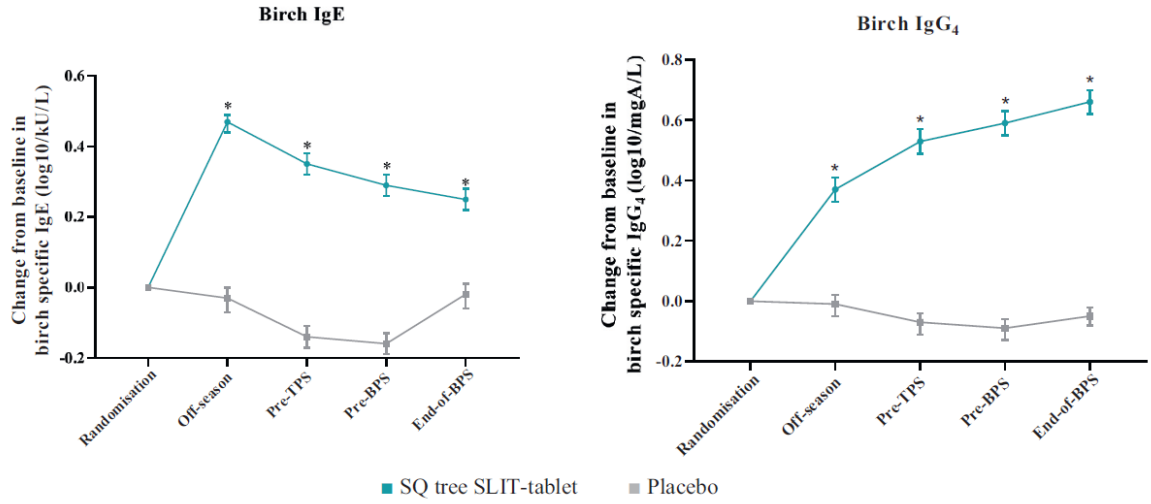
Average apple-specific IgE was similar across treatment groups before treatment initiation. 12 SQ-Bet treatment increased serum levels of apple-specific IgE and IgG4 compared with placebo at all measured time points (changes from baseline). No increases in apple-specific IgE or IgG4 were seen for the placebo group. The apple-specific immunological responses resembled that seen for birch. (104, 125)

2.6.5 Pharmacodynamic endpoints

As part of the inclusion criteria of TT-04, patients were required to have a positive Bet v 1–specific IgE level (IgE class 2 or greater, >0.7 kU/L). All subjects were sensitised to birch pollen and 57% of participants belonged to the IgE class 4 to 6 (≥17.5 kU/L). 12 SQ-Bet increased serum specific levels of both birch-specific IgE

and IgG4 at all time points compared with placebo (p<0.0001 for all), as shown in Figure 16.

Figure 16: Birch IgE and IgG4 results from the TT-04 trial



Abbreviations: BPS, birch pollen season; IgG4, immunoglobin G4; TPS, tree pollen season.
Reference: Biedermann et al., 2019. **(99)**

The immunological data shows that 12 SQ-Bet induced increases in birch-specific IgE from randomisation until approximately 1 month after initiation of treatment, after which time the levels began to decrease. Levels of birch-specific IgG4 increased throughout the entire course of the study. Birch-specific IgE and IgG4 remained rather constant at all time points assessed in the placebo group.

The data from TT-04 clearly show that 12 SQ-Bet has an immunomodulatory effect, which may provide persistent clinical improvement beyond the end of a 3-year course of treatment for individuals with birch pollen-induced AR. (99) Evidence to support this theory comes from a 5-year study evaluating SQ® grass SLIT-tablets in patients with grass pollen allergy, a SLIT-tablet with the same mechanism of action as 12 SQ-Bet. The results showed that the significant improvements in rhinoconjunctivitis symptoms obtained at the end of a 3-year treatment period were sustained for a further 2 years. (134) Outside of this study, a comparison of the immunological data for 12 SQ-Bet with SQ® grass SLIT-tablet has shown that the

two products elicit a similar immune response during the first year of treatment. (104, 135)

By inducing immunological tolerance in a similar manner to SQ® grass SLIT-tablet, it can be assumed that 12 SQ-Bet will provide persistent clinical improvement beyond the end of a 3-year course of treatment. This has been demonstrated for 75,000 SQ-T (SQ® grass SLIT-tablet), which alongside, 12 SQ-Bet (SQ® tree SLIT-tablet), and 12 SQ-HDM (SQ® HDM SLIT-tablet) were developed using the same high-quality standardised manufacturing processes. (12, 103, 136)

2.6.6 Additional analysis

In addition to the primary, secondary, other secondary, exploratory, and pharmacodynamic endpoints listed in Sections 2.6.1, 2.6.2, 2.6.3, 2.6.4 and 2.6.5, additional analyses were also performed on the TT-04 trial data to demonstrate the benefit of 12 SQ-Bet for birch pollen homologous group-induced AR.

Cross-reactivity results

As part of the TT-04 trial, blood samples were collected from 397 birch allergic patients during SQ tree SLIT-tablet or placebo treatment (1:1) for up to 40 weeks. Serum IgE and IgG4 specific to birch, and birch homologous tree pollens from alder, hazel, hornbeam, beech, and chestnut were measured by ImmunoCAP. IgE-Blocking Factor for alder, birch and hazel during treatment was measured by Advia Centaur and blocking effects for birch and all these birch homologous tree pollens were further investigated by basophil activation (BAT). Antibody readouts were investigated in patient subsets. T-cell responses (proliferation) to allergen extracts and peptide pools (group 1 allergens) were investigated in T-cell lines from 29 untreated birch pollen-allergic individuals.

The results of the various parameters listed are described below in Table 29.

Table 29: Results of the cross-reactivity study of TT-04

Parameter	Explanation and/or Relevance, and Results
IgE changes during treatment	Serum levels of allergen-specific IgE were analysed to investigate how 12 SQ-Bet treatment modulates the existing allergen-specific immune response. • An initial induction of allergen-specific IgE was seen for alder, birch, and hazel peaking at 4 weeks after initiation of treatment with an approximate threefold increase • This was followed by a decrease during the remaining treatment period for the three tree pollen allergens investigated • At the end of treatment, allergen-specific IgE was still significantly increased in the SQ tree SLIT-tablet group compared to placebo, even though the serum concentrations for the two treatment groups were approaching the same level
IgG4 changes during treatment	Induction of allergen-specific IgG4 is a hallmark of AIT and seen as an indicator of the competing non-IgE antibody response induced by AIT. • A significant induction of allergen-specific IgG4 was observed in the current trial for alder, birch, and hazel after 4 weeks of treatment • The serum IgG4 concentrations increased further until 4 months of treatment, followed by a slight further increase for birch and a plateau for alder and hazel. The max increase during the trial for birch was 4-5 fold whereas a 2-3 fold increase was observed for alder and hazel
IgE-Blocking Factor induction during treatment	The IgE-Blocking Factor reflects the competition between allergen-specific IgE and treatment-induced non-IgE antibodies and this assay is used to address the functionality of the quantitative changes seen for allergen-specific IgE and IgG4. • A significant induction of IgE-BF was demonstrated after 4 weeks of treatment for the three tree pollen allergen extracts investigated • The inhibitory effect was further increased until 4 months of treatment, followed by a plateau towards the end of treatment • The strongest blocking effect was observed for birch, followed by alder, and with hazel showing slightly delayed induction with optimal level after 7 months of treatment
Cross-reactivity of pre-treatment serum IgE	Sensitisation towards closely related tree species may be the result of cross-reactivity of IgE antibodies.

Parameter	Explanation and/or Relevance, and Results
	• Clear correlations (Pearson) between serum IgE concentrations specific to different trees indicate cross-reactivity • The majority of the birch allergic patients had serum IgE binding to multiple related trees ranging from 95% (beech) to 99% (alder), whereas only 14% reacted to chestnut • The data demonstrate significant correlations between IgE reactivity towards birch and alder, hazel and hornbeam (birch homologous group species) (r≥0.93) as well as beech (r=0.93) • The strongest correlation in IgE titres was seen between birch and alder (r=0.98) and the weakest was between birch and hazel or beech (r=0.93). There was no correlation between birch and chestnut (r=0.047)
Cross-reactivity of end of treatment serum IgG	Cross-reactivity of IgG4 indicates that treatment-induced immune modulation affects the response to different closely related tree species • Serum from the majority of the patients treated with 12 SQ-Bet contained IgG4 binding to multiple related trees ranging from 80% (birch/hornbeam) to 90% (birch/alder), whereas only 8% contained IgG4 towards chestnut in addition to birch • Significant correlation was found between IgG4 towards birch and alder, hazel and hornbeam (birch homologous group species) (r≥0.85) as well as beech (r=0.84) • The strongest correlation in IgG4 titres was seen between birch and alder (r=0.93). There was no correlation between birch and chestnut (r=0.011)
BAT	Sera from 12 actively treated and 7 placebo patients were analysed for basophil activation by six different pollen allergen extracts to address the functionality of the changes in allergen-specific antibodies towards all of these allergens. • Sera from all patients facilitated activation for alder, birch and hornbeam, 18/19 for hazel, 17/19 for beech and 12/19 for chestnut • The allergen concentrations needed to activate the basophils differed considerably with EC50 (the allergen concentration at which 50% of maximal basophil activation occurs) for all donors below 100 ng for alder and birch whereas 16/19 (hornbeam), 12/18 (hazel), 3/17 (beech) and 4/12 (chestnut) donors had EC50 below 100 ng for the other allergen extracts investigated • Significant increases in median EC50 compared to baseline were observed in the treatment group for birch, alder and hornbeam, and no significant difference was observed in the placebo group for these tree pollen allergens
T-cell cross-reactivity to birch homologous trees in	An allergic immune response includes both production of allergen-specific IgE and activation of allergen-specific Th2 cells.

Parameter	Explanation and/or Relevance, and Results
untreated birch allergic patients	• The proliferation data illustrate that T-cell lines respond to allergen extracts from various tree species • Even though significant variations in the strength of the responses are seen, the majority of patients respond to birch, alder, hazel and hornbeam (66%-100%) whereas beech and chestnut were recognised by 50%-60% of the T-cell lines • T-cell responses to peptide pools covering the entire aa sequence of the individual major allergens show a clear pattern with almost equally frequent responses (90%-100%) to group 1 allergens from birch, alder, hazel and hornbeam and with reduced frequencies of responses to beech and chestnut (70%-80%) • The strength of the responses to all peptide pools apart from Aln g 1 peptides differed significantly from the responses to the Bet v 1 peptides

Abbreviations: AIT, allergen immunotherapy; BAT, by basophil activation; IgE, immunoglobin E; IgG4, immunoglobin G4.
Reference: Wurtzen et al., 2020 ***(17)***

2.6.7 Post-hoc analyses of TCS, DSS, and DMS by tree pollen seasons

Post-hoc analysis of the TCS data in the TT-04 has been conducted that demonstrates the efficacy of 12 SQ-Bet throughout the TPS, additionally extending to the oak pollen season (OPS).

Alder/hazel pollen season analysis of TCS, DSS, and DMS

The TPS in the TT-04 trial consisted of the BPS as well as the alder and hazel pollen season (AHPS). The treatment effect of 12 SQ-Bet was demonstrated throughout the TPS. Furthermore, when the AHPS was considered alone, 12 SQ-Bet was also found to be superior to placebo.

In general, the average symptom levels and medication use (and hence TCS) were lower for both treatment groups during the AHPS compared to the BPS and TPS. 12 SQ-Bet reduced patient TCS by 29.66%(p=0.0015), DSS by 26.04% % (p=0.0031) and DMS 43.81% (p=0.0016) relative to placebo (104) (Table 30).

Table 30: Post-hoc analysis of average TCS, DSS, and DMS in the AHPS of TT-04 (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo (95% CI)	p-value
Average TCS in the AHPS					
Placebo	286	4.07	-	-	0.0015
12 SQ-Bet	278	2.87	1.21 [0.46, 1.96]	29.66 [12.61, 43.80]	
Average DSS in the AHPS					
Placebo	286	2.08	-	-	0.0031
12 SQ-Bet	278	1.54	0.54 [0.18, 0.90]	26.04 [9.73, 39.63]	
Average DMS in the AHPS					
Placebo	286	1.45	-	-	0.0016
12 SQ-Bet	278	0.82	0.64 [0.23, 1.04]	43.81 [19.54, 62.45]	

Abbreviations: AHPS, alder, and hazel pollen season; CI, confidence interval; DMS, Daily Medication Score; DSS, Daily Symptom Score; FASBPS, full analysis set BPS; TCS, Total Symptom Score.
References: TT-04 CSR. ***(104)***

Continuous TPS analysis of TCS, DSS, and DMS

The continuous TPS includes all days regardless of pollen counts from the start to the end of the tree pollen season. The duration of the continuous TPS was approximately 2 months. In the continuous TPS 12 SQ-Bet reduced patient, TCS by 34.97% (p<0.0001), DSS by 31.57% (p<0.0001) and DMS by 45.33% (p<0.0001) relative to placebo (Table 31). These relative reductions are similar to those observed for the TPS.

Table 31: Post-hoc analysis of the average TCS, DSS, and DMS during the continuous TPS of TT-04 (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo [95% CI]	p-value
Average TCS during the continuous TPS					
Placebo	292	5.96	-	-	<0.0001

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo [95% CI]	p-value
12 SQ-Bet	283	3.88	2.09 [1.27, 2.90]	34.97 [23.12, 45.30]	
Average DSS during the continuous TPS					
Placebo	292	2.89	---	-	<0.0001
12 SQ-Bet	283	1.98	0.91 [0.53, 1.29]	31.57 [20.02, 41.61]	
Average DMS during the continuous TPS					
Placebo	292	2.48	-	-	<0.0001
12 SQ-Bet	283	1.36	1.13 [0.63, 1.62]	45.33 [28.76, 59.14]	

Abbreviations: CI, confidence interval; DMS, Daily Medication Score; DSS, Daily Symptom Score; TCS, Total Symptom Score; TPS, tree pollen season.
*References: TT-04 CSR **(104)**; Nolte et al., 2021. **(116)***

Oak pollen season analysis of TCS, DSS, and DMS

Nolte *et al.*, 2021(116) conducted a post-hoc analysis of the TT-04 trial in the OPS. Only 1% of participants in the TT-04 trial were IgE mono-sensitised to birch pollen, while 87% were also sensitised to oak pollen. Nolte *et al.*, analysed the symptom outcome results from February to June specifically for the OPS that excluded all the days which overlapped with the BPS.

The average TCS began to separate between 12 SQ-Bet and the placebo groups approximately four weeks before the start of the BPS (coinciding with the alder/hazel pollen seasons). It was maintained throughout the BPS and the OPS. The most pronounced treatment effect on TCS was observed during the BPS when pollen counts were at their highest. Improvements in TCS during the OPS were more pronounced for patients treated with 12 SQ-Bet compared to the placebo arm with a 25% relative treatment difference ($p<0.001$), when DSS and DMS were considered separately, there was a 22% ($p<0.001$) improvement in DSS and a 32% ($p<0.001$) improvement in DMS with 12 SQ-Bet treatment during the OPS compared to placebo (116) (Table 32).

Table 32: Post-hoc analysis of the average TCS, DSS, and DMS during the oak pollen season of TT-04 (all randomised subjects)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% Relative to placebo [95% CI]	p-value
Average TCS during the OPS					
Placebo	225	4.80	-	-	<0.001
12 SQ-Bet	211	3.59	1.21 [0.32, 2.11]	25 [8, 41]	
Average DSS during the OPS					
Placebo	225	2.34	-	-	<0.001
12 SQ-Bet	211	1.82	0.52 [0.07, 0.98]	22 [4, 39]	
Average DMS during the OPS					
Placebo	225	1.76	-	-	<0.001
12 SQ-Bet	211	1.19	0.57 [0.06, 1.07]	32 [6, 54]	

Notes: The OPS excludes all days that overlapped with the BPS.
Abbreviations: CI, confidence interval; DMS, Daily Medication Score; DSS, Daily Symptom Score; OPS, oak pollen season TCS, Total Symptom Score.
Reference: Nolte et al., 2021. ***(116)***

Oak is a member of the birch homologous group, and the oak allergen is an important Bet v 1 cross-reactive tree pollen allergen. These results further demonstrate the efficacy of 12 SQ-Bet in birch pollen-induced AR over the course of the TPS and extending through the OPS.

2.6.8 Real-world evidence: REACT study

The real-world effectiveness in AIT (REACT) study was a retrospective observational, propensity score-matched (PSM) cohort study using claims data between 2007 and 2017 from a German health insurance fund database (Betriebkrankenkasse [BKK]). (137) The study aimed to assess the long-term effectiveness of AIT modalities for the treatment of AR with or without AA in a real-world setting. Primary outcomes included AR prescriptions, while secondary outcomes assessed asthma-related factors, including prescriptions, exacerbations, treatment changes, and new asthma onset. The study also looked at healthcare resource use, costs, sick leave, respiratory infections, and anaphylaxis events as exploratory outcomes. Subgroup and sensitivity analyses were conducted to ensure the accuracy of the evaluations. The study aimed to validate its findings by

comparing results for SLIT-tablets with previous RCTs (137). An overview of the REACT study is provided in Table 33.

Table 33: Overview of the REACT study design

N	Main cohort of 92,048 subjects. 46,024 subjects eligible for inclusion (36,927 SCIT; 4,816 SLIT-drops; 3,754 SLIT-tablets) Tree AIT subgroup N = 11,897
Region	Germany
Population	AR with/without asthma
Age groups	No age inclusion criteria
Trial design	Retrospective, observational, PSM cohort study. Trial duration of 10 yrs, 11 months: January 2007 – December 2017
Primary objective	To demonstrate long-term effectiveness of AIT in the real-world using claims data from Germany from 2007 to 2017

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis, PMS, propensity score-matched
Reference: Fritzsching et al., 2022. ***(137)***

During the study period, 115,098 out of the 5,983,511 available patients in the database had at least one AIT prescription, of which 46,024 were eligible for inclusion. AIT-treated subjects had an average age of 29.5 years, and 53% were male. The AIT-treated patients were exposed to treatment for an average of 549 (SD: 284 days). The eligible (46,024 subjects) AIT-treated subjects were matched 1:1 with control group subjects who were not treated with AIT. Subgroups based on the route of AIT administration (SCIT, SLIT-drops, and SLIT-tablets) and specific allergens (e.g., grass, house dust mites, and tree allergens) were also analysed. (137)

AIT was administered as SCIT in 36,927 patients, SLIT-drops in 4,816 patients, and SLIT-tablets in 3,754 patients. In total, 11,897 (26%) patients were on tree AIT. Outcomes were analysed as within-group (pre- versus post-AIT) and between-group (AIT versus control) differences over 9 years of follow-up. (137)

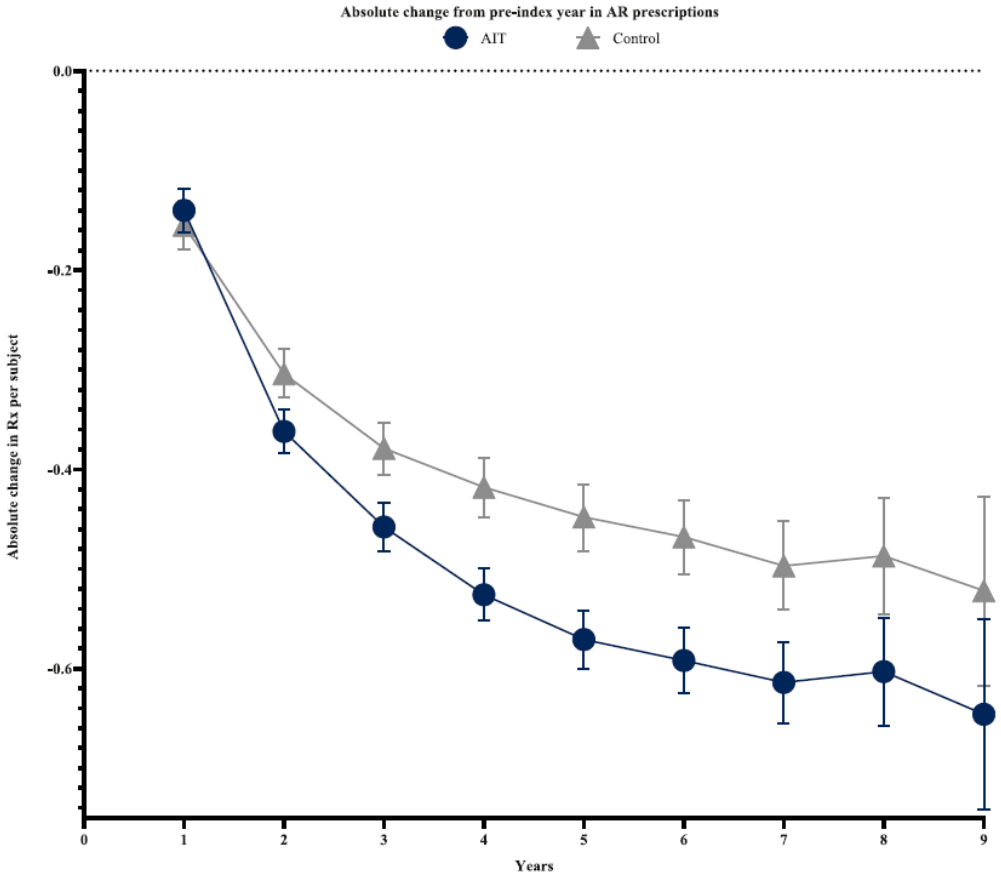
Compared to the pre-index year, AIT was consistently associated with greater reductions compared to control subjects in both asthma and AR prescriptions, which

was sustained for 9 years. Furthermore, an improvement in the treatment effect was observed over the 9-year period. (137)

The AIT group had a significantly greater likelihood of stepping down asthma treatment in comparison with the control group in Year 3 (OR: 1.15, p<0.0001), in Year 5 (OR: 1.27, p<0.0001), and in Year 9 (OR: 1.30, p=0.032). In addition, a consistent reduction in hospitalisations was observed, with ORs of 0.72 (95% CI: 0.54, 0.98), 0.66 (95% CI: 0.46, 0.93), and 0.85 (95% CI: 0.55, 1.30) for all hospitalisations, inpatient stays, and outpatient stays, respectively, for 9 years after treatment initiation. There was also a reduction in ambulatory visits for patients treated with AIT, with an OR of 0.88 (95% CI: 0.49, 1.57) observed at Year 9. (137)

The primary outcome of AR prescription reductions was consistently more favourable for the AIT group compared to control across subgroups, and sensitivity analyses confirmed the benefits of asthma treatment step-down for follow-up Years 4 to 6. The change in the average number of AR prescriptions per subject per follow-up year, compared to the pre-index year, is presented in Figure 17. AR Validation analyses also supported greater AR prescription reductions for SLIT-tablet users. The results of the REACT study evidence a treatment benefit with AIT, with no evidence of treatment waning over the 9 years of follow-up. (137)

Figure 17: Absolute change from pre-index year in AR prescriptions in the REACT study



Abbreviations: AIT, allergen immunotherapy; Rx, prescriptions
Notes: AR prescriptions include symptom-relieving allergic rhinitis medication, e.g. antihistamine and Intranasal corticosteroids (INCS). the first AIT prescription constituted the index date.
Reference: Taken from Fritzsching et al., 2022 (137)

2.7 Subsequent treatments used in the relevant studies

Not applicable as there were no subsequent treatments provided to participants in the TT-04 trial.

2.8 Subgroup analysis

No subgroup analysis relevant to the appraisal population was performed in the TT-04 trial, please see Appendix C for more information.

2.9 Meta-analysis

No meta-analyses were conducted for inclusion in this submission.

The TT-04 trial includes head-to-head data with established clinical management as patients in both treatment arms were permitted to use selected symptom-relieving medications for AR and conjunctivitis during the trial.

2.10 Indirect and mixed treatment comparisons

Not applicable.

2.11 Adverse reactions

2.11.1 Most frequently reported adverse events

An overview of the adverse events (AEs) in the TT-04 trial is presented in Table 34. A total of 262 (82%) subjects in the 12 SQ-Bet group experienced 1,028 AEs, while 176 (56%) subjects in the placebo group experienced 404 AEs. In the 12 SQ-Bet group, 76% of the AEs were IMP-related, while this was the case for 33% of the AEs in the placebo group. (104)

The most frequently reported AEs belonged to the System Organ Classes (SOCs) Gastrointestinal disorders and respiratory, thoracic, and mediastinal disorders, and all the AEs were reported by less than 1% of the subjects. (104) The majority of AEs were mild or moderate in severity in both groups; 4-5% of AEs were assessed as severe. The proportion of subjects experiencing severe AEs were higher for 12 SQ-Bet (7%) than for placebo (2%). The most frequent severe AEs in the 12 SQ-Bet treatment group belonged to the SOCs Gastrointestinal disorders and respiratory, thoracic, and mediastinal disorders, and included AEs such as oral pruritus, hypoaesthesia oral, and throat irritation, all reported by 1% or more of the subjects. In the placebo group, 5 subjects (2%) reported 16 AEs assessed as severe.

Table 34: Overview of AEs (Safety analysis set)

Parameter	Placebo (N=314)				Active 12 SQ-Bet (N=320)			
	n	%n	e	%e	n	%n	e	%e
All AEs	175	56%	404	100%	262	82%	1,028	100%
Causality								

Parameter	Placebo (N=314)				Active 12 SQ-Bet (N=320)			
	n	%n	e	%e	n	%n	e	%e
Unlikely	145	46%	271	67%	127	40%	245	24%
Possible	73	23%	133	33%	239	75%	783	(76%)
Severity								
Mild	134	43%	258	64%	218	68%	583	57%
Moderate	82	26%	130	32%	142	44%	394	38%
Severe	5	2%	16	4%	22	7%	51	(5%)
Seriousness								
No	175	(56%)	398	(99%)	262	(82%)	1,024	(>99%)
Yes	6	(2%)	6	(1%)	4	(1%)	4	(<1%)
Changes to IMP								
None	154	(49%)	319	(79%)	240	(75%)	828	(81%)
Temporary interrupted	38	(12%)	70	(17%)	47	(15%)	102	(10%)
IMP discontinued	8	(3%)	15	(4%)	25	(8%)	98	(10%)
Outcome								
Recovered/resolved	168	(54%)	369	(91%)	260	(81%)	983	(96%)
Recovered/resolved with sequelae	3	(<1%)	3	(<1%)	3	(<1%)	3	(<1%)
Not recovered/resolved	20	(6%)	23	(6%)	25	(8%)	35	(3%)
Unknown	8	(3%)	9	(2%)	5	(2%)	5	(<1%)

Abbreviations: %e, percentage of AEs; %n = percentage of subjects with AEs; AE, adverse event; e, number of AEs; IMP, investigational medicinal product; n, number of subjects with AEs; N, number of subjects in safety analysis set.
Reference: TT-04 CSR. **(104)**

The most frequently reported AEs were local reactions related to the sublingual administration of the IMP, and belonged to the SOC Gastrointestinal disorders, the SOC respiratory, thoracic, and mediastinal disorders, the SOC Infections, and infestations and the SOC Ear and labyrinth disorders. The two most frequently reported AEs were oral pruritus and throat irritation.

The majority of AEs were resolved by the end of the trial (96% for 12 SQ-Bet, 91% for placebo). At the end of the trial, 25 (8%) subjects in the 12 SQ-Bet group and 20 (6%) subjects from the placebo group had AEs that were not yet resolved. (104)

2.11.2 Treatment-related adverse events

A summary of the IMP-related AEs in the TT-04 trial is presented in Table 35. The proportion of subjects experiencing IMP-related AEs and the number of IMP-related AEs were higher for the 12 SQ-Bet group compared to placebo. The majority of IMP-

related AEs in both groups were mild or moderate in severity (94% for 12 SQ-Bet, 90% for placebo). Subjects in the 12 SQ-Bet group experienced on average 2 IMP-related AEs more than subjects in the placebo group, and for the sub-population of subjects with AEs, the 12 SQ-Bet group had on average 1.5 IMP-related AEs more than the placebo group. (104)

Table 35: Overview of IMP-related AEs (Safety analysis set)

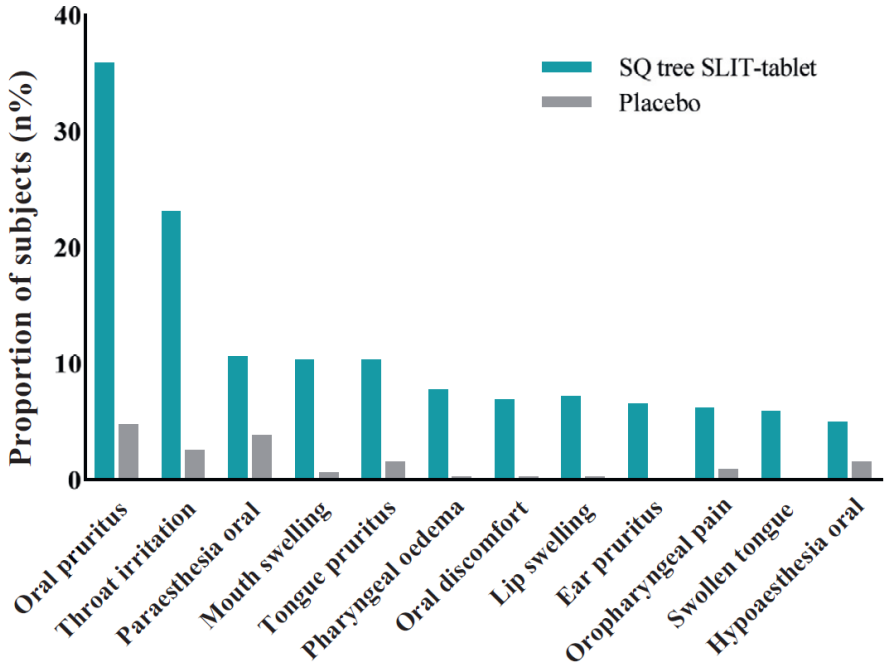
	Placebo (N=314)				Active 12 SQ-Bet (N=320)			
	n	**%n**	**e**	**%e**	**n**	**%n**	**e**	**%e**
All IMP-related AEs	73	(23%)	133	(100%)	239	(75%)	783	(100%)
Severity								
Mild	66	(21%)	99	(74%)	192	(60%)	457	(58%)
Moderate	11	(4%)	21	(16%)	97	(30%)	282	(36%)
Severe	2	(<1%)	13	(10%)	16	(5%)	44	(6%)
Seriousness								
No	72	(23%)	132	(>99%)	239	(75%)	782	(>99%)
Yes	1	(<1%)	1	(<1%)	1	(<1%)	1	(<1%)
Action taken								
None	65	(21%)	113	(85%)	221	(69%)	638	(81%)
Temporary interrupted	5	(2%)	8	(6%)	19	(6%)	48	(6%)
IMP discontinued	5	(2%)	12	(9%)	24	(8%)	97	(12%)
Outcome								
Recovered/ resolved	72	(23%)	129	(97%)	239	(75%)	775	(99%)
Recovered/ resolved with sequelae	-	-	-	-	1	(<1%)	1	(<1%)
Not recovered/ resolved	2	(<1%)	2	(2%)	6	(2%)	7	(<1%)
Unknown	1	(<1%)	2	(2%)	-	-	-	-

Notes: Safety analysis set: all subjects exposed to at least one dose of IMP, N = number of subjects in safety analysis set.
Abbreviations: %e, percentage of AEs; %n = percentage of subjects with AEs; 12 SQ-Bet, 12 SQ-Bet sublingual lyophilisate; AEs, adverse events; e, number of AEs; n, number of subjects with AEs,
IMP, investigational medicinal product.
References: TT-04 CSR. (104)

The most frequently reported treatment-related AEs were mild or moderate local reactions related to sublingual administration of the tablet (placebo: 89%, 12 SQ-Bet: 94%). In the 12 SQ-Bet group, the two most frequently reported IMP-related AEs were oral pruritus (36% of subjects) and throat irritation (23% of subjects), see Figure 18. With the exception of nasopharyngitis, the most frequently reported IMP-

related AEs were identical to the most frequently reported AEs. A majority of these had median onset on the first or second day of treatment and a median duration of 1 to 2 weeks. Typically, local reactions had onset within a few minutes after treatment and recurrent events had median daily durations of 10 to 45 minutes. (99, 104)

Figure 18: Percentage of subjects with the most frequent treatment-related AEs



Notes: If the proportion of subjects was <1%, the value it is displayed as 1%.
Abbreviations: AE, adverse events.
References: Biedermann et al., 2019 ***(99)*** *and TT-04 CSR.* ***(104)***

All severe IMP-related AEs are presented by SOC and PT in Table 36. Sixteen subjects (5%) in the 12 SQ-Bet treatment group reported 44 severe AEs that were assessed as related to the IMP, while 13 IMP-related severe AEs were reported by 2 subjects (<1%) in the placebo group. (104)

Table 36: Overview of severe IMP-related AEs by SOC and PT (Safety analysis set)

	Placebo (N=314)			Active 12 SQ-Bet		
	n	**(%n)**	**e**	**n**	**(%n)**	**e**
All AEs	2	(<1%)	13	16	(5%)	44
Gastrointestinal disorders						
Dry mouth	-	-	-	1	(<1%)	2
Dysphagia	1	(<1%)	1	1	(<1%)	1

	Placebo (N=314)			Active 12 SQ-Bet		
	n	(%n)	e	n	(%n)	e
Glossodynia	-	-	-	1	(<1%)	1
Lip oedema	1	(<1%)	1	-	-	-
Lip swelling	-	-	-	2	(<1%)	2
Swollen tongue	-	-	-	1	(<1%)	1
Oral pruritus	2	(<1%)	2	4	(1%)	6
Hypoaesthesia oral	1	(<1%)	1	4	(1%)	4
Paraesthesia oral	-	-	-	3	(<1%)	3
Tongue pruritus	1	(<1%)	1	1	(<1%)	1
Lip pruritus	-	-	-	1	(<1%)	1
Mouth swelling	-	-	-	2	(<1%)	2
General disorders and administration site conditions						
Swelling	-	-	-	1	(<1%)	1
Respiratory, thoracic, and mediastinal disorders						
Cough	1	(<1%)	1	1	(<1%)	1
Pharyngeal oedema	1	(<1%)	1	1	(<1%)	2
Rhinitis allergic	-	-	-	1	(<1%)	1
Throat irritation	1	(<1%)	1	7	(2%)	8

Notes: Safety analysis set: all subjects exposed to at least one dose of IMP.
Abbreviations: %n, percentage of subjects with AEs; AE, adverse event; e, number of AEs; n, number of subjects with AE; N, number of subjects in safety analysis set; PT, Preferred Term; SOC, System Organ Class.
References: TT-04 CSR. **(104)**

2.11.3 Serious adverse events

Ten subjects (2%) experienced a total of 10 Serious AEs (SAEs); six of these were reported by subjects in the placebo group and four were reported by subjects in the 12 SQ-Bet group. There were no reports of death, anaphylactic shock, airway obstruction, administration of epinephrine, or treatment-related anaphylactic reactions. (104)

Two SAEs were assessed as related to the IMP; one occurred in the active group and one in the placebo group. Both events involved children not part of the trial who were accidentally exposed to trial medication intended for their parents:

- One event involved a 5-year-old boy who accidentally ingested six tablets of blinded IMP (placebo) intended for his father. The boy had no registered allergies and was asymptomatic but was omitted to the hospital, where a

gastric lavage was performed as a safety precaution. The boy was kept in the hospital for observation for one day, but remained asymptomatic, and in good condition.

- The other event involved a 4-year-old girl who accidentally ingested one tablet of blinded IMP (12 SQ-Bet) intended for her father. The girl had no registered allergies, was asymptomatic, and was in good condition. As a safety precaution, she was administered 2.5 mg of antihistamine.

2.11.4 Discontinuations due to adverse events

During the trial, 172 AEs in 85 subjects led to a temporary interruption of IMP intake: 47 subjects (15%) in the 12 SQ-Bet group and 38 subjects (12%) in the placebo group. 24 subjects (4%) temporarily interrupted IMP intake due to an IMP-related AE, and the majority of these (19 subjects) were in the 12 SQ-Bet group. IMP-related AEs leading to temporary interruption of IMP belonged to the SOCs Gastrointestinal disorders and respiratory, thoracic, and mediastinal disorders, and included AEs such as oral pruritus, mouth swelling, pharyngeal oedema, and throat irritation. (104)

By the end of the trial 33 subjects (5%) were discontinued from the trial, 25 (8%) subjects in the 12 SQ-Bet group discontinued due to 98 AEs, while 8 (3%) subjects in the placebo group discontinued due to 15 AEs. The majority of AEs (96%) leading to discontinuations were assessed as related to the IMP. Most subjects in the 12 SQ-Bet treatment group who discontinued due to AEs did so within the first month. Most symptoms resolved the same day and were primarily mild to moderate irritation or swelling in the mouth or throat. (104)

2.11.5 Adverse events of interest

Local administration site reactions (swelling, itching, pain, redness, blister, etc.) are, per default, a potential risk when administrating an oral lyophilisate for sublingual use. However, in rare cases, local administration site reactions may cause severe reactions such as ulcers or swellings and were flagged as an area of interest for 12 SQ-Bet. Additionally, an area of interest for 12 SQ-Bet was systemic allergic

reactions. As 12 SQ-Bet is developed for treatment of an allergic disease by exposing the subject to the allergen, there is a risk that the immunotherapy itself can trigger a systemic allergic reaction. In rare cases, the systemic allergic reaction can develop into an anaphylactic shock. Finally, local allergic reactions such as swellings in the laryngo-pharyngeal area may put the patient at risk by leading to breathing difficulties or suffocation and were also flagged as an area of interest for 12 SQ-Bet. A search was performed among all reported AEs to identify the events of interest for 12 SQ-Bet: Local administration site reactions, systemic allergic reactions, and Laryngo-pharyngeal AEs. (104)

The proportion of subjects experiencing IMP-related local administration site reactions, and the number of reported AEs were higher for the 12 SQ-Bet group (576 AEs in 223 (70%) subjects) compared to placebo (70 AEs in 50 (16%) subjects). The majority (94% for 12 SQ-Bet, 91% for placebo) of the IMP-related local administration site reactions were mild or moderate in severity, did not lead to any change in IMP (86% for 12 SQ-Bet, 94% for placebo) and resolved spontaneously (99% for both treatment groups). (104)

A total of ten subjects (5%) in the 12 SQ-Bet group and three subjects (1%) in the placebo group had co-reported AEs that could indicate a potential systemic allergic reaction/anaphylactic reaction according to the pre-specified algorithm. The majority of these reactions had onset within a few days after the first IMP intake, were mild to moderate in intensity and did not lead to discontinuation. None of the reactions were serious and all subjects recovered; no administration of epinephrine was reported. (104)

The proportion of subjects experiencing IMP-related laryngo-pharyngeal reactions and the number of reported AEs were higher for the 12 SQ-Bet group (346 AEs in 164 (51%) subjects) compared to placebo (35 AEs in 30 (10%) subjects). The majority (92% for 12 SQ-Bet, 89% for placebo) of the IMP-related laryngo-pharyngeal reactions were mild or moderate in severity, did not lead to any changes in IMP (80% for 12 SQ-Bet, 97% for placebo), and resolved spontaneously (>99% for

both treatment groups). The most common laryngo-pharyngeal reactions had median onset on day 1 or 2 after the first IMP intake. (104)

2.12 Ongoing studies

There are no ongoing studies applicable to the population specified in this appraisal. A Phase 3 study (TT-06) has been completed to evaluate the efficacy and safety of 12 SQ-Bet in children and adolescents (5-17 years) who have rhinoconjunctivitis (with or without asthma) induced by pollen from birch trees or by trees belonging to the birch homologous group. Results have been submitted to ClinicalTrials.gov (NCT04878354) and have been published by Gappa *et al.*, 2024. (138)

The TT-06 trial population (5-17 years) is beyond the scope of this appraisal, which is limited to adults. The evaluation of 12 SQ-Bet for treating moderate to severe AR, conjunctivitis, or both caused by tree pollen in people 5 to 17 years has been topic selected for a separate appraisal (TSID 12054).

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Summary of clinical efficacy

The TT-04 Phase 3 randomised double-blind placebo-controlled trial demonstrated the benefits of 12 SQ-Bet over placebo during the BPS as well as the entire TPS on improving symptoms, reducing medication use, improving HRQoL, and lessening PFS and AA symptoms for birch pollen-induced AR patients. The findings also reflect an additional benefit of 12 SQ-Bet over symptomatic pharmacotherapy as the use of selected symptomatic medications was permitted during the pollen season.

Impact of 12 SQ-Bet on symptoms and medication use for birch pollen-induced AR patients

The average TCS of patients in the FASBPS group during the BPS, the primary endpoint in the TT-04 trial, measured patient use of medication and their self-

reported AR symptoms during the trial. 12 SQ-Bet significantly reduced the symptoms of AR and medication use combined (average TCS; primary efficacy endpoint), by 39.6% versus placebo during the BPS ($p<0.0001$). The average TCS during the TPS was assessed as a secondary endpoint in the TT-04 study. 12 SQ-Bet significantly reduced the average TCS by a relative difference of 36.5% versus placebo ($p<0.0001$). These results demonstrate the significant reduction in medication use and improved symptom control for AR patients during both the BPS and TPS with the use of 12 SQ-Bet. This reduction in TCS was also seen across the alder and hazel seasons and OPS in post-hoc analysis of the TT-04 dataset.

These results are further supported when subjects' use of symptom-relieving medication in the TT-04 trial was scored using the EAACI medication score. 12 SQ-Bet reduced the TCS by 37.88% ($p<0.0001$) and 34.94% relative to the placebo group during both the BPS and TPS, respectively. The observed reduction in TCS is particularly notable as confirmation of efficacy in immunotherapy trials is often confounded by the issue of a placebo effect. An advisory board conducted with nine allergists (Appendix J2), highlighted that the TT-04 trial likely included a placebo effect, as mentioned further in section 2.13.3; therefore, the trial may underestimate the clinical benefit of 12 SQ-Bet.

The clinically relevant effect observed throughout the TPS showed that subjects can benefit from symptom improvement and a reduced need for medication not only during the BPS but also during the entire TPS. Post-hoc analyses showed that treatment with 12 SQ-Bet improved symptoms and medication use during the alder and hazel seasons alone as well as the OPS. This suggests that the previously identified immunologic cross-reactivity (see Section 2.6.5) also manifests as a clinical effect across other pollen seasons.

Impact of 12 SQ-Bet on the health-related quality of life of birch pollen-induced AR patients

The impact of 12 SQ-Bet on birch pollen-induced AR has been further demonstrated through the HRQoL endpoints included in the TT-04 trial.

Patient RQLQ is a significant consideration for new treatment options for AR, as the condition impacts all areas of a patient's life, ranging from sleep, outdoor activities, mental wellbeing, and productivity (see Section 1.3.8). These impacts often result in absenteeism, and frequent visits to healthcare services, placing a strain on allergy service provisions in the UK. Patient QoL remains low with current treatment options, highlighting a clear unmet need for a more effective treatment in this pathway.

12 SQ-Bet significantly reduced the overall RQLQ score, indicating improved QoL for AR patients in the TT-04 trial by 31% relative to placebo during the BPS, and by 28% relative to placebo during the TPS.

[redacted] (99, 104)

The impact of AR on patient productivity was assessed during the TT-04 trial with 12 SQ-Bet significantly improving patient productivity by 33.3% (95% CI: 17.7, 46.8; p=0.0002) during the BPS and 31.7% (95% CI: 15.5, 45.8; p=0.0004) throughout the TPS relative to placebo. To provide a broader insight, the adjusted mean rhinoconjunctivitis symptoms VAS during the BPS and the TPS was also significantly

reduced by 12 SQ-Bet by 32% and 30% (p<0.0001), respectively, compared to placebo.

In addition, patient-rated clinical global improvement (secondary efficacy endpoint) was higher with 12 SQ-Bet treatment compared to placebo (91.1% versus 71.7%; OR=0.25; p<0.0001), indicating that patients felt their rhinitis and/or conjunctivitis symptoms had improved in the BPS/TPS compared to the previous season where they did not receive 12 SQ-Bet treatment. (99, 104)

This improvement in RQLQ translated to an improvement in the number of days patients considered their symptoms to be 'severe' in the TT-04 trial. During the BPS, 12 SQ-Bet halved the odds of experiencing a severe day compared with placebo (OR, 0.47; p<0.0001). In addition, 12 SQ-Bet reduced the number of sick days taken during the TT-04 trial during both in the BPS (OR, 2.07; p<.0001) and the TPS (OR, 1.72; p<0.0001). (104, 131)

Long-term effectiveness of 12 SQ-Bet

Data from the TT-04 trial demonstrates that 12 SQ-Bet has an immunomodulatory effect, with an increase in birch-specific IgG4 observed throughout the entire course of the study. The observed immunological changes indicate that 12 SQ-Bet has a pronounced effect on the immune system, which can modulate allergen-specific responses towards immunological tolerance in the long-term. This immunological data is consistent with the immune response observed with 75,000 SQ-T (SQ® grass SLIT-tablet) during the first year of treatment. (104, 135) The long-term effectiveness of SQ® grass SLIT-tablet has been established in a 5-year study, which demonstrated that improvements in rhinoconjunctivitis symptoms obtained at the end of a 3-year treatment period were sustained for a further 2 years (134). In a Delphi panel of three consultant allergists and immunologists and two GP's with a specialist interest in allergy, all agreed that due to the similar mechanisms of action, and identical manufacturing and standardisation technology for ALK's sublingual immunotherapy portfolio (ITULAZAX® 12 SQ-Bet, GRAZAX® 75,000 SQ-T, ACARIZAX® 12 SQ-HDM), it is reasonable to assume that the long-term

effectiveness and any treatment waning would be similar for these treatments. (Appendix J6) (12, 103, 136) In addition, it has also been demonstrated that Japanese cedar pollen SLIT-tablets have a sustained clinical efficacy over a three-year study period and disease modifying effects for at least two years after treatment cessation, alleviating the symptoms of Japanese cedar pollinosis, a common AR in Japan. (139)

Real-world evidence from the REACT study further supports the long-lasting clinical benefit of 12 SQ-Bet, extending beyond the end of treatment. While the REACT study included patients treated with different forms of AIT, 26% of the patients were treated with tree AIT. Compared to the pre-index year, patients treated with AIT had consistently greater reductions compared to control subjects in both asthma and AR prescriptions. There was no evidence of treatment waning over the 9-year study period, providing evidence for lasting clinical benefit beyond the end of treatment for at least 9 years.

The long-term effectiveness of 12 SQ-Bet is further supported by clinical opinion elicited to support a previous appraisal for an AIT (12 SQ-HDM), TA834. In a modified Delphi advisory panel conducted with eight secondary care allergy specialists, it was agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years, with potential waning over the subsequent decade. However, it was thought that treatment effectiveness is unlikely to completely disappear for HDM-sensitised AA patients. (Appendix J4) These results were presented in a second advisory board conducted with eight clinical experts across the UK who similarly agreed that treatment effectiveness of 12 SQ-HDM is likely to have a sustained and clinically significant effect for at least 10 years, with potential waning over the subsequent decade. (Appendix J5) Due to the similar mechanisms of action, albeit for a different allergen, it is assumed that the long-term effectiveness for 12 SQ-Bet will have a similar profile to 12 SQ-HDM, as supported by a Delphi panel with 5 UK allergy experts. (Appendix J6)

Additional effects of 12 SQ-Bet in the TT-04 trial

12 SQ-Bet also demonstrated beneficial effects on other aspects of birch pollen-induced AR. 12 SQ-Bet demonstrated a beneficial effect of relieving the oral symptoms of PFS, a condition developed by ~70% of birch allergic individuals. 12 SQ-Bet showed superiority over placebo in PFS symptom levels and in the dose of apples able to be consumed without experiencing any of the objective symptoms. The efficacy of 12 SQ-Bet treatment on PFS observed in the TT-04 trial is further supported by a prospective study conducted across six European countries by Pfaar *et al.* This study demonstrated that the proportion of patients with PFS symptoms decreased by approximately 38% from the baseline visit to each patient's final visit with 12 SQ-Bet treatment. (140)

Similarly, a high proportion of AR patients also suffer with AA. The TT-04 trial demonstrated that 12 SQ-Bet reduces asthma symptoms by 29.3% during the BPS and by 24.2% during the TPS, relative to placebo. In addition, average ACT scores during the BPS were higher for patients with 12 SQ-Bet compared to placebo, indicating good asthma control.

2.13.2 Summary of clinical safety

The SQ tree SLIT-tablet was well tolerated, with no major safety concerns, and a safety profile consistent with the safety profile in previous trials with 12 SQ-Bet as well as other SLIT-tablets (e.g., house dust mite (ACARIZAX), grass (GRAZAX)). (99) The most frequently reported treatment-related AEs were mild or moderate local reactions related to sublingual administration. The safety data for 12 SQ-Bet generated from the TT-04 trial supports daily at-home administration once tolerability to the initial dose, administered under medical supervision, has been confirmed.

2.13.3 Strengths and limitations of the clinical evidence base

Strengths of the TT-04 trial

The efficacy and safety of 12 SQ-Bet in birch pollen-induced allergic rhinoconjunctivitis has been established in the randomised, placebo-controlled TT-04 Phase 3 study. Notably, participants in the trial were provided with selected symptomatic medication (oral antihistamine tablets, nasal corticosteroid spray and antihistamine eye drops); therefore, the results of the TT-04 trial also demonstrate the superiority of 12 SQ-Bet relative to standard symptomatic pharmacotherapy.

The TT-04 trial successfully demonstrated a significant and clinically meaningful treatment effect of 12 SQ-Bet compared to placebo for TCS, DMS, and DSS during both the BPS, throughout the TPS during the alder and hazel season alone and also continuing through to the OPS, demonstrating a clinical effect above the threshold for clinical relevance threshold. (127) Overall, 12 SQ-Bet demonstrates a significant advantage over SoC medication in reducing symptomatic medication use, reducing symptoms of AR, improving patient QoL, regulating the immune response, and has shown to have a manageable safety profile.

Limitations of the TT-04 trial

The TT-04 trial had some limitations; one challenge was that the treatment duration was less than a year, which could have reduced the opportunity for the detection of AEs that might have a late onset. Two clinical trials in adults and children treated for 3 years with the SQ grass SLIT-tablet, a SLIT-tablet treatment for a seasonal allergen with the same mechanism of action as 12 SQ-Bet, did not detect any adverse reactions that had a long latency period or caused by prolonged exposure. Therefore, it is likely that all AEs associated with 12 SQ-Bet treatment were captured in the TT-04 trial. (134, 141)

Immunotherapy trials are often faced with the issue of a placebo effect, making it difficult to confirm efficacy. The placebo effect, along with regression to the mean, and the Hawthorne effect can make it harder to definitively determine how well the

treatment works. These issues may have impacted the TT-04 trial results, as the trial was placebo-controlled, patients in the placebo arm of the trial had free access to symptom-relieving medication, and symptom assessment was based on subjective measurement scales. However, these issues are typical of immunotherapy trials but may imply that the results of the TT-04 trial underestimate the efficacy of 12 SQ-Bet.

2.13.4 Conclusion

The TT-04 trial demonstrates the significant reduction that treatment with 12 SQ-Bet has on the use of symptomatic medications, and symptoms in adult patients with birch pollen-induced AR compared to placebo. This was observed during the BPS, as well as throughout the TPS, extending through to the OPS. The TT-04 trial results demonstrate the highest efficacy observed to date in an aeroallergen trial. The findings of TT-04 also demonstrate the additional benefit of 12 SQ-Bet over symptomatic pharmacotherapy, as the use of selected symptomatic medications was permitted during the trial. 12 SQ-Bet treatment's beneficial effect on improving birch pollen induced AR symptoms and reducing symptomatic medication use in the TT-04 trial highlights the impact in lowering healthcare resource utilisation.

Treatment with 12 SQ-Bet provided clinically meaningful QoL benefits to significantly more patients compared to the placebo treatment arm. This superior treatment benefit with 12 SQ-Bet was evidenced by the greater reduction in patient sick days, severe symptom days, and an improvement in patient productivity.

In addition, the observed changes in IgE and IgG4 with 12 SQ-Bet treatment provides evidence of the profound effect of 12 SQ-Bet on the immune system, which can modulate allergen-specific responses towards immunological tolerance in the long-term. By 12 SQ-Bet targeting the underlying cause of birch pollen-induced AR, it suggests that treatment is expected to provide lasting clinical relief for birch pollen-induced AR patients beyond the 3-year treatment course. (12) Real-world evidence from the REACT study supports the long-lasting treatment effect of 12 SQ-Bet extending beyond the end of treatment. Patients treated with AIT had consistently

greater reductions compared to control subjects in both asthma and AR prescriptions. This treatment effect was maintained over the course of the 9-year study.

Combined evidence from the TT-04 trial regarding clinical efficacy and safety for the 12 SQ-Bet indicates a positive benefit-risk balance with a clinically relevant treatment effect during both the BPS and TPS, and a favourable safety profile. In summary, when assessing all the data available, there is sufficient evidence to regard 12 SQ-Bet as a novel, effective and well tolerated treatment for AR that delivers meaningful clinical benefits over current established clinical management and effectively addresses the unmet needs of these patients.

3 Cost-effectiveness

3.1 Published cost-effectiveness studies

An SLR was conducted to identify published health economic evaluation studies and costs and healthcare resource use associated with birch pollen-induced AR. Searches were performed on 27th May 2024. Full details of the SLR search strategy, study selection process, and results are presented in Appendix E. MEDLINE, Embase, Cochrane Library incorporating all EBM Reviews, and EconLit databases were searched. Additional secondary sources were interrogated including searching of HTA body websites (including NICE), the international HTA database, RePEc, the Cost-Effectiveness Analysis registry, and The Professional Society for Health Economics and Outcomes Research (ISPOR) presentations database, as well as reference lists of included studies and reviews. Records were eligible for inclusion if they reported an economic evaluation or included summary cost and/or health resource use in patients >5 years old with birch pollen-induced AR.

The electronic database search retrieved a total of 3,271 records, of which 13 studies met the inclusion criteria after full-text screening. (142-154) Of the 13 studies, 7 were economic evaluations including one cost-benefit analysis (153), 2 cost-minimisation analyses (145, 152), 2 cost-effectiveness analyses (reporting outcomes other than QALYs) (142, 146, 147), and 2 cost-utility analyses (143, 150). A summary of the included cost-utility analyses is presented in Table 37.

One of the cost-utility studies was deemed relevant to this appraisal. This analysis performed by Pollock *et al.*, 2023, evaluated the cost-effectiveness of 12 SQ-Bet versus placebo in patients with moderate to severe birch pollen-induced AR, from a Swedish societal perspective. (150) Population characteristics, medication resource use, and QoL data incorporated in the analysis were derived from the TT-04 trial. This analysis was funded and developed by ALK. A separate model was commissioned by ALK and has been developed to address the decision problem of

the current appraisal; however, the developed model is aligned with the conceptual design of that described by Pollock *et al.*, 2023.

Table 37: Summary list of published cost-utility studies

Study	Country	Summary of model	Patient population	QALYs	Costs	ICER
Pollock *et al.*, 2023 (150)	Sweden	Discrete-time, cohort-level, cost-utility model 10-year time horizon	TT-04 trial population (Mean age: 36.1 years)	12 SQ-Bet: 7.591 Placebo: 7.992	SEK 12 SQ-Bet: 103,981 Placebo: 113,057	SEK 223,445 per QALY gained
CADTH, 2014 (155)	Canada	Cost-utility analysis using a trial-based model that estimated, on the basis of daily symptom scores, the differences between AZE/FP, FP, AZE, and placebo in terms of mean costs and effectiveness 14-day time horizon	NR	Total QALHs: Placebo, 235.182 FP, 242.530 AZE, confidential AZE/FP confidential Incremental QALHs versus placebo: FP, 7.348 AZE, confidential AZE/FP, confidential	CAD Total costs: Placebo, 0 FP, 10.25 AZE, confidential AZE/FP, confidential Incremental costs, versus placebo: FP, 10.25 AZE, confidential AZE/FP, confidential	CAD per QALY gained: FP, 12,233 AZE, 27,207 AZE/FP, 31,936 Sequential ICER: FP, 12,223 AZE, dominated AZE/FP, 70,957

Abbreviations: AZE, azelastine hydrochloride; CAD, Canadian dollar; FP, fluticasone propionate; QALHs, quality-adjusted life hours; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NR, not reported; SEK, Swedish Krona.

3.2 Economic analysis

A *de novo* economic model was developed to assess the cost-effectiveness of 12 SQ-Bet compared with established clinical management for treating birch pollen-induced AR. As described above, the modelling approach and model structures of other previously published cost-effectiveness models for birch pollen-induced AR, notably Pollock *et al.*, 2023, were considered during the development of the model for this appraisal. (150) The key features of the economic analysis and their justifications are presented in Table 38.

Table 38: Features of the economic analysis

Factor	Chosen values	Justification
Model structure	2-state Markov model (alive and dead), with time-dependent transitions governed by annual probabilities derived from ONS life tables.	Consistent with approach used in Pollock *et al.*, 2023. (150) Differences in costs and QALYs modelled as treatment-specific and occurred within the alive health state.
Time horizon	Lifetime.	NICE reference case. (107) Considered to reflect that AR is chronic and expected to continue for the duration of patients' lifetime.
Comparator	Established clinical management without 12 SQ-Bet.	NICE scope. Considered as treatments for AR are bundled and aimed at managing symptoms.
Source of utilities	Dick *et al.*, 2019. (124)	Mapping analysis that estimated EQ-5D health state utility values directly from TT-04 symptom and medication score data, and RQLQ scores. (124) This study was also used as the source of utilities in Pollock *et al.*, 2023. (150)
Source of costs	NHS and personal social services (PSS) perspective; sourced from national databases including the British National Formulary, National Cost Collection,	NICE reference case. (107)

Factor	Chosen values	Justification
	drugs, and pharmaceutical electronic market information tool (eMIT), and PSS Research Unit (PSSRU).	
Discounting	3.5% per year for costs, QALYs, and life years.	NICE reference case. (107)
Half-cycle correction	Applied in each model cycle (annual cycles).	NICE reference case. (107)
Long-term effectiveness and treatment waning effect	In the base case, to reflect the improving treatment effect observed in the REACT study, the proportion of patients in the 12 SQ-Bet arm receiving treatment benefit increases by 2.5% in each model cycle up to Year 10. Treatment waning starts at 15 years, and by Year 20, 80% of patients in the 12 SQ-Bet arm will have lost the treatment benefit.	Based on assumptions in a previous NICE appraisal (TA834) for an AIT product, 12 SQ-HDM. Clinical expert opinion and real-world evidence (RWE) sources were used to inform the waning assumptions in TA834. In a 2025 Delphi panel comprising five UK allergy experts, all participants stated that due to the similar mechanisms of action, and identical manufacturing and standardisation technology, the long-term effectiveness and treatment waning effect for 12 SQ-HDM would be applicable to 12 SQ-Bet (Appendix J6).

Abbreviations: AIT, allergy immunotherapy; AR, allergic rhinitis; eMIT; drugs and pharmaceutical electronic market information tool; HDM, house dust mite; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ONS, office for national statistics; PSS, personal social services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RWE, real-world evidence; TA, technology appraisal.

3.2.1 Patient population

As detailed in Section 1.1, 12 SQ-Bet is licensed for the treatment of adult patients (aged 18-65 years) with a confirmed diagnosis of moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group despite the use of symptom-relieving medication. (12)

The clinical evidence supporting the use of 12 SQ-Bet in this population is provided by the TT-04 trial. As discussed in Section 2.6.1, the primary endpoint of the TT-04 trial was met with 12 SQ-Bet demonstrating a statistically significant improvement in average TCS during the BPS compared to placebo. The estimated absolute difference between 12 SQ-Bet and placebo was 3.02, corresponding to a difference of 40% relative to placebo ($p<0.0001$) and thus meeting the pre-specified clinically relevant differences of 20% and 15% as recommended by the WAO and FDA, respectively. (104, 127, 128) Furthermore, all analyses of key secondary endpoints showed a statistically significant improvement for the 12 SQ-Bet treatment group compared to placebo, including statistically significant improvements in TCS, DMS, DSS, and RQLQ during the BPS and TPS. (104)

The starting cohort age and proportion by sex are used as inputs in the model to account for variation in costs and health outcomes due to demographic factors. To be consistent with the efficacy data used in the model, these inputs are informed by the baseline characteristics of the TT-04 trial population. Therefore, the starting cohort had a mean age of 36.01 years, and 47.01% of the cohort were male. (104)

3.2.2 Model structure

A simplified Markov model was constructed to calculate lifetime costs and QALYs for treatment with 12 SQ-Bet compared with established clinical management. The model comprises two core health states: alive and dead, with time-dependent transitions governed by annual mortality rates derived from ONS life tables. Differences in costs and QALYs are modelled as treatment-specific and occur only within the ‘alive’ health state. This modelling approach was deemed most appropriate based on the available data, allowing for the incorporation of treatment-specific utility values derived from Dick *et al.*, 2019. (124) This study performed a mapping analysis to estimate EQ-5D health state utility values directly from the TT-04 symptom and medication score data and RQLQ scores, reporting the difference between the 12 SQ-Bet and placebo arms in the trial. (124) This approach is also consistent with the previously published cost-utility analysis of 12 SQ-Bet by Pollock

et al., 2023. (150) A more complex modelling approach was also considered to incorporate multiple health states based on disease severity. However, given the available data, opting for a treatment-specific approach was deemed most appropriate to provide an accurate assessment of the cost-effectiveness of 12 SQ-Bet compared with established clinical management.

In each model cycle, the cohort accrues costs and benefits. In the base case, the model estimates total lifetime costs and QALYs for each treatment arm, and the corresponding ICER. A half-cycle correction is applied in the model for all model cycles. The cycle length of the model is 1 year, as the transitions in the model are based only on annual mortality rates rather than any changes in disease severity. Therefore, using a shorter cycle length would provide no further granularity in the modelling. Furthermore, a cycle length of 1 year is consistent with the seasonal nature of the disease, as each model cycle includes an entire pollen season. It is important to note that treatment benefit is only accrued for a proportion of the cycle length, depending on the duration of the selected pollen season. In the base case, treatment benefit is accrued for 137 days in each cycle, aligned with the full dataset from Dick *et al.*, 2019 (124), as discussed in Section 3.3.1.

Although international treatment guidelines refer to a treatment period of three years for AIT to achieve disease modification (12), during TT-04 patients discontinued treatment due to AEs and other reasons. (104) In the model, patients who discontinue treatment with 12 SQ-Bet continue to receive established clinical management. Furthermore, during an advisory board (Appendix J5), experts noted that patients who discontinue AIT treatment early may still receive treatment benefit. To reflect this, the model allows for a proportion of patients to continue receiving the benefit associated with 12 SQ-Bet, depending on the year in which treatment with 12 SQ-Bet is discontinued.

The model allows for the waning of the treatment effect of 12 SQ-Bet over time. The assumptions around treatment waning in the model are based on the assumptions in a previous appraisal (TA834) for an AIT (12 SQ-HDM). Due to the similar

mechanisms of action, and identical manufacturing and standardisation technology, it is assumed that the treatment waning effect for 12 SQ-Bet will follow that assumed for 12 SQ-HDM. This assumption was validated in a 2025 Delphi panel comprising three consultant allergists and two general practitioners with a specialist interest in allergy, who all stated that the treatment waning effect for 12 SQ-HDM would be applicable to 12 SQ-Bet (Appendix J6). In TA834, clinical expert opinion and RWE sources were used to inform the waning assumptions. In the base case, it is assumed treatment waning will start in Year 15, and by Year 20, 80% of patients in the 12 SQ-Bet arm will have lost treatment benefit. The model also allows for a proportion of patients to be retreated with 12 SQ-Bet after 10 years. The same assumptions regarding treatment waning are applied to the retreated population.

3.2.3 Intervention technology and comparators

The proposed intervention is 12 SQ-Bet administered sublingually as a tablet daily. 12 SQ-Bet does not require any special temperature storage conditions and is suitable for at-home sublingual administration following administration of the first tablet under physician supervision (to enable discussion and possible treatment of any immediate side effects). (12) It is proposed that 12 SQ-Bet be used as an adjunct to current established clinical management. International treatment guidelines and consensus statements refer to a treatment period of three years for AIT to achieve disease modification after its cessation. (12)

The proposed comparator is established clinical management without 12 SQ-Bet. The NICE Clinical Knowledge Summary on AR (48) incorporates recommendations from the BSACI (156) and the ARIA international guidelines (2016 revision) (46) for the diagnosis and management of patients with AR. For patients with mild to moderate intermittent or mild persistent symptoms, oral or intranasal antihistamines are the first line of therapy. For patients with moderate to severe persistent symptoms or those for whom initial treatment is ineffective, intranasal corticosteroids (INCS) are recommended. If symptoms continue to persist despite these treatments,

combination therapies can be explored, including combinations of oral antihistamines and INCS, or combined preparations of INCS and intranasal antihistamines. (46, 48)

3.3 Clinical parameters and variables

3.3.1 Efficacy

The data informing treatment efficacy in the model is primarily derived from Dick *et al.*, 2019, a mapping analysis that estimated EQ-5D health state utility values directly from clinical data collected in the TT-04 trial. (124) This study was performed to map the disease-specific measures collected during TT-04 to preference-based utilities for use in cost-effectiveness analyses. The regression model developed to generate the mapping function included DSS, DMS, and RQLQ data from TT-04 as covariates. (124) As previously described, the DSS, DMS, and RQLQ were all secondary endpoints in the TT-04 trial. (104) The mapping methodology used in Dick *et al.*, 2019 (124) is discussed in further detail in Section 3.4.2.

Dick *et al.*, 2019 reported pooled mean utility differences and differences in quality-adjusted life days (QALDs) between 12 SQ-Bet and placebo across three different time periods: the BPS, TPS, and the full dataset. (124) As in TT-04, the TPS was defined as the period spanning from the first and last of three consecutive days with a pollen count above 10 grains/m^3. However, the duration of the BPS and TPS in Dick *et al.*, 2019 is longer than those recorded in TT-04 because it includes data from the intervals between pollen seasons where pollen counts drop below the defined thresholds, and because pollen seasons from different regions overlap. (124) The BPS and TPS were defined in this way to include all EQ-5D responses, which was necessary to capture the full difference in QoL between the two arms. The full dataset analysis included all days over which there was at least one EQ-5D response in each treatment arm, regardless of whether the pollen count of the respondent's region was above the threshold. QALDs were calculated by multiplying the mean utility difference by the length of the season of interest. (124) The mean

utility differences and differences in QALDs between 12 SQ-Bet and placebo across the three different seasons reported in Dick *et al.*, 2019 are presented in Table 39.

Table 39: Estimated mean utility difference between 12 SQ-Bet and placebo

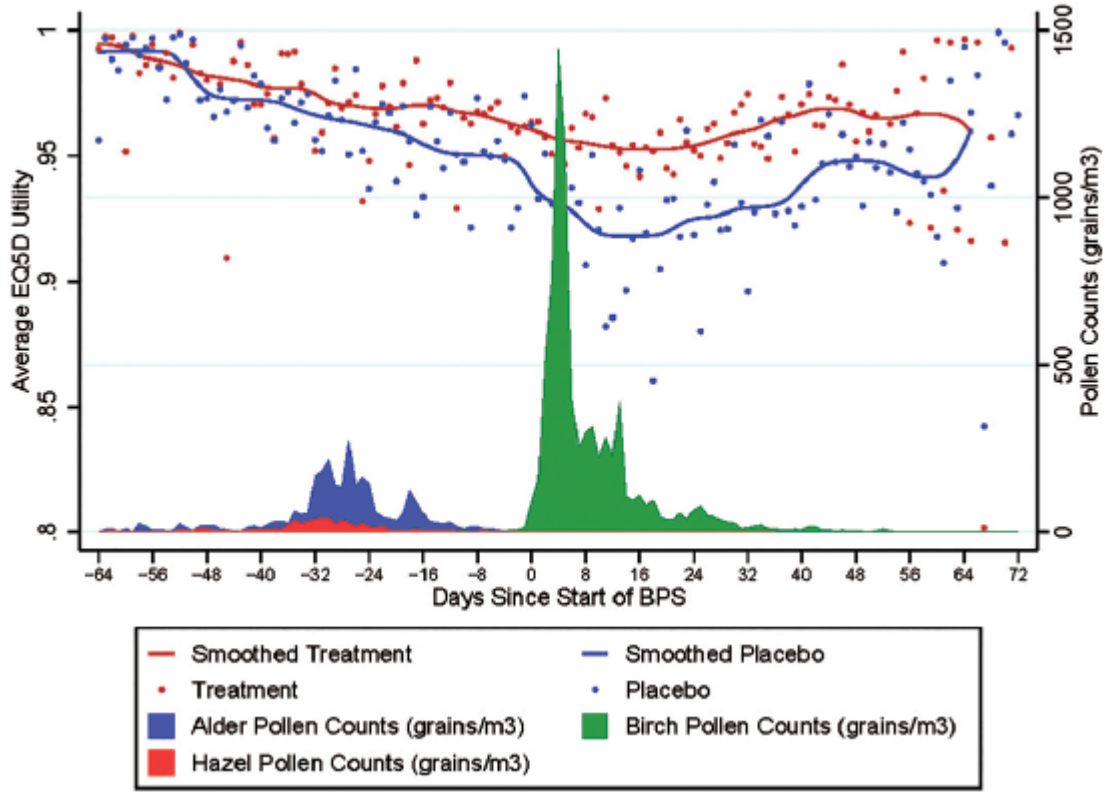
Season	Duration (days)	Mean utility difference [95% CI]	QALDs [95% CI]
BPS	42	0.030 [0.015, 0.046]	1.26 [0.619, 1.917]
TPS	100	0.019 [0.007, 0.030]	1.90 [0.692, 3.047]
Full dataset	137	0.018 [0.007, 0.030]	2.47 [0.930, 4.101]

Abbreviations: BPS, birch pollen season; CI, confidence interval; TPS, tree pollen season; QALD, quality-adjusted life day.
Reference: Dick et al., 2019. (124)

The mean utility difference across the full dataset from this study was deemed most appropriate for inclusion in the economic model, to capture the full treatment benefit of 12 SQ-Bet. The pooled mean utilities presented in Figure 19 shows a clear difference between treatment arms that begins during the start of the alder and hazel pollen seasons, is greatest during the BPS, and is maintained beyond the end of the BPS. As well as birch, alder, and hazel allergen extracts, 12 SQ-Bet inhibits human IgE binding of oak extracts. (157, 158) The extended treatment effect beyond the end of the BPS may be caused by a treatment-related reduction in oak allergy symptoms as the peak of the OPS occurs a month after the peak of the BPS. (20, 124) As described in Section 2.6.7, Nolte *et al.*, 2021 conducted a post-hoc analysis of the TT-04 trial in the OPS, reporting significant improvements in the TCS, DSS, and DMS for patients treated with 12 SQ-Bet compared to placebo. (116) Given that 12 SQ-Bet is indicated in adult patients for the treatment of moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group and has demonstrated cross-reactivity across tree pollen allergens (i.e., not restricted to birch pollen specifically), combined with the demonstration in Dick *et al.*, 2019 (124) of a treatment effect across the full dataset, it was deemed most appropriate to include the mean utility difference across the full dataset in the economic model. Furthermore, this approach is consistent with the findings of a Delphi panel consisting of 5 UK allergy experts who unanimously agreed that birch pollen-induced AR patients experience symptoms for a prolonged period, extending beyond the specific BPS (Appendix J6). In the economic model, the treatment benefit of 12 SQ-

Bet is applied as a disutility to the SoC arm, with the 12 SQ-Bet arm taking on general population utilities. It is assumed that the treatment benefit of 12 SQ-Bet lasts for the proportion of the year aligned with the length of the full dataset from Dick *et al.*, 2019 (137 days). (124)

Figure 19: Pooled mean daily utilities and pollen counts



Notes: Dates were defined relative to the first day of the BPS. The BPS spanned days 0 to 41 (42 days), the TPS spanned days -58 to 41 (100 days), and the full dataset spanned days -64 to 72 (137 days).
Abbreviations: BPS, birch pollen season; EQ5D, EuroQol- 5 Dimension.
Reference: Dick et al., 2019. (124)

Data on pharmacotherapy use as part of the DMS from TT-04 was incorporated in the economic model to calculate pharmacotherapy costs for each arm. (104) The mean daily pharmacotherapy dose was multiplied by the unit cost of the medication and adjusted to correspond to the proportion of the year covered by the full dataset in Dick *et al.*, 2019 (137 days). (124)

3.3.2 Long-term effectiveness

Assessment of the long-term effectiveness of 12 SQ-Bet beyond 12 months has not been conducted in a controlled trial format, and the current key clinical studies do not assess the full guideline recommended three years of treatment, or data after treatment cessation.

The assumptions around treatment waning in the model are based on a previous appraisal for an AIT (12 SQ-HDM), TA834. Due to the similar mechanisms of action, and identical manufacturing and standardisation technology, albeit for a different allergen, it is assumed that the treatment waning effect for 12 SQ-Bet will have a similar profile to 12 SQ-HDM. This assumption was validated in a 2025 Delphi panel comprising three consultant allergists and two general practitioners with a specialist interest in allergy, who all agreed that it was reasonable to assume that the long-term effectiveness and any treatment waning would be similar for these treatments (Appendix J6). In TA834, clinical expert opinion, and RWE sources were used to inform the waning assumptions.

As previously described in Section 2.13.1, in a modified Delphi panel conducted with eight secondary care allergy specialists across Ireland, it was agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade, with treatment effectiveness unlikely to completely disappear (Appendix J4). These results were confirmed in a subsequent advisory board conducted with eight clinical experts across the UK who agreed that treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade (Appendix J5). Furthermore, five UK allergy experts stated that this waning effect would be applicable to 12 SQ-Bet, based on the similar mechanisms of action, and identical manufacturing and standardisation technology (Appendix J6).

The REACT study assessed the long-term effectiveness of AIT for the treatment of AR and asthma in a real-world setting. (137) AIT-treated subjects were propensity score match 1:1 with control subjects (not treated with AIT), using characteristic, and potential confounding variables. Control subjects who received AIT at a later timepoint were censored when they were prescribed the AIT alongside the matched subjects in the AIT group. Outcomes were analysed as within (pre- versus post-AIT) and between (AIT versus control) group differences across 9 years of follow-up. Although the results are not specific to the type of allergen, allergen product, or route of administration, compared to the pre-index year, AIT was consistently associated with greater reductions compared to control subjects in asthma prescriptions and in AR prescriptions, which was sustained for 9 years. Furthermore, an improvement in the treatment effect was observed over the 9-year period. (137) The results of the REACT study evidence a treatment benefit with AIT, with no evidence of treatment waning over the 9 years of follow-up.

In the base case, to reflect the improving treatment effect observed in the REACT study, the proportion of patients in the 12 SQ-Bet arm receiving treatment benefit increases by 2.5% in each model cycle up to Year 10. Treatment waning starts at 15 years, and by Year 20, 80% of patients in the 12 SQ-Bet arm will have lost the treatment benefit. This approach to modelling the long-term effectiveness of 12 SQ-Bet is consistent with the approach taken in TA834. The model also allows for a proportion of patients to be retreated with 12 SQ-Bet after 10 years. The same assumptions regarding treatment waning are applied to the retreated population.

3.3.3 Discontinuation

Patients receiving 12 SQ-Bet within the model have a per cycle probability of discontinuing treatment with 12 SQ-Bet due to AEs and other reasons, based on the rates of treatment discontinuation observed in the TT-04 trial.

No treatment discontinuation was modelled in the established clinical management arm.

Discontinuation due to AEs

The modelled rate of AE treatment discontinuation was derived from the TT-04 trial and is applied to all patients receiving treatment with 12 SQ-Bet. In the TT-04 trial, the majority of all AEs were reported as mild (61%) or moderate (33%), and 99% of subjects experiencing an AE had recovered by the end of the trial. (104) Furthermore, the majority of the most frequent treatment-related AEs (TRAEs) had a median onset within 1 to 12 minutes after first IMP intake with very few new AEs starting at a later time point. (104) As such, the model assumes that all AEs, and their associated costs and QALY loss, occur in the first model cycle only. Similarly, the probability of discontinuation due to AEs is applied in the first model cycle only. The probability of discontinuation due to AEs is informed by the number of patients who discontinued treatment as a result of IMP-related AEs: 7.50%. (104)

All patients who discontinue 12 SQ-Bet treatment incur 1 month's cost of 12 SQ-Bet treatment to account for any previous time on treatment prior to discontinuation. Although a likely overestimate of the time on treatment, as 12 SQ-Bet is provided in a pack of 30 tablets, this cost most appropriately reflects the cost to the healthcare system.

Patients who discontinue treatment with 12 SQ-Bet due to AEs experience the same healthcare costs and HRQoL as patients receiving established clinical management alone for the duration of the model.

Discontinuation due to other reasons

The modelled rate of treatment discontinuation due to other reasons was derived from the TT-04 trial and is applied to all patients receiving treatment with 12 SQ-Bet. The probability of discontinuation due to other reasons is applied in the first three model cycles, reflecting the treatment schedule with 12 SQ-Bet. The probability of discontinuation is informed by the number of patients who discontinued due to withdrawal or other reasons in the TT-04 trial and was estimated to be 4.38% for the

first model cycle. (104) In the absence of additional data on the discontinuation of 12 SQ-Bet beyond 12 months, a rate of 4.38% was also assumed in cycles 2 and 3.

During an advisory board, it was noted that patients who discontinue AIT treatment early may still receive treatment benefit. Two out of three clinicians said that half of patients who discontinue may still receive benefits, while one clinician said this would be a small number of patients (Appendix J5). To account for any potential treatment benefit achieved prior to discontinuation and sustained post discontinuation, a proportion of patients continue to experience the same healthcare costs and HRQoL as patients receiving 12 SQ-Bet for the duration of the model. In the base case the proportion of patients who discontinue treatment with 12 SQ-Bet but continue to receive the treatment benefit of 12 SQ-Bet is 50% for cycles 1, 2, and 3. This has been tested in sensitivity and scenario analyses.

All patients who discontinue treatment with 12 SQ-Bet incur the cost of 6 months' treatment with 12 SQ-Bet, to account for any previous time on treatment prior to discontinuation.

3.3.4 Mortality

The modelled mortality rate is assumed to follow age-adjusted all-cause mortality using rates obtained from UK life tables. A weighted age-dependent mortality probability was calculated using the proportion of male patients in the model.

There is no considered impact of AR on mortality as no deaths were reported in TT-04. (104)

3.3.5 Adverse events

The AEs considered in the model are based on the common TRAEs from the TT-04 trial. The most commonly reported TRAEs were oral pruritic, throat irritation, oral paraesthesia, mouth swelling, tongue pruritic, oral discomfort, pharyngeal oedema, and oropharyngeal pain. (104) The number of events, median duration of event (days), and annual probability of AEs used in the model are summarised in Table 40.

Table 40: Incidence and annual probability of AEs used in the model

Most common TRAEs	Number of events		Annual probability (%)		Median duration of event (days)
	12 SQ-Bet	Placebo			
	n=314	n=320	12 SQ-Bet	SoC	
Oral pruritis	160	16	50.96	5.00	6.0
Throat irritation	96	8	30.57	2.50	4.5
Oral paraesthesia	42	12	13.38	3.75	1.0
Mouth swelling	38	2	12.10	0.63	15.0
Tongue pruritis	35	6	11.15	1.88	5.0
Oral discomfort	33	1	10.51	0.31	2.0
Pharyngeal oedema	32	1	10.19	0.31	5.0
Oropharyngeal pain	29	3	9.24	0.94	3.5

Abbreviations: SoC, standard of care; TRAE, treatment-related adverse event.
Reference: TT-04 trial. (104)

In the TT-04 trial, the majority of all AEs were reported as mild (61%) or moderate (33%), and 99% of subjects experiencing an AE had recovered by the end of the trial. Furthermore, the majority of the most frequent TRAEs had a median onset within 1 to 12 minutes after first IMP intake, with very few new AEs starting at a later time point. There was a median resolution time of 6 days, 4.5 days, and 1 day for the 3 most common AEs. (104) As such, the model assumes that all AEs, and their associated costs and QALY loss, occur in the first model cycle only.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality of life data from clinical trials

The TT-04 trial collected data on HRQoL using the RQLQ. The RQLQ consists of 28 questions, each on a 7-point (0-6) scale, divided into seven domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). All items within each domain are weighted equally. The weekly domain scores were calculated as the average of all item scores for each domain. The weekly overall RQLQ score was the average of all 28 item scores, with higher scores indicating worse rhinoconjunctivitis HRQoL. 12 SQ-Bet was associated with a significant improvement in the QoL compared to placebo during both the BPS and

TPS. TT-04 reported that the overall RQLQ score was significantly improved for 12 SQ-Bet compared to placebo during the BPS (absolute difference: 0.45, p<0.0001) and the TPS (0.37, p<0.0001). Likewise, all individual domain scores were significantly different from placebo (absolute differences for all domains: 0.38, 0.51; p<0.0001 for BPS and 0.29, 0.45; p<0.0001 for TPS). The largest differences were found in: 'activities' (e.g. social and outdoor activities), 'eye symptoms', and 'practical problems' (e.g. inconvenience of having to carry tissues or need to blow nose repeatedly). (104)

Treatment-specific utility scores used in the model were derived from Dick *et al.*, 2019. This study developed a regression model to generate EQ-5D treatment-specific utility values using clinical data collected in the TT-04 trial, which included RQLQ scores as a covariate. (124)

3.4.2 Mapping

The data informing treatment efficacy in the model is primarily derived from Dick *et al.*, 2019, a mapping analysis that estimated EQ-5D utility values directly from clinical data, including RQLQ scores, collected in the TT-04 trial. (124) As the TT-04 trial did not collect preference-based measure (PBM) data e.g., EQ-5D, mapping of disease-specific measures e.g., RQLQ to generate preference-based utilities for use in cost-effectiveness analyses was required. As described in Dick *et al.*, 2019, the analysis used an estimation dataset with recorded PBM data similar to the dataset of interest that does not contain PBM data. Regression modelling was applied to the estimation dataset to develop a mapping function that quantifies the statistical relationship between the PBM and the other outcomes measured in the study. The two datasets must be similar because the mapping function assumes that the statistical relationship between the estimated utilities and the covariates are the same in both the estimation dataset and the study dataset. The regression developed from the estimation dataset is applied to the study dataset to estimate preference-based health state utilities. In the study, the algorithm developed from grass AIT trial data (GT-08), in which both RQLQ and EQ-5D data were collected. The algorithm was

applied to TT-04 that did not collect EQ-5D data to estimate health state utilities and QALYs. (124)

In both GT-08 and TT-04 subjects provided a daily diary of symptoms and medication use and RQLQ was registered weekly. The same symptoms and medications were recorded in both trials, except for prednisone, which was not one of the symptom-relieving medications provided to patients in the TT-04 trial. Prednisone made up only 1% of the overall medication scores in the GT-08 trial and was assumed to have little effect on the daily medication scores. (124) Baseline characteristics for both trials are presented in Table 41.

Table 41: Baseline characteristics of GT-08 and TT-04 trials

	GT-08		TT-04	
	Placebo (n=276)	**SQ grass SLIT-tablet (n=277)**	**Placebo (n=296)**	**12 SQ-Bet (n=284)**
Gender				
Male	167 (61%)	164 (59%)	141 (48%)	134 (47%)
Female	109 (39%)	113 (41%)	155 (52%)	150 (53%)
Age				
Mean (SD)	34.3 (10.1)	34.2 (9.5)	35.2 (13.4)	36.2 (13.5)
Median (IQR)	33 (27-40)	33 (27-39)	34.5 (25-45)	36 (26-46)
Symptom score				
Mean (SD)	2.8 (3.4)	2.0 (2.8)	3.1 (2.3)	2.3 (1.9)
Median (IQR)	2 (0-5)	0 (0-3)	2.7 (1.2-4.7)	1.8 (0.8-3.4)
Medication score				
Mean (SD)	2.1 (4.0)	1.5 (3.3)	3.5 (3.7)	2.5 (3.6)
Median (IQR)	0 (0-3)	0 (0-0)	2.4 (0.4-5.3)	1.0 (0.1-3.6)
Asthma symptom score				
Mean (SD)	0.3 (0.89)	0.2 (0.8)	0.7 (0.9)	0.6 (0.8)
Median (IQR)	0 (0-0)	0 (0-0)	0.2 (0.1-1.0)	0.2 (0.0-0.8)
History of asthma				
Yes (%)	33 (12%)	43 (15%)	123 (42%)	112 (39%)
No (%)	125 (45%)	145 (52%)	173 (58%)	172 (61%)
EQ-5D score				
Missing (%)	118 (43%)	89 (32%)	NR	NR
Mean (SD)	0.94 (0.14)	0.97 (0.10)	NR	NR

	GT-08		TT-04	
	Placebo (n=276)	**SQ grass SLIT-tablet (n=277)**	**Placebo (n=296)**	**12 SQ-Bet (n=284)**
Median (IQR)	1 (-0.5, 1)	1 (1-1)	NR	NR
RQLQ score				
Mean (SD)	0.91 (0.99)	0.69 (0.85)	1.14 (1.0)	0.9 (0.9)
Median (IQR)	1 (0-1.1)	0.61 (1-1)	0.9 (0.3-1.8)	0.6 (0.1-1.3)

Abbreviations: IQR, interquartile range; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; NR, not reported; SD, standard deviation; SLIT, sublingual immunotherapy.
Reference: Dick et al., 2019. (124)

As reported in Dick *et al.*, 2019, the model was developed using a two-part modelling approach, because the EQ-5D scores were strongly left-skewed, and 83% of EQ-5D responses were clustered at 1, indicating perfect health. This skewness is common with EQ-5D data, and a high percentage of subjects in perfect health were expected in this case because subjects were required to be healthy aside from rhinoconjunctivitis symptoms. The data was converted from left-skewed to right-skewed by transforming the data to a disutility scale. The model was developed in terms of disutility (d), then transformed back to the original utility scale (u) using the following equation: (124)

$$u = 1 - d$$

In the first stage of the GT-08 model, EQ-5D utilities were modelled as a binary variable (0 = imperfect health, 1 = perfect health). In the second stage, EQ-5D utilities were modelled as a continuous variable conditional upon having imperfect health. Several types of generalised estimating equation (GEE) models were tested for the second stage of the model, including identity and log link functions with Gaussian, Poisson, and Gamma distributions. The variables subject and year were tested as random effects. (124)

Covariates were chosen for inclusion in the model based on their availability in both the GT-08 and TT-04 trials and their expected clinical relevance. The candidate covariates included DSS, DMS, TCS, RQLQ, age, gender, asthma symptom score, history of asthma, and whether the measure was taken during or outside of a pollen season. An interaction term between DSS and DMS was also tested because

subjects taking higher doses of symptom-relieving medication are likely to experience reduced symptoms and vice versa. All candidate covariates were included in the preliminary model; however, only statistically significant variables ($p<0.05$) were retained in the final model. The first stage of the two-part model predicted the probability of imperfect health, and the second stage of the two-part model predicted disutility conditional on imperfect health. The best fit first stage model was a mixed effects logistic model. A mixed effects model provided a better fit for the second stage model as compared to the GEE model. The subject was included as a random effect in both stages of the model. (124) Both parts of the model are summarised in Table 42.

Table 42: Summary of GT-08 model

Parameter	Stage 1		Stage 2	
	Coef.	p-value	Coef.	p-value
DSS	-0.069	<0.001	-0.003	0.011
DMS	-0.070	<0.001	-0.002	0.089
Interaction	0.010	<0.001	0.000	0.001
RQLQ score	-1.869	<0.001	0.051	<0.001
Sex	0.623	0.009	-	-
Asthma symptoms	-	-	0.015	<0.001
Intercept	4.587	<0.001	0.141	<0.001
AIC	7,712		-3,487	

Abbreviations: AIC, Akaike information criterion; Coef., coefficient; DMS, daily medication score; DSS, daily symptom score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
Reference: Dick et al., 2019. ***(124)***

The model developed from the GT-08 trial data was then applied to the TT-04 trial data to predict EQ-5D utilities. (124) The predicted pooled mean utility differences and differences in QALDs between 12 SQ-Bet and placebo across the three different seasons are presented in Table 39.

The analysis assumes that grass pollen allergy and tree pollen allergy have the same relationship with EQ-5D utilities and other key covariates in the mapping algorithm. This assumption is supported by the fact that both grass and tree pollen induce similar AR symptoms. (124, 159, 160) The trials are also similar in terms of

patient population, exclusion criteria, and baseline characteristics (Table 41). Both trials collected symptom, medication, and asthma scores daily, and QoL data weekly, and symptoms were rated using the same scale. (124)

A notable difference between the trials is that prednisone was available to subjects in the GT-08 trial but was not available to the subjects in TT-04. The impact of prednisone on symptoms and medication use is captured in the mapping function even though it was not used in the TT-04 trial. However, prednisone represents only 1% of the overall medication scores in the GT-08 trial and is unlikely to have significantly impacted medication scores. Another difference between the trials is the overall duration of treatment. Subjects in the GT-08 trial were treated for 3 years and followed for 2 years after treatment discontinuation, while subjects in the TT-04 trial were treated for an average of 32 weeks. Furthermore, the lack of concordance between the time frames of RQLQ, a weekly measure, and EQ-5D, a daily measure, may dilute the association. (124)

3.4.3 Health-related quality of life studies

An SLR was conducted to identify HRQoL and/or health state utility value (HSUV) studies on the management and/or treatment of birch pollen-induced AR. Searches were performed on 29th May 2024. This SLR was conducted in accordance with NICE requirements and the Centre for Reviews and Dissemination (CRD) recommendations for SLRs (161). Full details of the SLR search strategy, study selection process, and results are presented in Appendix F.

In total, 27 publications were judged as relevant for inclusion in this review, which reported on 24 individual studies. (149, 162-186)

In 18 of the 24 included studies, HRQoL was measured using the RQLQ developed by Juniper *et al.* 1999. (187) The other HRQoL measures used were: the Rhinoconjunctivitis Quality of Life (Rcq-36) questionnaire (n=1), the Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) (n=2), both the RQLQ modified (RQLQm) and the International Study of Asthma and Allergies in Childhood

questionnaire (n=1). In 2 studies, the HRQoL measure used was not specified (167, 168) while EQ-5D utilities during the birch and TPS in the TT-04 trial were mapped in one linked study. (124)

Of the HRQoL data identified, only EudraCT-2015-004821-15 (188) (186) (TT-04 trial) provided data for 12 SQ-Bet in subjects with moderate to severe AR.

It is important to note that Dick *et al.*, 2019 (124), the primary source of utilities for the economic model, was the only publication identified in the SLR which published utility values for AR and/or conjunctivitis caused by pollen from the birch homologous group. This study performed a mapping analysis to estimate EQ-5D utilities from clinical data collected in the TT-04 trial. The regression model was developed using data from a grass AIT trial (GT-08) and applied to generate utility values for patients with birch pollen-induced AR. (124)

3.4.4 Adverse reactions

The AEs considered in the model are based on the common TRAEs from the TT-04 trial. As previously discussed, the majority of all AEs reported in the TT-04 were mild (61%) or moderate (33%), and 99% of subjects experiencing an AE had recovered by the end of the trial. Furthermore, the majority of the most frequent TRAEs had a median onset within 1 to 12 minutes after first IMP intake with very few new AEs starting at a later time point. Of the 8 TRAEs modelled, 7 had a median duration of 6 days or under, with mouth swelling having a median duration of 15 days. (104)

The SLR on the HRQoL of patients with birch pollen-induced AR did not identify any utility values for the AEs associated with SLIT. In the model base case, no AE-related utility decrements were applied to the modelled AEs. Given the reported severity and duration of the reported TRAEs, the exclusion of specific utility decrements is not anticipated to have any material impact on the cost-effectiveness of 12 SQ-Bet.

3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

The utility values used in the model are summarised in Table 43. In the model base case, the treatment-specific utilities derived from Dick *et al.*, 2019 were used to inform the QALY gains. (124) The treatment benefit of 12 SQ-Bet is applied as a disutility to the SoC arm, with the 12 SQ-Bet arm taking on general population utilities. As previously discussed in Section 3.3.1, in the base case it is assumed that the treatment benefit of 12 SQ-Bet lasts for the proportion of the year aligned with the length of the full dataset from Dick *et al.*, 2019 (137 days). (124)

Table 43: Summary of utility values for cost-effectiveness analysis

Season	Duration (days)	Mean utility difference [SE]	95% CI
BPS	42	0.030 [0.008]	0.015, 0.046
TPS	100	0.019 [0.006]	0.007, 0.030
Full dataset	137	0.018 [0.006]	0.007, 0.030

Abbreviations: BPS, birch pollen season; CI, confidence interval; TPS, tree pollen season; SE, standard error.
Reference: Dick et al., 2019. (124)

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify published health economic evaluation studies and costs and healthcare resource use associated with birch pollen-induced AR. Searches were performed on 27th May 2024. Full details of the SLR search strategy, study selection process, and results are presented in Appendix E. MEDLINE, Embase, Cochrane Library ALL EBM Reviews, and EconLit were searched. Additional grey literature searching was performed including searching of HTA body websites (including NICE), the international HTA database, RePEc, CEA registry, and ISPOR presentations database, as well as reference lists of included studies. Records were eligible for inclusion if they reported an economic evaluation or included summary cost and health outcomes in patients >5 years old with birch pollen-induced AR.

The electronic database search retrieved a total of 3,271 records, of which 13 studies met the inclusion criteria after full-text screening. Of these, five studies reported on both cost and resource use, (145, 150, 152, 154, 189) 7 studies reported only costs, (142-144, 146, 147, 149, 151, 153) and one reported on resource use only. (148) Reported direct costs were largely made up of drug acquisition costs and costs associated with healthcare professional (HCP) interactions, calculated using tariff-based micro costing approaches. Indirect costs associated with loss of productivity due to seasonal AR were commonly reported using a human capital approach.

No cost and resource use data identified in the SLR were deemed appropriate for inclusion in the model. The model includes treatment costs associated with 12 SQ-Bet and established clinical management, the cost of managing AEs, as well as costs associated with the management of patients in primary and secondary care. All unit costs were identified from UK sources, including NHS reference costs, the British National Formulary (BNF), and EMIT drug costs databases. None of the studies reported on healthcare resource utilisation associated with management of the disease beyond medication use e.g., general practitioner (GP)/outpatient visits. Rather the studies reporting on resource use associated with HCP interactions assumed individuals treated with 12 SQ-Bet required one annual evaluation consultation and did not consider HCP interactions associated with poor disease control. (145, 152) While medication use by treatment arm in the TT-04 trial was reported in Pollock *et al.*, 2023, as summarised in Table 44, it was not reported how this was calculated. (150) Therefore, data on medication use was derived directly from the integrated clinical trial report for TT-04. (104)

Table 44: Symptom-relieving medication resource use based on the TT-04 trial

Medication	Symptom-relieving medication dosing		Proportion of patients requiring symptom-relieving medication (%)	
	12 SQ-Bet	Placebo	12 SQ-Bet	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%

Reference: Pollock et al., 2023. ***(150)***

3.5.1 Intervention and comparators' costs and resource use

12 SQ-Bet treatment costs

12 SQ-Bet should be initiated by physicians with experience in the treatment of allergic diseases. Following this, patients can self-administer at home. 12 SQ-Bet is provided as an oral lyophilisate. The recommended dose for adults and adolescents (12-17 years) is one oral lyophilisate (12 SQ-Bet) daily. The onset of the clinical effect is expected 8-14 weeks after treatment initiation. If no improvement is observed during the first year of treatment with 12 SQ-Bet, there is no indication for continuing treatment. (12)

The list price of 12 SQ-Bet is £80.12 per pack of 30 tablets of 12 SQ-Bet. The average annual cost of 12 SQ-Bet treatment is £975.46 per patient. In the model, the cost of treatment is applied to all patients receiving treatment with 12 SQ-Bet for the first three model cycles (to reflect 3 years of treatment). The cost of treatment for patients who discontinue treatment due to AEs and other reasons is discussed in Section 3.3.3.

The cost of a non-admitted face-to-face attendance with a respiratory specialist (£264.58, National Schedule of NHS costs, WF01B) is included in the administration costs of treatment. Additionally, in line with the NICE final scope, to account for a requirement of a positive test for birch pollen sensitisation, the cost of a diagnostic blood test is included in the administration costs of treatment (£2.75, National Schedule of NHS costs, DAPS05). In the model, administration costs are applied to all patients in the 12 SQ-Bet arm in cycle 0 only.

Established clinical management treatment costs

The proposed comparator is established clinical management without 12 SQ-Bet. As treatment with 12 SQ-Bet is additive, the background established management costs are added to the 12 SQ-Bet treatment costs in the 12 SQ-Bet arm.

Established clinical management costs were estimated based on data collected on medication use throughout the TT-04 trial. As stated previously, symptomatic medications were permitted in the TT-04 trial and provided at randomisation as pre-defined, open-labelled medication used in addition to the IMP. Participants were provided with:

- Oral antihistamine tablets (Desloratadine tablets, 5 mg)
- Nasal corticosteroid spray (Mometasone, 50 µg/dose)
- Antihistamine eye drops (Olopatadine eye drops, 1 mg/mL)

Notably, the use of oral antihistamine tablets, nasal corticosteroid sprays, and antihistamine eye drops in the trial was considered representative of the typical standard of care medication for patients with AR by nine UK clinical experts in allergy management in an advisory panel conducted in 2024 (Appendix J2) and a 2025 Delphi panel comprising three consultant allergists and immunologists, along with two GPs with a specialist interest in allergy (Appendix J6).

Symptomatic treatments could be used as required by participants in both study arms. Data on symptomatic treatment use by treatment arm was reported. Table 45 provides the average daily doses for each pharmacotherapy during the BPS and TPS for the 12 SQ-Bet and placebo arms. (104)

Table 45: Symptomatic treatment use in the TT-04 trial

Pharmacotherapy	Placebo		12 SQ-Bet	
	BPS	TPS	BPS	TPS
Desloratadine (5 mg), tablets	0.46	0.37	0.32	0.26
Mometasone nasal spray (50 ug/dose), puffs	0.66	0.52	0.39	0.33
Olopatadine eye drop (1 mg/mL), drops	0.58	0.48	0.31	0.27

Abbreviations: BPS, birch pollen season; TPS, tree pollen season
Reference: TT-04 CSR (104)

Table 46: Unit costs for pharmacotherapies provided during the TT-04 trial

Pharmacotherapy	Pack cost	Pack size	Cost/unit	Source (190)
Desloratadine (5 mg), tablets	£0.90	30	£0.03	*eMIT*

Pharmacotherapy	Pack cost	Pack size	Cost/unit	Source (190)
Mometasone nasal spray (50 ug/dose), puffs	£1.93	140	£0.01	*eMIT*
Olopatadine eye drop (1 mg/mL), drops	£3.29	100	£0.03	*eMIT*

Notes: In calculating the pack size for olopatadine, it was assumed that there were 100 drops per 5ml vial (0.05ml per drop).
Abbreviations: eMIT, drugs and pharmaceutical electronic market information tool. ***(190)***

To calculate the per cycle treatment costs, the mean daily pharmacotherapy dose is multiplied by the cost per unit of the medication. It is assumed that pharmacotherapy costs are only incurred during the pollen season. Therefore, in the base case, the resultant mean daily cost is applied for the proportion of the year aligned with the length of the full dataset from Dick *et al.*, 2019 (137 days). (124) The annual pharmacotherapy costs for the 12 SQ-Bet and established clinical management arms for the BPS, TPS, and full dataset (as defined in Dick *et al.*, 2019) are detailed in Table 47. In the 12 SQ-Bet arm, the proportion of the cohort receiving treatment benefit also incur the pharmacotherapy costs associated with the 12 SQ-Bet arm. Those in the 12 SQ-Bet arm who lose treatment benefit through discontinuation or treatment waning incur the pharmacotherapy costs associated with the established clinical management arm.

Table 47: Established clinical management treatment costs

Treatment arm	BPS	TPS	Full dataset
Established clinical management	£1.76	£3.41	£4.67
12 SQ-Bet	£1.06	£2.12	£2.91

Abbreviations: BPS, birch pollen season; TPS, tree pollen season.
References: TT-04 CSR ***(104)****; eMIT.* ***(190)***

3.5.2 Health state unit costs and resource use

The model includes costs associated with the management of patients in primary and secondary care. The cost per GP surgery consultation lasting 10 minutes was sourced from the Unit Costs of Health and Social Care 2023 (£42.00, PSSRU 2023). The average cost of outpatient attendance (consultant-led) in the Respiratory Medicine Service was sourced from the National Schedule of NHS costs – Year 2022/23 (£199.00). These costs are also applied in a treatment-specific manner, with

the baseline number of visits modelled in the established clinical management arm and a relative reduction in the number of visits applied in the 12 SQ-Bet arm, reflecting the improvement in disease control in these patients.

The cost and resource use SLR identified no studies reporting on healthcare resource utilisation associated with management of the disease beyond medication use e.g., GP/outpatient visits. Furthermore, no data on healthcare resource utilisation other than medication use was collected in TT-04.

In addition to the SLR on cost and resource use, the company commissioned a probabilistic Delphi panel comprising three consultant allergists and two GPs with a specialist interest in allergy, to derive clinically informed estimates for the healthcare resource utilisation (number of visits to primary and secondary care) of patients with birch pollen-induced AR. Full details of the methodology and analysis are reported in Appendix J6, and the key results are summarised in Table 48.

For primary care resource utilisation, the participants were asked to provide probabilistic judgements on the number of visits to a GP that an average patient with moderate to severe birch pollen-induced AR treated with symptomatic pharmacotherapy (i.e., established clinical management) would make in a year. Following this, the participants provided judgements on the number of visits to a GP that an average patient receiving the average treatment effect of 12 SQ-Bet would make in a year. All participants in the Delphi panel responded that they would anticipate a reduction in primary care appointments for patients with moderate to severe birch pollen-induced AR receiving the average treatment effect of 12 SQ-Bet compared to patients treated with symptomatic pharmacotherapy alone. For patients treated with symptomatic pharmacotherapy, the median number of visits to a GP was judged to be 2.61; for patients receiving the average treatment effect of 12 SQ-Bet, the median number of GP visits was judged to be 1 (relative risk reduction: 61.7%) (Appendix J6).

For secondary care resource utilisation, the participants were asked to provide probabilistic judgements on the number of visits to secondary that an average patient with moderate to severe birch pollen-induced AR treated with either symptomatic pharmacotherapy (i.e., established clinical management), or receiving the average treatment effect of 12 SQ-Bet, would make in a year. All participants in the Delphi panel responded that they would anticipate a reduction in secondary care appointments for patients with moderate to severe birch pollen-induced AR receiving the average treatment effect of 12 SQ-Bet compared to patients treated with symptomatic pharmacotherapy alone. For patients treated with symptomatic pharmacotherapy, the median number of visits to secondary care was judged to be 1.93; for patients receiving the average treatment effect of 12 SQ-Bet, the median number of secondary care visits was judged to be 0.75 (relative risk reduction: 61.1%) (Appendix J6). Notably, the average annual number of secondary care appointments for patients treated with symptomatic pharmacotherapy is comparable to the number of appointments (2.66) modelled in a previous appraisal (TA834) for an AIT, 12 SQ-HDM SLIT. This figure was derived from an assessment of hospital episodes statistics (HES) data to identify the average number of episodes per patient for each hospital setting (elective day case, elective inpatient, emergency, outpatient) for the overall allergy patient cohort at a national level.

Table 48: Survey results from probabilistic Delphi panel (January 2025)

	Symptomatic pharmacotherapy (established clinical management)	12 SQ-Bet*	Relative risk reduction
Annual GP visits	2.61	1.00	61.7%
Annual secondary care visits	1.93	0.75	61.1%

*Notes: *Participants considered patients who were receiving the average treatment effect of 12 SQ-Bet.*
Abbreviations: GP, general practitioner.
Reference: Appendix J6.

The anticipated reduction in healthcare resource utilisation with 12 SQ-Bet is consistent with the findings of an online survey and advisory board with UK allergy

specialists used to support TA834. 46 respondents completed the survey, representing a significant proportion of the community of healthcare professionals actively managing ARD in the UK. Most respondents described themselves as being allergy or immunology consultants (n = 22, 47.8%), with 13 (28.3%) being nurses, 3 (6.5%) being ENT consultants, 3 (6.5%) being respiratory consultants, 3 (6.5%) being GPs, and 2 (4.3%) describing themselves as other healthcare professionals. Only 2% of respondents did not anticipate a reduction in primary or secondary care visits associated with treatment, and all participants anticipated a reduction in hospitalisations (Appendix J3).

In the base case, primary and secondary care resource utilisation in each treatment arm is informed by the results of the probabilistic Delphi panel (Appendix J6). In the 12 SQ-Bet arm, the proportion of the cohort receiving treatment benefit incur the primary and secondary care costs associated with the 12 SQ-Bet arm. Those in the 12 SQ-Bet arm who lose treatment benefit through discontinuation or treatment waning incur the primary and secondary care costs associated with the established clinical management arm.

3.5.3 Adverse reaction unit costs and resource use

The costs associated with AEs are considered in the model. The AEs and probability of events occurring in the model has been previously discussed in Section 3.3.5. Of the events in the TT-04 trial, 18.52% and 15.04% required action in the 12 SQ-Bet and placebo groups, respectively. (104)

As the majority of adverse events were reported as mild or moderate, and because no relevant or appropriate costs for AEs were identified in the SLR, in the base case analysis AEs were costed as a single GP appointment (£42.00; PSSRU 2023) and weighted by the proportion requiring management.

3.5.4 Miscellaneous unit costs and resource use

No other miscellaneous unit costs and resource use are included in the cost-effectiveness analysis.

3.6 Severity

The technology does not meet the criteria for a severity weight. A summary of the QALY shortfall analysis based on the baseline characteristics of the TT-04 trial (mean age: 36.01 years; % male: 47.01) is provided in Table 49.

Table 49: Summary of QALY shortfall analysis

	Value
Expected total QALYs for the general population	19.61
Expected total QALYs for population with the disease	19.51
Absolute shortfall	0.10
Proportional shortfall	0.51%

Abbreviations: QALY, quality-adjusted life year

3.7 Uncertainty

Not applicable.

3.8 Managed access proposal

Not applicable.

3.9 Summary of base case analysis inputs and assumptions

3.9.1 Summary of base case analysis inputs

A summary of the base case cost-effectiveness analysis inputs is provided in Table 50.

Table 50: Summary of variables applied in the economic model

Variable	Value	SE (distribution)
Section 3.2 Economic analysis		
Mean age	36.01	3.60% (Normal)
Sex (% male)	47.01%	4.7% (Beta)
Section 3.5 Cost and healthcare resource use		
12 SQ-Bet annual treatment cost	£975.46	£97.55 (Gamma)

Variable	Value	SE (distribution)
12 SQ-Bet initiation cost	£264.58	£26.46 (Gamma)
12 SQ-Bet diagnostic test cost	£2.75	£0.28 (Gamma)
Pharmacotherapy costs – 12 SQ-Bet – BPS	£1.06	£0.11 (Gamma)
Pharmacotherapy costs – 12 SQ-Bet – TPS	£2.12	£0.21 (Gamma)
Pharmacotherapy costs – 12 SQ-Bet – Full dataset	£2.91	£0.29 (Gamma)
Pharmacotherapy costs – SoC – BPS	£1.76	£0.18 (Gamma)
Pharmacotherapy costs – SoC – TPS	£3.41	£0.34 (Gamma)
Pharmacotherapy costs – SoC – Full dataset	£4.67	£0.47 (Gamma)
Primary care costs – 12 SQ-Bet	£41.98	£4.20 (Gamma)
Primary care costs – SoC	£109.62	£10.96 (Gamma)
Secondary care costs – 12 SQ-Bet	£149.40	£14.94 (Gamma)
Secondary care costs – SoC	£384.07	£38.41 (Gamma)
Annual GP visits – SoC	2.61	0.26 (Gamma)
Annual GP visits – 12 SQ-Bet relative reduction	61.7%	6.17% (Beta)
GP visit cost	£42.00	£4.20 (Gamma)
Annual outpatient visits – SoC	1.93	0.19 (Gamma)
Annual outpatient visits – 12 SQ-Bet relative reduction	61.1%	6.11% (Beta)
Outpatient visit cost	£199.00	£19.90 (Gamma)
Proportion of AEs requiring management – SoC	15.04%	1.50% (Beta)
Proportion of AEs requiring management – 12 SQ-Bet	18.52%	1.85% (Beta)
AE management cost	£42.00	£4.20 (Gamma)
Section 3.4 Health-related quality of life		
Utility gain – BPS	0.0300	0.008 (Beta)
Utility gain – TPS	0.0190	0.006 (Beta)
Utility gain – Full dataset	0.0180	0.006 (Beta)
Section 3.3 Clinical parameters and variables		
Time on treatment prior to discontinuation due to AEs (days)	30.44	3.04 (Normal)
Proportion discontinuing due to AEs	7.50%	0.75% (Beta)
Time on treatment prior to treatment discontinuation (days)	182.63	18.26% (Normal)
Treatment discontinuation Year 1	4.38%	0.44% (Beta)
Treatment discontinuation Year 2	4.38%	0.44% (Beta)
Treatment discontinuation Year 3	4.38%	0.44% (Beta)
Discontinuation benefit Year 1	50.00%	5.00% (Beta)
Discontinuation benefit Year 2	50.00%	5.00% (Beta)
Discontinuation benefit Year 3	50.00%	5.00% (Beta)
Proportion of patients who are retreated at Year 10	5.00%	0.50% (Beta)

Abbreviations: AE, adverse event; BPS, birch pollen season; SE, standard error; SoC, standard of care; TPS, tree pollen season.

3.9.2 Assumptions

Model input	Description of assumption	Justification
Discontinuation	It is assumed that a proportion of people who discontinue treatment in Year 1, 2, or 3, may continue to receive the benefit associated with 12 SQ-Bet. In the base case, 50% of patients who discontinue treatment with 12 SQ-Bet may continue to receive treatment benefit.	Consistent with assumptions used in a previous appraisal for an AIT (TA834). During an advisory board, it was noted that patients who discontinue AIT treatment early may still receive treatment benefit (Appendix J5).
Long-term treatment effectiveness	In the base case, to reflect the improving treatment effect observed in the REACT study, the proportion of patients in the 12 SQ-Bet arm receiving treatment benefit increases by 2.5% in each model cycle up to Year 10. Treatment waning starts at 15 years, and by Year 20, 80% of patients in the 12 SQ-Bet arm will have lost the treatment benefit. This waning effect impacts patient's pharmacotherapy costs, primary and secondary care costs, and QALYs. It is assumed that patients receiving established clinical management will remain stable during all years following Year 1.	These assumptions are based on the accepted assumptions in a previous appraisal (TA834) for an AIT (12 SQ-HDM). In a 2025 Delphi panel comprising five UK allergy experts, all participants stated that due to the similar mechanisms of action, and identical manufacturing and standardisation technology, the treatment waning effect for 12 SQ-HDM would be applicable to 12 SQ-Bet (Appendix J6). In TA834, clinical expert opinion and RWE sources were used to inform the waning assumptions.
Management costs	The number of visits to primary and secondary care is derived from the probabilistic Delphi panel. In the model, patients receiving the treatment benefit of 12 SQ-Bet have reduced primary and secondary care use, reflecting improvements in disease control.	All participants in the Delphi panel responded that they would anticipate a reduction in primary and secondary care appointments for patients with moderate to severe birch pollen-induced AR receiving the average treatment effect of 12 SQ-Bet compared to patients treated with symptomatic pharmacotherapy alone.
Utilities	The utility decrement applied in the SoC arm (associated with the treatment benefit of 12 SQ-Bet) is applied for 137 days in each yearly cycle.	The duration of treatment benefit in each cycle is aligned to the length of the full dataset in Dick *et al.*, 2019, (124) to capture the full benefit of 12 SQ-Bet. This included all days over which there was at least one EQ-5D response in each treatment arm, regardless of whether the pollen count of the respondent's region was above the threshold. A utility difference was observed across the full dataset period, likely due to the cross-reactivity of 12 SQ-Bet to different

Model input	Description of assumption	Justification
		members of the birch homologous group and the overlapping pollen seasons.
Utilities	It is assumed that any AE-related utility decrements are implicitly captured in the treatment-specific utilities used in the model base case.	The majority of AEs reported in TT-04 were considered mild or moderate. Furthermore, of the 8 TRAEs modelled, 7 had a median duration of 6 days or under, with mouth swelling having a median duration of 15 days. HRQoL data in the TT-04 trial were collected from treatment initiation. As such, any utility decrements associated with AEs will be implicitly captured in the average treatment-specific utility values.

Abbreviations: AE, adverse event; AR, allergic rhinitis; HDM, house dust mite; HRQoL, health-related quality of life; QALY, quality-adjusted life year; RWE, real-world evidence; SoC, standard of care; TRAE, treatment-related adverse event

3.10 Base case results

3.10.1 Base case incremental cost-effectiveness analysis results

The deterministic base case cost-effectiveness analysis results of 12 SQ-Bet compared with established clinical management for the treatment of birch pollen-induced AR over a lifetime time horizon are summarised in Table 51.

Table 51: Base case deterministic results

Parameter	12 SQ-Bet	SoC	Incremental	ICER
Total costs (£)	£9,486	£11,339	-£1,853	12 SQ-Bet dominant
Total life years	22.75	22.75	0.00	
Total QALYs	19.34	19.24	0.10	

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Treatment with 12 SQ-Bet compared with established clinical management alone was associated with 0.10 increased QALYs at an incremental cost of -£1,853 at list price, resulting in a dominant ICER. As such, treatment with 12 SQ-Bet is cost-effective at a willingness-to-pay threshold of £20,000/QALY. The incremental net monetary benefit (INMB) at a willingness-to-pay (WTP) threshold of £20,000/QALY is £3,877.

Table 52 provides a summary of the disaggregated costs.

Table 52: Disaggregated costs

	12 SQ-Bet	SoC	Incremental
12 SQ-Bet treatment and administration	£2,790.32	£0.00	£2,790.32
Pharmacotherapy	£79.26	£106.17	-£26.90
Primary care	£1,458.74	£2,494.04	-£1,035.30
Secondary care	£5,146.17	£8,738.24	-£3,592.07
Adverse events	£11.51	£0.97	£10.55
Total costs	**£9,486.00**	**£11,339.41**	**-£1,853.40**

Abbreviations: SoC, standard of care.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with key model inputs. PSA results for 2,000 iterations are presented in Table 53. The mean incremental costs and QALYs of 12 SQ-Bet compared with established clinical management alone were calculated to estimate the probabilistic ICER. The incremental costs and QALYs from the probabilistic analysis were comparable with the deterministic analysis.

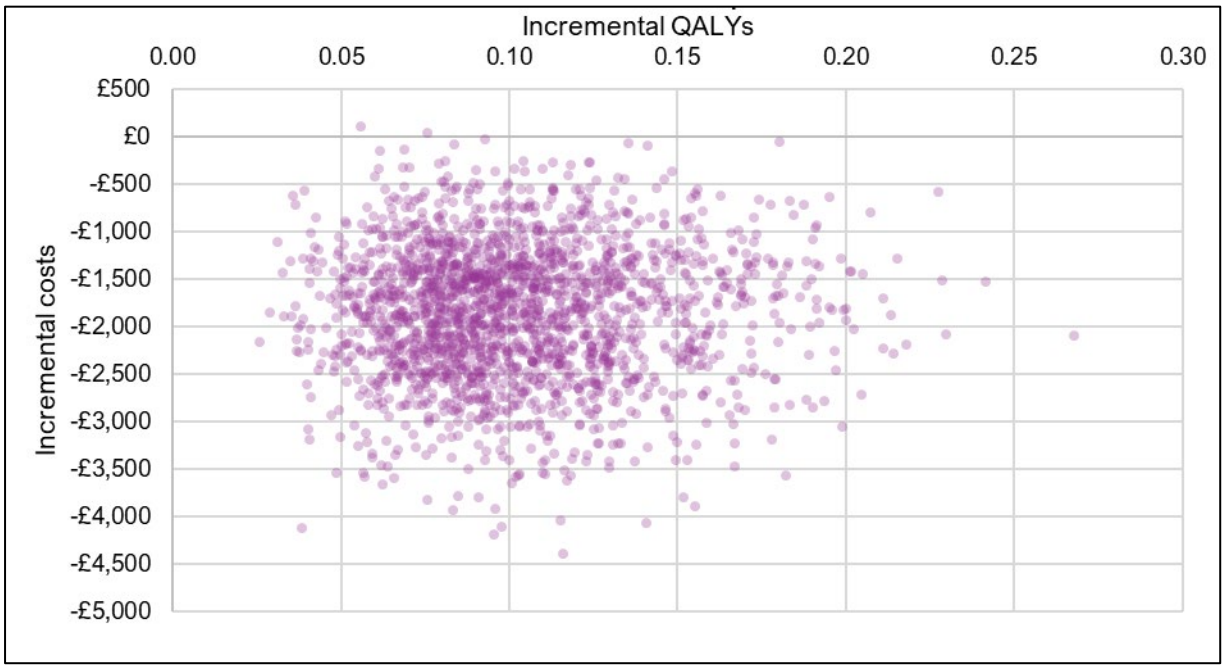
Table 53: Base case probabilistic results

	12 SQ-Bet	SoC	Incremental	ICER
Total costs	£9,449	£11,300	-£1,851	12 SQ-Bet dominant
Total life years	22.69	22.69	0.00	
Total QALYs	19.28	19.18	0.10	

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

The PSA scatter plot is shown in Figure 20. The ICER in the probabilistic analysis remained cost-effective with a dominant ICER in 100% of the iterations, and a probability of cost-effectiveness of 100% at a WTP threshold of £20,000/QALY.

Figure 20: Cost-effectiveness plane



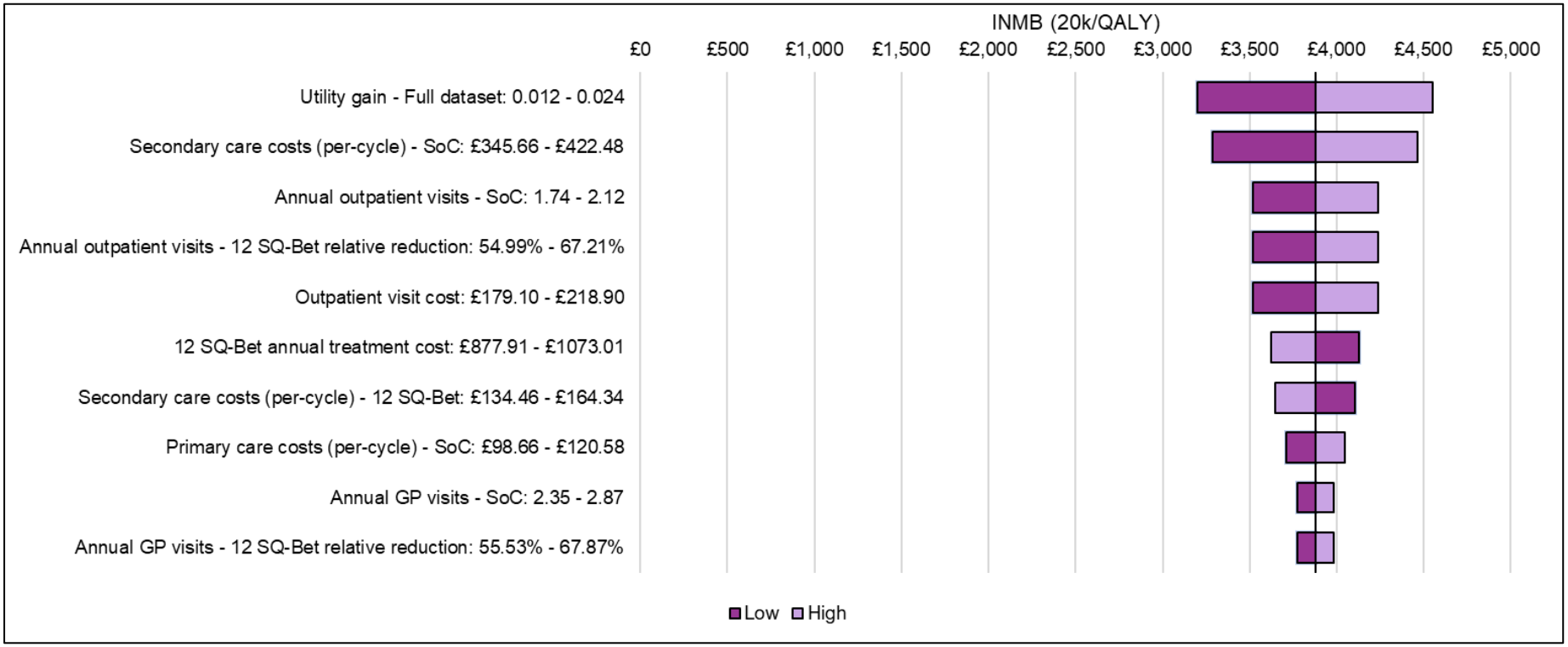
Abbreviations: QALY, quality-adjusted life year.

3.11.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs. The inputs with the greatest impact on the INMB are presented in descending order as a tornado plot in Figure 21.

In none of the varied parameters did the ICER or INMB exceed a WTP threshold of £20,000/QALY. The cost-effectiveness of 12 SQ-Bet is most sensitive to changes in secondary care costs as well as the treatment-specific utility difference associated with the treatment benefit 12 SQ-Bet.

Figure 21: Tornado plot of sensitive parameters in DSA



Abbreviations: INMB, incremental net monetary benefit; QALY, quality-adjusted life year; SoC, standard of care.

3.11.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. The details of the undertaken scenario analyses and the results, presented as the incremental costs, QALYs and cost-effectiveness ratio of 12 SQ-Bet compared with established clinical management alone, are shown in Table 54. In none of the scenarios did the ICER exceed a WTP threshold of £20,000/QALY.

Table 54: Scenario analysis

Scenario	Description	Incremental costs	Incremental QALYs	ICER
Base case deterministic results		**-£1,853**	**0.10**	**12 SQ-Bet dominant**
1	Time horizon In the model base case, a lifetime time horizon is used to reflect that AR is a chronic disease and expected to continue for the duration of a patient's lifetime. Results are presented using alternative time horizons.			
1.a.	**Time horizon: 10 years**	**£28**	**0.06**	**£458**
1.b.	**Time horizon: 20 years**	**-£1,382**	**0.09**	**12 SQ-Bet dominant**
2	Treatment waning In the base case, it is assumed treatment waning will start in Year 15, and by Year 20, 80% of patients in the 12 SQ-Bet arm will have lost treatment benefit. The following scenarios present the results assuming 100% loss of treatment effect after the first 15 and 20 years.			
2.a.	**100% loss of treatment benefit after 15 years**	**-£880**	**0.08**	**12 SQ-Bet dominant**
2.b.	**Full treatment benefit for 20 years (100% loss at year 20)**	**-£1,977**	**0.11**	**12 SQ-Bet dominant**
3	12 SQ-Bet treatment benefit following discontinuation To account for any potential treatment benefit achieved prior to discontinuation and sustained post discontinuation, a proportion of discontinued patients maintain the treatment benefit of 12 SQ-Bet. In the base case 50% of patients are assumed to experience benefits of 12 SQ-Bet following discontinuation. This scenario analysis presents the results using alternative proportions maintaining treatment benefit following discontinuation in cycles 1, 2, and 3.			
3.a.	**Proportion to receive 12 SQ-Bet benefit following discontinuation: 0%**	**-£1,552**	**0.09**	**12 SQ-Bet dominant**
3.b.	**Proportion to receive 12 SQ-Bet benefit following discontinuation: 100%**	**-£2,155**	**0.11**	**12 SQ-Bet dominant**
4	Relative reduction in secondary care visits			

Scenario	Description	Incremental costs	Incremental QALYs	ICER
	In the base case, the relative reduction in outpatient visits (61.1%) was informed by the probabilistic Delphi (Appendix J6). This scenario presents results using data from the REACT study which showed a reduction in hospitalisations for patients treated with AIT 9 years after treatment initiation, with an OR of 0.72 (95% CI: 0.54-0.98). (137)			
4.a.	**Source of relative reduction: REACT study**	**£93**	**0.10**	**£915**
5	Proportion of each cycle for which treatment benefit is applied In the base case it is assumed that the treatment benefit of 12 SQ-Bet lasts for the proportion of the year aligned with the length of the full dataset from Dick *et al.*, 2019 (137 days; mean daily utility difference: 0.018; annual QALY gain: 0.0068), to capture the full treatment benefit of 12 SQ-Bet. This scenario presents results using a different time period over which the utility gain is accrued, based on the mean utility differences in the BPS and TPS as defined in Dick *et al.*, 2019. (124)			
5.a.	**Treatment benefit accrued for 100 days per cycle (TPS, as defined in Dick *et al.*, 2019) – mean daily utility difference: 0.019; annual QALY gain: 0.0052**	**-£1,846**	**0.08**	**12 SQ-Bet dominant**
5.b.	**Treatment benefit accrued for 42 days per cycle (BPS, as defined in Dick *et al.*, 2019) – mean daily utility difference: 0.030; annual QALY gain: 0.0035**	**-£1,837**	**0.05**	**12 SQ-Bet dominant**
6	Retreatment In the base case, it is assumed that 5% of patients are retreated with 12 SQ-Bet after 10 years. This scenario presents results for different assumptions regarding the proportion of patients who would be retreated.			
6.a.	**Proportion retreated: 0%**	**-£1,786**	**0.10**	**12 SQ-Bet dominant**
6.b.	**Proportion retreated: 20%**	**-£2,056**	**0.11**	**12 SQ-Bet dominant**
6.c.	**Proportion retreated: 50%**	**-£2,460**	**0.14**	**12 SQ-Bet dominant**

Abbreviations: AIT, allergy immunotherapy; AR, allergic rhinitis; BPS, birch pollen season; ICER, incremental cost-effectiveness ratio; OR, Odds Ratio; QALY, quality-adjusted life year; TPS, tree pollen season.

3.12 Subgroup analysis

No subgroups were considered in the cost-effectiveness analysis.

3.13 Benefits not captured in the QALY calculation

As previously discussed, individuals with moderate to severe SAR had greater odds of and missing days at work due to SAR, as well as experiencing impaired productivity compared to patients with mild SAR (64). This wider societal impact of SAR may result in additional reductions in health-related outcomes that are unlikely to be directly included in the QALY calculation.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Technical validation of the model was conducted based on the TECH-VER checklist, which is included as a sheet in the model. (191) Overall, the validation identified no issues with the structural or computational accuracy of the model.

3.15 Interpretation and conclusions of economic evidence

The cost-effectiveness of 12 SQ-Bet compared with established clinical management for treating birch pollen-induced AR has been evaluated in line with the NICE final scope.

A simplified Markov model was constructed to calculate lifetime costs and QALYs for treatment with 12 SQ-Bet compared with established clinical management. The model comprised two core health states: alive and dead, and differences in costs and QALYs were modelled as treatment-specific, occurring only within the alive health state. The treatment effect of 12 SQ-Bet was applied as a treatment-specific utility difference between the two arms, with the utility gain associated with 12 SQ-Bet applied as a utility decrement in the SoC arm. This data was derived from a mapping study that generated EQ-5D health state utilities from clinical data collected in the TT-04 trial, using an estimation dataset from a similar trial in grass pollen-induced AR. (124)

Costs associated with the treatment and management of patients with AR were modelled, including pharmacotherapy costs, and costs associated with GP and outpatient visits. All unit costs were identified from UK sources, including NHS reference costs, the BNF, and EMIT drug costs databases.

In the base case, treatment with 12 SQ-Bet compared with established clinical management alone was associated with 0.10 increased QALYs at an incremental cost of -£1,853 at list price, resulting in a dominant ICER. The ICER in the probabilistic analysis remained cost-effective with a dominant ICER in 100% of the iterations, and a probability of cost-effectiveness of 100% at a WTP threshold of £20,000/QALY. Furthermore, extensive scenario analyses demonstrated the base case cost-effectiveness results to be robust to variation in model inputs and assumptions, with none of the scenarios resulting in an ICER that exceeded a WTP threshold of £20,000/QALY. Deterministic sensitivity analysis demonstrated the results to be sensitive to changes in secondary care costs as well as the treatment-specific utility difference associated with the treatment benefit 12 SQ-Bet.

In summary, the results of this analysis demonstrate that 12 SQ-Bet represents a cost-effective use of NHS resources for treating birch pollen-induced AR with a dominant ICER compared to established clinical management.

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Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report	Appendix A1.1 ITULAZAX SmPC Appendix A1.2 ITULAZAX UK public assessment report Appendix A1.3 ITULAZAX Patient information leaflet
Appendix B: Identification, selection and synthesis of clinical evidence	Included in separate folder 'Appendix B'
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Appendix E: Published cost-effectiveness studies	Included in separate folder 'Appendix E'
Appendix F: Health-related quality of life studies	Included in separate folder 'Appendix F'
Appendix G: Cost and healthcare resource identification, measurement and valuation	Included in separate folder 'Appendix E'
Appendix H: Clinical outcomes and disaggregated results from the model	Included in separate document 'Appendix H'
Appendix I: Price details of treatments included in the submission	Included in separate document 'Appendix I'
Appendix J	Appendix J1: ARD treatment pathway Clinician opinion and consensus report (May 2023) Expert elicitation and evidence generation

Appendix J2: Advisory board meeting report

Appendix J3: ARD survey report

Appendix J4: - ALK Ireland Delphi panel report

Appendix J5: Respiratory advisory board report

Appendix J6: Probabilistic Delphi panel report

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

1.1 SmPC

Please see the separate document ‘Appendix A1.1’.

1.2 UK public assessment report

Please see the separate document ‘Appendix A1.2’.

Appendix B: Identification, selection and synthesis of clinical evidence

1.1 Identification and selection of relevant studies

Included in ‘Appendix B’.

1.2 Participant flow in the relevant randomised controlled trials

Included in the full submission, see Section 2.4.3.

1.3 Critical appraisal for each study

Included in ‘Appendix B’.

Appendix C: Subgroup analysis

The Statistical Analysis Plan for the TT-04 trial pre-specified a subgroup analysis of average TCS during the BPS with respect to the age groups adults (18-65 years) and adolescents (12-17 years). The data has not been included in this submission as adolescent subjects were only included in the polish sites of the TT-04 trial, the adolescent population was small, there was no statistical difference in treatment effect between the adult and adolescent populations, and the adolescent population is beyond the scope of this appraisal.

Appendix D: Adverse reactions

There are no other studies available that have data reporting on additional adverse reactions. Therefore, the only AEs of consideration are those reported in the TT-04 trial.

Appendix E: Published cost-effectiveness studies

Please see the folder ‘Appendix E’.

Appendix F: Health-related quality of life studies

Please see the folder ‘Appendix F’.

Appendix G: Cost and healthcare resource identification, measurement and valuation

Included in ‘Appendix E’.

Appendix H: Clinical outcomes and disaggregated results from the model

Please see the separate document ‘Appendix H’.

Appendix I: Price details of treatments included in the submission

Please see the separate document ‘Appendix I’.

Appendix J1: ARD treatment pathway Clinician opinion and consensus report (May 2023)

Please see ‘Appendix J1’.

Appendix J2: Advisory board meeting report

Please see the separate folder ‘Appendix J2’.

Appendix J3: ARD survey report

Please see ‘Appendix J3’.

Appendix J4: - ALK Ireland Delphi panel report

Please see ‘Appendix J4’.

Appendix J5: Respiratory advisory board report

Please see ‘Appendix J5’.

Appendix J6: Probabilistic Delphi report

Please see the separate folder ‘Appendix J6’.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Betula verrucosa (ITULAZAX 12 SQ-Bet) for treating moderate-to-severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen [ID6462]

Summary of Information for Patients (SIP)

February 2025

File name	Version	Contains confidential information	Date
ALK Abello_ Summary of Information for Patients_ITULAZAX 12 SQ-Bet	Final	No	04/02/25

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: 12 SQ-Bet oral lyophilisate (12 SQ-Bet) Brand name: ITULAZAX®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population will match directly with 12-SQ-Bet's approved use: 12 SQ-Bet is approved for the treatment of adult patients with moderate to severe allergic rhinitis and/or allergic conjunctivitis (eye inflammation) caused by pollen from the birch homologous group (pollen from trees related to birch). These individuals have a history of symptoms that don't improve with standard allergy medications and have tested positive for sensitivity through a skin test or blood test (specific IgE). The trees that are considered part of the birch homologous group includes birch, alder, hornbeam, hazel, oak, and beech. (Appendix A1.1)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is a licence needed to sell a medicinal product on the market and sets out the conditions for use of a drug based on evidence of its safety and effectiveness. 12 SQ-Bet has received marketing authorisation on 9th June 2021 from the Medicines and Healthcare products Regulatory Agency (MHRA), which oversees the approval process in the UK. (Appendix A1.2)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

ALK Abello have no UK specific collaborations or conflicts of interest with any patient groups relevant to 12 SQ-Bet.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Main conditions that the medicine plans to treat: allergic rhinitis (AR), is an allergic reaction triggered by allergens such as pollen, dust mites, mould, or pet dander. Allergic rhinitis is a common and burdensome condition, estimated to affect 11.3 million people within the UK, with approximately 3.4 million of these being sensitive to tree pollen. (Appendix J1) An allergic reaction happens when the immune system in someone who is sensitive to certain things such as pollen, certain foods, or pet dander, overreacts and treats them as harmful. The body tries to protect itself by releasing chemicals like histamine, which can cause symptoms such as itching, sneezing, a runny nose, swelling, or more serious problems like difficulty breathing. AR refers to this kind of allergic reaction that specifically affects the nose and sinuses, causing symptoms like a stuffy, runny, or itchy nose, and sneezing. (1) The nasal (nose) symptoms of AR can also be accompanied by allergic conjunctivitis (eye symptoms), or allergic conjunctivitis can occur on its own. Allergic conjunctivitis is a condition describing the eye-related symptoms that occur when an allergic reaction takes place. These symptoms are triggered when the clear layer covering the white part of your eye and the inside of your eyelids becomes irritated or inflamed, making your eyes look red, feel itchy, go puffy and watery, and produce a sticky discharge. (1) 12 SQ-Bet aims to treat both allergic rhinitis and/or allergic conjunctivitis that is triggered by the allergic reaction to birch pollen from trees. **Impact:** People who have allergic rhinoconjunctivitis (ARC) triggered by birch pollen allergen from trees can experience a wide range of symptoms. ARC symptoms can depend on what specific allergens

you're exposed to, how sensitive you are to them, and where in your airways the reactions occur. (2-4)

12 SQ-Bet aims to treat individuals with moderate to severe symptoms. This means that individuals experiencing one or more of the following: symptoms that are hard to manage, affected sleep, difficulty with taking part in school or work, or daily activities, leisure, and/or sport. Consequently, patients have a reduced quality of life (QoL), struggle with their mental health and need to visit their healthcare provider more regularly. (5) (6-9)

ARC often occurs alongside other allergic disease conditions, including allergic asthma, eczema, food allergies, and severe allergic reactions known as anaphylaxis. While ARC mainly affects the nose and eyes, it can also lead to other problems, including nasal and ear infections, non-cancerous growths in the nose or sinuses, loss of smell, and inflammation in the throat or oesophagus (the tube that carries food from your mouth to your stomach). (10) Pollen food syndrome is a common issue for people with birch pollen allergies, affecting about 73% of those with birch pollen-induced AR. It occurs when someone allergic to pollen reacts to certain raw fruits, vegetables, nuts, or seeds. Symptoms include itching in the lips, gums, tongue, and throat, often with swelling. (11-13)

Rhinitis and asthma are closely linked, as more than 80% of people with asthma also have AR. (5, 14, 15) When AR isn't controlled, it can make asthma symptoms worse. (14, 16) Allergic asthma causes symptoms like coughing, trouble breathing, chest tightness, and wheezing. Every year, around 1,541 people die from respiratory failure related to asthma. (17)

Pollen from trees in the birch family is the most common of all of the allergenic trees across most parts of Europe. (18, 19) The tree pollen season (TPS) can start as early as December in Europe, with hazel and alder trees releasing pollen from December to April, meaning the allergy symptoms can last for a large portion of the year. (20, 21)

Therefore, a treatment that targets the immune response to birch pollen allergens can help reduce symptoms, build up tolerance to the allergens, prevent the condition from getting worse, and improve the quality of life for patients.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The ARC treatment pathway in the UK initially consists of self-care and/or pharmacy treatments, followed by some patients visiting their doctor. (1)

Patients are mostly diagnosed with ARC based on their medical history. If the patients' medical history is unclear, further tests may be carried out. This most commonly takes the form of skin prick testing and blood tests to check allergy antibodies.

For more complex cases, a detailed diagnosis, including identifying specific allergens, is done in specialised care. This involves a combination of medical history, FeNO testing, skin prick tests, and/or blood tests (IgE). (Appendix J1)

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The treatment pathway for allergic rhinitis in the UK is based on the British Society for Allergy and Clinical Immunology (BSACI) rhinitis treatment guideline. (22)

If someone is diagnosed with AR, they're usually advised to avoid allergens. For pollen allergies, this might mean making some lifestyle changes, such as avoiding walking in grassy areas, staying indoors during the morning or evening when pollen is highest, keeping windows closed, planning vacations to avoid the pollen season, and washing hair every night to remove pollen. (1, 22) For patients with mild-to-moderate intermittent, or mild persistent symptoms, the first treatment option is usually oral or nasal antihistamines. For patients with moderate to severe persistent symptoms, or those for whom initial treatment is not working, intranasal corticosteroids (medications that are sprayed into the nose to help reduce inflammation) are recommended. If symptoms still don't improve, doctors may suggest using a combination of treatments, like oral antihistamines with nasal corticosteroids, or nasal corticosteroids with nasal antihistamines. If these treatments don't work, doctors might consider adding other therapies, depending on the ongoing symptoms. (1, 22) Some of the recommended treatments such as systemic corticosteroids, intranasal decongestants, Leukotriene receptor antagonists, ipratropium are rarely used because of their potential side effects. (Appendix J1 and J6)

the BSACI guidelines recommend considering allergy immunotherapy (AIT) for AR in patients with a seasonal pollen allergy if their symptoms don't improve, even with strong medications like nasal corticosteroids and antihistamines. (22) The ARIA guidelines also recommend AIT for patients with allergic rhinitis, conjunctivitis, or asthma caused by allergens, especially if their symptoms don't improve enough during allergy season, even with proper medication. (23)

Current treatments for ARC don't address the root cause of the condition, so they don't provide long-lasting or complete relief from symptoms. This can leave patients feeling unsatisfied, especially those with moderate to severe symptoms. For these patients, the symptoms often come back or are consistently present having a large impact on their daily life and overall well-being. (24-26)

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers

and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Even with proper use of current treatments, a portion of people with moderate to severe allergic respiratory disease (ARD) still have uncontrolled symptoms. Around 36% of people with moderate allergic rhinitis, and 45% with severe allergic rhinitis still have uncontrolled disease, leading to low satisfaction with current treatments. (Appendix J1) There is a clear need for better treatment options for these patients. Despite following treatment guidelines, 59-66% of ARD patients are unhappy with how their symptoms are being managed. (24)

AR symptoms can greatly affect sleep, which is a key concern for allergy sufferers. Two surveys in Europe found that most patients with AR reported not getting enough sleep or not feeling rested when they woke up. (27, 28) These results are supported by studies in the US and Spain. (29) (30) The US study showed that people with AR were more likely to have poor sleep quality, struggling to fall asleep or dealing with issues like insomnia, sleep apnoea (a condition where a person temporarily stops breathing while asleep), or needing sleep medication. People with AR also reported waking up too early, not getting enough rest, and feeling tired during the day, which affected their daily activities. (29) The Spanish study found that during the pollen season, people with AR had more sleep problems, snoring, and even trouble breathing when they woke up. (30)

AR can have a moderate to severe emotional impact, driven by feelings of tiredness, irritability, and poor concentration. (27, 28, 31) For example, 31% of patients with AR reported that tiredness/feelings of being worn out had a moderate impact on their life, and 22% felt that the impact was severe. (27) Other emotional effects of AR include nervousness/anxiety, sadness/depression, discomfort, stress, and a loss of motivation. (27, 28, 32)

A large proportion of individuals report that AR has a moderate to severe impact on aspects of their social life, such as going out with friends and visiting friends' houses. AR can also influence an individuals' choice of daily activity; approximately 33% of AR patients reported that their condition impacts their ability to take part in outdoor activities. (8, 27)

The symptoms of AR can have a negative effect on work activities and productivity, as supported by various patient surveys. (28, 31) In the European Allergy Disease-Specific Programme, a high number of individuals with AR (79%) reported that their symptoms had a large impact on their work/school performance over a 7-day period. (28) This finding is supported by data from a Spanish survey in which 72.7% of people with AR reported that their symptoms significantly affected their performance at work or school. (31)

For working individuals, symptomatic AR can affect their professional development, through days missed from the workplace, with an average of 4.1 days absent per AR patient per year (33-35), or as a result of performing with a reduced work capacity. (27, 28, 31, 32) A US study has shown that individuals with AR were twice as likely to have difficulties at work compared to those without AR. (29) The European Patient Voice Allergy Survey found that 36% of working respondents felt their work activities were frequently impacted by AR, while 13% reported that their work was affected

all of the time by their disease. (32) A large online survey conducted in the US showed that nasal congestion affected 59% of respondents at work, through difficulty concentrating (42%) or poor productivity (36%). (32)

The combined effects of physical, emotional, and social impairments from AR led to a lower quality of life for those with AR, often causing mental health concerns. (6-9) Studies show that AR is linked to a lower quality of life, and this worsens as the disease becomes more severe.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a Summary of Product Characteristics or patient information leaflet, please provide a link to these.

12 SQ-Bet is an AIT that takes the form of a sublingual (dissolves under the tongue) tablet. As an AIT, 12 SQ-Bet is a treatment that helps your body get used to allergens (such as pollen, pet dander, or dust) over time. It involves taking regular tablets that contain a large amount of the birch pollen allergen, gradually increasing the level of the allergen in your body. This helps the immune system to build up a tolerance, so that the individual will experience fewer allergy symptoms in the long run. It's a way to "train" the body to react less to things that trigger a patient's allergies. (Appendix A1.1)

Unlike current treatments, 12 SQ-Bet is able to treat the root cause of birch pollen allergic disease unlike other treatments that just relieve the symptoms; 12-SQ-Bet aims to modify a patient's immune response to birch pollen allergens. This effect has been demonstrated through 12 SQ-Bet increasing the production of IgG4 antibodies (antibodies specific to birch pollen allergens), which in turn block IgE antibodies from triggering an allergic response in the immune system.

A clinical effect has been demonstrated for 12 SQ-Bet in the upper airways but there is also some evidence of protection in the lower airways. The protection provided by 12 SQ-Bet leads to better disease control and an improved quality of life with symptom relief, less need for other medications, and a reduced risk for allergy flare-ups. (Appendix A1.1)

International guidelines for AIT suggest a treatment period of 3 years to see long-term changes in the disease after treatment stops. If no improvement is seen within the first year of treatment with 12 SQ-Bet, the treatment can be stopped. (Appendix A1.1)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

12 SQ-Bet is to be used as an add-on to current treatments (used in addition to other treatments). (Appendix A1.1)

12 SQ-Bet is an aetiological treatment (meaning it treats the root cause of a problem) that aims to modify a patient's immune response to the birch pollen allergen, as opposed to current treatments which aim to only treat the symptoms of birch pollen allergic disease. (Appendix A1.1)

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

12 SQ-Bet treatment should only be started by a doctor who has experience in treating allergic diseases. (Appendix A1.1)

The first dose should be taken under the supervision of a doctor, who will monitor the patient for at least 30 minutes to assess for any immediate side effects. 12 SQ-Bet is a tablet that dissolves under your tongue. The recommended dose for adult patients is one tablet daily. (Appendix A1.1)

It is recommended that 12 SQ-Bet treatment is started at least 16 weeks before the start of the TPS and continued throughout the season. (Appendix A1.1)

International treatment guidelines refer to a treatment period of 3 years for AIT to achieve disease modification. If no improvement is observed during the first year of treatment with 12 SQ-Bet then there is no need for treatment to be continued. (Appendix A1.1)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Table 1 outlines the clinical trial programme for Phase 2 and Phase 3 trials for 12 SQ-Bet. They include:

TT-04:

The TT-04 trial is the key Phase 3 trial investigating the safety and effectiveness of 12-SQ-Bet in patients with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from trees in the birch (or birch-related) group. (36)

This trial was random, meaning some participants received the treatment while others got a placebo (a non-active treatment), and it took place in multiple locations internationally. The trial lasted between 6.5 to 9.5 months, starting 16 weeks before the TPS. Patients were checked at the start of the pollen season, two weeks before it started, and at the end of the season. (36)

Before the pollen season, patients were given medications to help manage their symptoms. These included common treatments like antihistamines (for allergies), nasal sprays (to reduce swelling in the nose), and eye drops (to relieve itching and redness). Participants were allowed to use these treatments during the trial.

TT-03:

The TT-03 trial was a Phase 2 study that tested different doses of the SQ® tree sublingual immunotherapy (SLIT)-tablet in people with moderate to severe allergic rhinitis and conjunctivitis (ARC) caused by tree pollen. Similar to TT-04 trial, it was also a randomised, double-blind, placebo-controlled study, meaning some participants received the treatment, while others got a placebo, and neither group knew which one they were getting. The trial took place at multiple centres and involved controlled exposure to tree pollen. (37)

The main goal of the study was to show that the SQ® tree SLIT-tablet, at doses of 2, 7, and 12 dose units (DU), worked better than the placebo in treating birch pollen-induced ARC. The study lasted for 24 weeks. (37)

TT-02:

The TT-02 trial was a Phase 2 study designed to test different doses of the SQ-Bet tablet in adults and adolescents with moderate to severe allergic rhinitis and conjunctivitis (ARC) caused by birch pollen. It was randomised, parallel-group, double-blind, placebo-controlled study that took place in multiple locations to evaluate the dose response of the SQ-Bet tablet in doses 0.5, 1, 2, 4, 7, and 12. The main goal of the study was to find the best dose of the SQ-Bet tablet in terms of effectiveness and safety for treating birch pollen-induced ARC. The trial started 16 weeks before the birch pollen season (BPS) began and continued for at least 6 months after participants were randomly assigned to a treatment group. (38)

Table 1: Clinical trial programme for 12 SQ-Bet

Study name	Intervention(s), comparator(s) and dosing	Patient group size and location	Key selection criteria
TT-04 (36, 39-41)	**Intervention:** 12 SQ-Bet **Comparator:** Placebo **Treatment duration:** between 6½ months and 9½ months for subjects completing the trial	**Patient group size:** 634 subjects with moderate to severe ARC despite use of symptom-relieving medication were randomised **Location:** EU and Russia	- Adults (18–65 years) and adolescents (12–17 years) in Poland with moderate to severe allergic rhinitis and/or conjunctivitis caused by tree pollen, with or without controlled asthma, despite allergy treatment in the past two pollen seasons. - Participants had at least one ARIA QoL issue (e.g., sleep disturbance or impaired daily activities) - A positive skin prick test for birch extract, and IgE (proof of antibodies) against Bet v 1 (birch pollen allergen) - Patients can't have had a severe asthma attack or uncontrolled asthma in the past 3 months

TT-03 (42)	**Intervention:** SQ® tree SLIT-tablet (2, 7, and 12 DU) **Comparator:** Placebo **Treatment duration:** 24 weeks	**Patient group size:** 219 subjects were randomised to receive either active treatment (n=163) or placebo (n=56) **Location:** EU	- Male or female aged 18 to 65 years. - A history of moderate to severe rhinoconjunctivitis induced by pollen from the birch group with or without asthma despite having received treatment with symptom-relieving medication during the previous two tree pollen seasons. - Positive specific IgE against Bet v1 (≥ IgE Class 2; ≥0.70 kU/L) obtained at screening or a documented positive result obtained within 6 months before screening. - Minimum level of rhinoconjunctivitis symptoms, defined as a Total Symptom Score (TSS) of at least 7 (of 18) at one time point during the 6-hour birch baseline Environmental Exposure Chamber (a controlled environment where individuals can be exposed to specific allergens, such as birch pollen, under standardised conditions) session
TT-02 (43)	**Intervention:** SQ® tree SLIT-tablet (0.5, 1, 2, 4, 7, and 12 DU) **Comparator:** Placebo **Treatment duration:** 16 weeks prior to the onset of the birch pollen season until ≥6 months after randomisation	**Patient group size:** 637 patients were randomised **Location:** EU	- Male or female aged 12-65 years with moderate to severe birch pollen-induced allergic rhinoconjunctivitis (with or without asthma), with symptoms despite having received pharmacotherapy during the birch pollen seasons 2011 and 2012 - A total daily symptom score of at least 8 on the worst day in the previous birch pollen season - Participants had at least one ARIA QoL issue (e.g., sleep disturbance or impaired daily activities) - No clinical history of uncontrolled asthma (according to GINA (GINA Executive Committee 2011)) within 3 months prior to randomisation - No reduced lung function, defined as FEV1<70% in adults or FEV1<80% in adolescents (of predicted value after adequate pharmacologic treatment)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

For a description of terms please refer to the glossary

The effectiveness and safety of 12 SQ-Bet for treating moderate to severe allergic rhinitis and conjunctivitis (ARC) caused by birch tree pollen was proven in the Phase 3 TT-04 trial. This trial compared 12 SQ-Bet with a placebo. The treatment's effectiveness was measured during two specific time periods; the BPS (which lasted about 24 days) and the TPS (which lasted about 50 days) at the trial locations. (36)

Reduction in rhinoconjunctivitis symptoms during the birch pollen season and the extended tree pollen season

The Total Combined Score is a sum of two scores: the allergic rhinoconjunctivitis daily symptom score and the allergic rhinoconjunctivitis Daily Medication Score. A lower Total Combined Score means that the person is likely to be using less medication and has better control over their symptoms. The Total Combined Score has been deemed the optimal endpoint for AIT trials for allergic rhinoconjunctivitis. (36)

In the TT-04 trial, the Total Combined Score was used as the main measure to see if the treatment worked during the BPS. 12 SQ-Bet showed a significant improvement in Total Combined Score during the birch pollen season (BPS), with a 40% better result compared to the placebo. This improvement was above the target difference of 20%, as recommended by the World Allergy Organisation, and also met the US Food and Drug Administration's requirement of a 15% difference to prove the treatment works. (36)

12 SQ-Bet also showed a 37% improvement in Total Combined Score during the TPS compared to the placebo. This means that patients using 12 SQ-Bet had better control over their symptoms and used less medication than those using the placebo, both during the BPS and the full TPS. Additionally, 12 SQ-Bet significantly reduced the daily symptom score, with a 36.75% improvement during the BPS and a 32.73% improvement during the TPS compared to the placebo.(36)

In the TT-04 trial, the effect of 12 SQ-Bet on allergy symptoms in patients with birch pollen-induced ARC was measured by tracking how many days during the BPS and TPS patients had mild or severe symptoms. During the birch pollen season, which lasted around 24 days, the number of days with severe symptoms dropped from 5.1 days with the placebo treatment to 2.7 days with 12 SQ-Bet. During the TPS, which lasted about 50 days, the number of severe days was reduced from 7.8 days with the placebo treatment to 4.6 days with 12 SQ-Bet. With 12 SQ-Bet, patients were half as likely to have a day with severe symptoms during the BPS, although they were more likely to experience mild symptoms. Similar results were observed during the TPS. (36)

Additionally, patients were asked to rate how severe their symptoms were using a scale that lets them choose a point between 'no symptoms' and the 'worst possible symptoms', this is known as a visual analogue scale. The average symptom scores were significantly lower for patients using 12 SQ-Bet compared to the placebo, showing a 32.37% improvement during the BPS and a 29.63% improvement during the TPS. This indicates patients' ARC is less severe and their symptoms are being better controlled with 12 SQ-Bet treatment. (36)

Patients also rated their overall improvement in symptoms using a survey. A higher percentage of patients on 12 SQ-Bet (91.06%) reported feeling 'improved' compared to those on the placebo treatment (71.71%). (36)

Reduction in medication use

As mentioned before, the Total Combined Score considers how much medication patients used during the trial by calculating their Daily Medication Score. Each dose of allergy medication was given a score to track how much medication patients needed. The results showed that patients treated with 12 SQ-Bet needed significantly less allergy medication. During the BPS, medication use was reduced by 49.20% relative to the placebo group. Similarly, during the extended TPS, medication use was reduced by 46.71% compared to the placebo group. This demonstrates that 12 SQ-Bet helped patients rely less on additional allergy treatments. (36)

The Real-World Effectiveness in allergy immunotherapy (REACT) study looked at how well AIT works over time by using health data from a German insurance database between 2007 and 2017. The study compared 46,024 people with AR who received AIT treatment to a matched group of people who didn't receive AIT. The study found that people treated with AIT had a greater reduction in the number of prescriptions for their AR condition compared to those who weren't treated. This was true across different groups of patients, with SLIT-tablet users seeing the biggest reduction in prescriptions. (44)

Improvement in patient asthma control
Uncontrolled ARC can increase the risk of asthma flare-ups. During the TT-04 trial the effect of 12 SQ-Bet on asthma was explored. Patients were asked questions about their asthma symptoms and how much asthma medication they used to understand the treatment's impact. Overall, the asthma daily symptom score was low (~1 on a scale from 0-12) both in subjects with a history of asthma and in general for all subjects assessed during the BPS. 12 SQ-Bet reduced asthma symptoms by 29.3% during the BPS and by 24.2% during the TPS relative to placebo. In general, asthma control was good throughout the trial, as shown by high average scores on the Asthma Control Test. Patients in the 12 SQ-Bet group had higher Asthma Control Test scores during the birch pollen season than those in the placebo group, suggesting better asthma control. (36)

Improvement in pollen food syndrome symptoms
In the TT-04 trial, 124 participants took part in an apple challenge to assess their pollen food syndrome symptoms. Before the challenge, pollen food syndrome symptoms were similar in both treatment groups. However, a larger percentage of people in the 12 SQ-Bet group reported improvement in their pollen food syndrome symptoms compared to those in the placebo group (86.89% vs. 63.93%). When asked about the overall effectiveness of the treatment, more participants in the 12 SQ-Bet group felt their symptoms improved (87% vs. 64%). Although both groups showed low scores on the food allergy quality of life and food allergy impact measures (indicating food allergies didn't greatly affect their daily life), there were no significant differences between the groups when these scores were measured 30 days after the challenge. (36, 40)

Limitations of the clinical evidence base
The TT-04 trial had some limitations. One challenge was the small number of participants who were exposed to the treatment, and that the treatment duration was less than a year, which could have reduced the chances of detecting rare side effects or those that might appear later. The trial also couldn’t capture the full three years of treatment recommended in clinical guidelines, nor did it provide follow-up data after treatment stopped or long-term results for 12 SQ-Bet beyond the first treatment season. However, unlike symptom-relieving medications, AIT is known to have the potential to treat the root cause of allergies and modify the disease. Additionally, other trials with similar treatments for seasonal allergies, such as the SQ grass SLIT-tablet, did not find long-term side effects after three years of use. (45, 46)

Immunotherapy trials can also be affected by the placebo effect, where people feel better simply because they believe they are receiving treatment. In this trial, the placebo group, like the 12 SQ-Bet group, had access to certain medications to relieve symptoms. The placebo effect, along with natural changes in symptoms over time and the Hawthorne effect (where people change their behaviour because they know they are being observed), can make it harder to definitively determine how well the treatment works.

Conclusion
The TT-04 trial shows that 12 SQ-Bet significantly reduces the use of symptomatic medications and improves patient symptoms and quality of life in adult patients with moderate to severe birch pollen-induced ARC compared to placebo. The trial also demonstrated that 12 SQ-Bet provided additional benefits over typical allergy medications, as patients were allowed to use symptom-relieving drugs during the pollen seasons. The results from TT-04 showed the highest effectiveness seen so far in an allergy treatment trial, observed both during the BPS and throughout the entire TPS. Real-world evidence from the REACT study further supports the long-lasting treatment effect of 12 SQ-Bet extending beyond the end of treatment. Patients treated

with AIT had consistently greater reductions compared to control subjects in both asthma and AR prescriptions. This positive treatment effect was maintained over the nine years of the study.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

One of the main goals of treatment is to help people maintain or improve their quality of life. The Rhinoconjunctivitis Quality of Life Questionnaire is a helpful tool that looks at how allergies affect a person's daily life. It asks questions about how severe symptoms are and how they impact activities, sleep, and general well-being. (36)

In the TT-04 trial, patients' quality of life was assessed using this questionnaire during the TPS. The results showed that treatment with 12 SQ-Bet significantly improved symptoms, with a 31% reduction in the overall impact of patient symptoms on quality of life during the BPS, and a 28% reduction during the TPS. This means patients felt better and experienced less disruption to their daily lives with 12 SQ-Bet treatment. (36)

Further analysis showed that 12 SQ-Bet provided even more benefits compared to a placebo in areas like daily activities, sleep, nasal and eye symptoms, emotional well-being, and practical issues. This was true throughout both pollen seasons (BPS and TPS). (47)

The trial also tracked how many sick days patients took during the pollen seasons. The group treated with 12 SQ-Bet had fewer sick days than those on the placebo, with a significant difference in both the BPS and TPS. While the number of sick days was generally low for all participants, the placebo group took more sick days than those treated with 12 SQ-Bet. (36)

For people with moderate to severe AR, work and daily activities can be greatly impacted by their disease. 12 SQ-Bet helped reduce the impact of allergies on work performance and productivity during both the birch and tree pollen seasons, significantly improving the quality of life for patients. (36)

For a description of terms please refer to the glossary

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The TT-04 trial along with other trials that investigated 12-SQ-Bet have shown that 12 SQ-Bet treatment is well tolerated, with no major safety concerns. (36) The safety of 12 SQ-Bet was

consistent with that of other SLIT-tablets that are used to treat house dust mite allergy and grass pollen allergy.

The TT-04 trial looked at different safety outcomes to understand any negative effects of the treatment being tested. The study checked for common side effects (adverse events), serious side effects, side effects related to the treatment, and side effects that caused people to stop treatment. It was found that the most frequently reported treatment-related side effects were mild or moderate local reactions related to tablet treatment administration. The rate of patients stopping treatment in the trial was similar between placebo and 12 SQ-Bet with more side effects occurring with 12 SQ-Bet compared to placebo that led to the patient stopping treatment. By the end of the trial 25 (8%) subjects in the 12 SQ-Bet group had stopped treatment due to side effects while 8 (3%) of subjects in the placebo group stopped treatment. (36)

Overall, 12 SQ-Bet showed a favourable safety profile and has shown to be well tolerated by adults with moderate to severe ARC induced by pollen from the birch homologous group. The safety data from the TT-04 trial supports using 12 SQ-Bet for daily at-home treatment after confirming that the patient can tolerate the initial dose, which is administered under medical supervision. (36)

For a description of terms please refer to the glossary

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

At-home administration: The safety data from the TT-04 trial supports using 12 SQ-Bet for daily at-home treatment after confirming that the patient can tolerate the initial dose, which is administered under medical supervision. Being able to take 12 SQ-Bet at home may make it easier for patients to stick to their treatment plan, especially when compared to other AIT treatment options like subcutaneous immunotherapy (SCIT), which requires multiple injections and frequent visits to a medical clinic for treatment. The convenience of administering 12 SQ-Bet at home could help improve patient compliance with their treatment.

Allergy symptom relief: 12 SQ-Bet offers relief from the symptoms of AR, helping alleviate discomfort and reduce the number of days patients report mild or severe symptoms. 12 SQ-Bet also offers relief from other allergic conditions such as allergic asthma and pollen food syndrome.

Long-lasting effect: 12 SQ-Bet may provide long-term benefits even after completing the treatment. This concept has been supported by clinicians that specialise in allergic disease.

Reduced need for other medications: Treatment with 12 SQ-Bet results in decreased reliance on other allergy medications, such as antihistamines, eye drops and nasal corticosteroids. This can be especially valuable as those medications may have long-term side effects.

Improvement in patients with moderate to severe ARC's quality of life during the birch pollen season and tree pollen season: Treatment with 12 SQ-Bet improves patients' quality of life by

reducing their symptoms, which in turn improves sleep, boosts productivity, and reduces the number of sick days needed.

Benefits of treatment with 12 SQ-Bet extends beyond birch trees specifically:
Due to the way the immune system reacts to similar proteins in different tree pollens, 12 SQ-Bet is not only effective during the BPS but also throughout the entire TPS, as shown in the clinical trials investigating 12 SQ-Bet. Cross-reactivity means that the immune system can recognise similar proteins from different allergens. Birch pollen has proteins that cause allergic reactions, and these proteins are similar to those found in other trees like alder, hazel, and oak. So, if you are allergic to birch pollen, you might also react to these other tree pollens. Since 12 SQ-Bet contains a small amount of birch pollen allergen, it helps the immune system become more tolerant, potentially reducing allergic reactions to birch and other similar tree pollens.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

When asked at a Delphi panel (a meeting with a group of experts who give their opinions on a specific topic, usually through multiple rounds of surveys or discussions), the majority of comments from allergy experts were positive about the effects of 12 SQ-Bet for patients. The main unmet need for patients with moderate to severe ARC was the lack of access to sublingual immunotherapy (SLIT e.g., 12 SQ-Bet) treatments in the UK. (Appendix J6) Additionally, the lack of accessible and well-resourced specialist services for moderate to severe ARC patients was flagged by allergy experts, with patient treatment currently dependent on the patient's postcode, the local health care service's capacity in terms of workforce, and availability of SLIT treatment in the service, which differs regionally. (Appendix J1)

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

It is proposed that 12 SQ-Bet be used alongside current symptomatic treatments for AR offered in the NHS. Data from the key clinical trial (TT-04) supports the idea that patients with moderate to severe AR have a greater response to treatment with 12 SQ-Bet (i.e., reduced symptoms, reduced medication use, and improved quality of life) than patients treated with placebo throughout the TPS. (36) Evidence from real-world studies also suggests that this effect is maintained up to nine years post-treatment, with no reduction in the treatment benefit over this time. (44)

An economic model was constructed to calculate the lifetime costs and benefits for treatment with 12 SQ-Bet compared with using current treatments alone. In the model, utility values are used to estimate a patient's state of health, with a utility value of '1' representing a valuation of perfect health, and a utility of '0' representing a valuation of death. A higher utility value was applied to patients receiving 12 SQ-Bet compared to current treatments alone, to reflect the greater response to treatment observed in the TT-04 trial (i.e., patients are in a better state of health with 12 SQ-Bet), with the difference in utility calculated based on the outcomes of the TT-04 trial. (48) This benefit is applied for the duration of the TPS in which patients are most likely to be experiencing symptoms.

Healthcare costs are applied in the model and include the cost of treatments, medical appointments and any diagnostic tests that may be required. For patients treated with 12 SQ-Bet, additional costs associated with a specific diagnostic test for allergen sensitivity, a medical appointment for starting treatment, and the costs of 12 SQ-Bet itself are included. Patients with moderate to severe AR are more likely to visit healthcare services and, as 12 SQ-Bet improves disease control and reduces symptoms, the resultant reduced number of healthcare visits results in cost savings. (Appendix J6)

Due to the lack of data, there is some uncertainty around the long-term effectiveness of 12 SQ-Bet. Evidence from real-world studies suggests that the treatment effect can last up to nine years, with no reduction in the treatment benefit over this time. (44) As such, the model assumes that the treatment benefit is maintained for the first ten years, with a gradual loss of treatment benefit beyond this period. This approach was confirmed with UK clinical experts. (Appendix J4 and J6) The uncertainty around the time at which treatment benefit begins to decrease, and the rate at which it does, is explored using different scenarios in the model.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Current treatments for ARC don't address the root cause of the condition, so they don't provide adequate or long-term relief from all the symptoms of ARC. This can leave patients feeling unsatisfied, especially those with moderate to severe symptoms. For these patients, the symptoms often come back or are constantly present having a large impact on their daily life and overall well-being. (24-26) Unlike symptomatic treatments, 12 SQ-Bet aims to change patients' immune system response to allergens, preventing disease progression. (Appendix A1.1)

There are currently no other immunotherapies that work in this way for birch pollen that have been recommended by NICE.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no known equality issues relating to the use of 12 SQ-Bet for treatment of adult patients (aged 18-65 years) with a confirmed diagnosis of moderate to severe AR and/or conjunctivitis induced by pollen from the birch-related group despite use of symptomatic treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on 12 SQ-Bet and its pivotal trial, TT-04: • Biedermann et al., 2019 main publication describing the findings of the TT-04 trial- https://www.jacionline.org/article/S0091-6749(19)30018-1/fulltext • Würtzen et al., 2020 cross-reactivity study a substudy of the TT-04 trial - https://onlinelibrary.wiley.com/doi/10.1111/cea.13788 • Till et al., 2020 publication focussed on the apple challenge part of the TT-04 trial (40) • Nolte et al., 2021 publication that explores the effect of 12 SQ-Bet on allergic rhinoconjunctivitis during the oak pollen season (41) Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse Event (AE): An adverse event is any unexpected and usually undesired medical occurrence in a patient or clinical trial participant who has received a medication or undergone a medical procedure. Adverse events can range from mild side effects, such as nausea or headache, to more serious or severe reactions.
Allergen: A substance that triggers an allergic reaction, like pollen, dust, or pet dander.

Aero-allergen: Substances in the air, like pollen, dust, or mould, that can trigger allergies when inhaled.

Allergic Rhinitis (AR): A condition where your immune system overreacts to allergens (like pollen or dust) that you breathe in, causing symptoms like sneezing, a stuffy nose, and itchy eyes.

Allergic Rhinoconjunctivitis (ARC): A condition that affects both the nose and eyes, causing symptoms such as sneezing, runny nose, and itchy or watery eyes, usually triggered by allergens like pollen.

Allergy Immunotherapy (AIT): A treatment aimed at reducing your body's allergic reaction over time by gradually exposing it to small amounts of allergens, either through injections (shots) or tablets.

Antihistamines: Medications that block the action of histamine, a natural substance produced by the body during allergic reactions. Histamine can cause symptoms like sneezing, itching, runny nose, and watery eyes. Antihistamines help relieve these allergy symptoms and are commonly used to manage allergic rhinitis (hay fever) and other allergic reactions.

Birch Pollen: Pollen from birch trees that can cause allergic reactions in people who are sensitive to it.

Corticosteroids: Medications that reduce inflammation in the body. They work by suppressing the immune system's response to inflammation, helping to alleviate symptoms such as swelling, redness, and discomfort. Corticosteroids can be used to treat various conditions, including allergies, asthma, and skin conditions.

Cross-reactivity: When the immune system mistakes one allergen for another because they are similar in structure, like reacting to birch pollen and other tree pollen.

Efficacy: How well a treatment works to reduce or control the symptoms of a condition.

EQ-5D, or EuroQol-5D: A widely used generic health-related quality of life instrument. It evaluates a person's overall health by assessing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D provides a comprehensive snapshot of an individual's health status and is often used for comparing the impact of different health conditions and treatments.

Health Economics Model: A way to calculate the costs and benefits of a treatment over time, including things like the cost of medications, doctor visits, and the improvement in health.

Placebo: A treatment that has no active ingredients or real effects, used to compare against the actual treatment in clinical trials to see if the treatment works better than just the idea of receiving treatment.

Pollen Seasons (TPS and BPS): The time periods during which specific types of pollen are in the air and can trigger allergic reactions. "Tree Pollen Season" (TPS) and "Birch Pollen Season" (BPS) refer to the seasons when tree and birch pollen are most common.

Quality of life: The overall enjoyment of life. Many clinical trials assess the effects of AR, AA, and their treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living.

Real-World Evidence: Data collected from everyday situations, like doctor's offices or insurance records, to see how well a treatment works outside of controlled clinical trials.

RQLQ, or Rhinoconjunctivitis Quality of Life Questionnaire: A tool commonly used to assess the impact of allergic rhinitis (hay fever) and related conditions on a person's quality of life. It measures various aspects such as nasal and eye symptoms, sleep disturbances, daily activities, and emotional well-being.

SAE (Serious Adverse Event): A serious adverse event is a specific type of adverse event that is typically more severe or harmful in nature. It may result in serious consequences, including hospitalisation, life-threatening situations, disability, or death. SAEs are closely monitored and reported during clinical trials and medical research.

Sublingual Immunotherapy (SLIT): A type of allergy treatment where you place a tablet or drops under your tongue to help your body build resistance to allergens.

SF-36, or Short Form-36 Health Survey: A widely used questionnaire that measures a person's overall health-related quality of life. It assesses various physical and mental health dimensions, providing insights into a person's well-being beyond specific medical conditions.

Symptom-Relieving Medication: Medications used to reduce symptoms, like antihistamines, that do not cure the condition but help manage the symptoms.

Symptomatic Treatment: Medications used to relieve the symptoms of a condition (like antihistamines for allergies) without curing the underlying cause.

Utility Value: A way of measuring a person's health; a higher value means better health, and a lower value means worse health.

Visual Analogue Scale: A tool that helps patients' to describe how bad their symptoms are. It is a scale with one end showing "no symptoms" and the other end showing "the worst possible symptoms". Patients indicate the level on the scale that best matches how they're feeling, and that gives a score to show how severe their symptoms are.

The Japanese AR Standard QoL Questionnaire (JRQLQ): A questionnaire comprising 24 questions rated on a 5-point scale (0-4) designed to measure the impact of allergic rhinitis on various aspects of a person's life, including physical well-being, daily activities, and emotional well-being.

12 SQ-Bet: A specific allergy tablet treatment for people with allergic rhinitis caused by birch tree pollen. It helps your body become less sensitive to the allergen over time.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Betula verrucosa (ITULAZAX 12 SQ-Bet) for treating moderate to severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen [ID6462]

Clarification questions

February 2025

File name	Version	Contains confidential information	Date
ID6462_ 12 SQ-Bet Clarification questions – company response update [Con]	Final	Yes	20.03.25

Section A: Literature searches

Literature searches

A 1. Appendix B, Table 2 states that the International HTA database and the websites of relevant health technology assessment (HTA) bodies were searched to identify any data on cost-effectiveness, cost, or resource use associated with seasonal allergic rhinitis (AR).

a) Please confirm if these resources were also searched to identify relevant clinical evidence, and if so, provide details of the search terms used for the HTA body websites.

Economic evaluations, cost and resource use studies, and health technology assessments were not included in the review of clinical efficacy and safety evidence of interventions for treating and/or managing seasonal AR; rather, relevant evidence for this review was restricted to relevant randomised controlled trials (RCTs). However, if, during the course of searching these resources, relevant evidence for the clinical review or HRQoL review was identified, these would be included in the respective review under 'citation searching' identified during grey literature searching. We can confirm that no relevant information was identified from these resources in response to clinical review questions.

We would likewise be happy to provide the EAG with further information on the search dates and search terms used for the HTA body websites for the Economic evaluation, cost and resource use SLR.

- HTA assessment bodies: National Institute for Health and Care Excellence (NICE) – UK, Scottish Medicines Consortium (SMC), Canada Drug Agency (CDA), the Pharmaceutical Benefits Advisory Committee (PBAC), the Institute for Clinical and Economic Review (ICER), and Haute Autorité de santé (HAS)
- Search date: 29th July 2024
- Search terms: Hay fever AND birch OR Hay fever AND immunotherapy OR Seasonal allergic rhinitis AND birch OR Seasonal allergic rhinitis AND

immunotherapy OR Allergic rhinoconjunctivitis AND birch OR Allergic rhinoconjunctivitis AND immunotherapy

A 2. Appendix F states that EconLit was searched to identify health-related quality of life data, however this search strategy is not provided in Appendix B or Appendix F.

a) Please confirm if this was the case, and if so, provide full details of the search undertaken for this resource.

Table 2 of Section 2.3.2 of Appendix F details all the electronic databases and secondary sources searched to inform the HRQoL and utilities review, of which EconLit, primarily a source of economic evidence, was not included. To assure ourselves and therefore the EAG that by choosing not to search EconLit for HRQoL and utility evidence, no relevant evidence was missed, we adapted the Cochrane search strategy for the EconLit database and ran without date limitations, as demonstrated in the table below. This effort yielded a total of 5 records which were all irrelevant to the review question following dual screening and excluded at title and abstract or full publication screening.

- Excluded at full publication screening due to 'population not being of interest' – Hillerich V, Valbert F, Neusser S, Pfaar O, Klimek L, Sperl A, Werfel T, Hamelmann E, Riederer C, Wobbe-Ribinski S, Neumann A. Quality of life and healthcare costs of patients with allergic respiratory diseases: a cross-sectional study. The European Journal of Health Economics. 2024 Jun;25(4):579-600.

- Excluded at title and abstract screening due to 'no relevant outcomes of interest' – Alharbi NS. Determinants of Willingness to pay for employment-based health insurance among governmental school workers in Saudi Arabia. INQUIRY: The Journal of Health Care Organization, Provision, and Financing. 2021 Nov 18;58:00469580211060790.

- Excluded at title and abstract screening due to 'no relevant outcomes of interest' – Yayar R, Erol Y, Demir D. Determination of factors affecting

willingness to pay for low SAR value cell phones: A case study of Turkey. Theoretical and Applied Economics. 2014 May 1;21(5):594.

- Excluded at title and abstract screening due to 'no relevant outcomes of interest' – Pickard AS, Tawk R, Shaw JW. The effect of chronic conditions on stated preferences for health. The European Journal of Health Economics. 2013 Aug;14:697-702.

- Excluded at title and abstract screening due to 'no relevant outcomes of interest' – Itaoka K, Krupnick A, Saito A, Akai M. Morbidity valuation with a cessation lag: Choice experiments for public-and private-goods contexts in Japan. Resources for the Future; 2007 Jul 9.

Interface: OvidSP®, EconLit <1886 to February 27, 2025>

Search date: 5th March 2025

#	Search string	Hits
1	Seasonal Allergic Rhinitides.af.	0
2	(hayfever OR (hay adj fever) OR pollinosis OR pollenosis OR SAR OR (pollen adj allerg*)).af.	414
3	1 or 2	414
4	Rhinitis allergic.af. or rhinitis*.af.	12
5	((respiratory OR season* OR spring OR summer OR pollen* OR tree* OR weed* OR birch OR alder OR hornbeam OR hazel OR oak OR beech) AND allerg*).mp. OR ((“Betula verrcose” OR “Alnus glutinosa” OR “Alnus glutinosa” OR “Quercus alba” OR “Corylus avellana” OR “Carpinus betulus” OR “Fagus sylvactica”) AND allerg*).af.	11
6	4 AND 5	1
7	3 OR 6	415
8	quality adjusted life year.af or value of life.af. or socioeconomics.af.	1884
9	"quality of life index".tw.	60
10	((disabilit* or qualit*) adj2 (life year or wellbeing or well-being)).tw.	337
11	(wellbeing index or multiattribute* or multi attribute*).ti,ab.	667
12	(qal* or qwb* or daly* or qtime*).ti,ab.	897
13	(eq-5d or EQ-5D or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro* quality of life or european qol).ti,ab. OR (euro$ adj3 (5 d or 5d or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).ti,ab.	331
14	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.	343
15	((health or disease or mean or cost) adj utilit*).ti,ab.	388
16	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab.	2527

#	Search string	Hits
17	(HSUV* or “health* year* equivalent*”).tw. OR utilities.ti,ab.	5893
18	(hui or hui1 or hui2 or hui3).ti,ab.	117
19	(hye or hyes).ti,ab.	27
20	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.	49
21	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.	0
22	(sf16 or sf 16 or short form 16 or shortform 16 or shortform16).ti,ab.	0
23	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.	34
24	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.	1
25	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.	15
26	(willingness to pay or WTP or time tradeoff or time trade off or tto or SG or standard gamble*).ti,ab.	8159
27	(patient reported adj2 outcomes).ti,ab.	26
28	(“rhinitis symptom utility index” or (rhinitis adj2 utilit*)).ti,ab. OR (rhinitis adj2 “quality of life”).ti,ab.	1
29	((rhinoconjunctivitis adj3 questionnaire) or (rhinitis quality adj3 questionnaire) or rqlq* or arqlq* or prqlq* or “par-ent-qol”).ti,ab.	0
30	(“sino-nasal outcome test-22” or “sino-nasal outcome test” or “sinonasal outcome test-22” or “sinonasal outcome test” or “SNOT-22” or “SNOT 22”).ti,ab.	0
31	or/8-30	19456
32	7 and 31	7
33	(survey or letter or editorial or comment or note).ti,ab.	146209
34	32 not 33	5

Section B: Clarification on effectiveness data

Decision problem

B 1. Priority question. The population in the scope and the decision problem (DP) includes ‘moderate to severe’ AR, which is defined as having: *“one or more of the following items are present: troublesome symptoms, sleep disturbance, impairment of school or work, or impairment of daily activities, leisure, and/or sport”* (p. 26). Please provide objective criteria for:

a) troublesome symptoms,

b) sleep disturbance,

c) impairment of school or work,

d) **impairment of daily activities, leisure, and/or sport.**

The definition provided in the CS for moderate to severe AR was based on the ARIA AR disease classification. (1) According to the ARIA guideline, AR is classified as moderate to severe when one or more of the following items are present: troublesome symptoms, sleep disturbance, impairment of school or work, or impairment of daily activities, leisure, and/or sport. AR is classified as mild when none of these items are present. (1) There are no additional details on the objective criteria for these items as they are based on a patient's evaluation. Patients were included in the TT-04 trial if they stated that they had experienced one or more of these ARIA quality of life items due to allergic rhinitis and/or conjunctivitis during the previous birch pollen season (BPS), consistent with the definition of moderate to severe AR in the ARIA guideline.

B 2. Priority question. The scope and DP population are a mixture of AR and allergic conjunctivitis, as well as of species of tree pollen (within the birch homologous group) that patients are allergic to.

a) **What are the proportions in each of AR and allergic conjunctivitis likely to be found in clinical practice?**

There are a range of diagnosis codes used by GPs to refer to allergic rhinitis with or without conjunctivitis. Allergic rhinitis cannot be regarded as an isolated pathology, and as discussed in the CS, allergic rhinitis and allergic conjunctivitis are often concomitant diseases with a strong epidemiology correlation and similar pathophysiological mechanisms. Consequently, the published prevalence and diagnosis data about proportions of one specific aspect (e.g., allergic rhinitis alone or allergic conjunctivitis alone) is often inaccurate; AR is often used to refer to allergic rhinitis as well as allergic rhinoconjunctivitis with the two terms used interchangeably.

Throughout the CS, the term "AR" is used to refer to allergic rhinoconjunctivitis as a combined condition. Furthermore, the clinical evidence presented in TT-04 is relevant to allergic rhinoconjunctivitis patients, with the pivotal TT-04 trial's primary endpoint being specific to allergic rhinoconjunctivitis. Additionally, where specified, the secondary endpoints of the trial are specific to allergic rhinitis and conjunctivitis as a combined condition.

b) What are the proportions in each tree pollen species?

Pollen from the birch homologous group is the most prevalent allergenic tree pollen across most parts of Europe. (2, 3) The proportions of patients in each tree pollen species of the birch homologous group can be inferred from the population of the TT-04 trial. A breakdown of the tree pollen species in the TT-04 trial is presented in Table 1.

Table 1: Breakdown of tree pollen species in TT-04

Treatment group	Placebo (N=314)		12 SQ-Bet (N=320)		Overall (N=634)	
	n	n%	n	n%	n	n%
Allergy history						
Birch pollen allergy	314	100%	320	100%	634	100%
Asthma (all causes)	134	43%	142	44%	276	44%
PFS	209	67%	212	66%	421	66%
Sensitisations by skin prick test						
Birch	313	>99%*	320	100%	633	>99%
Alder	288	92%	293	92%	581	92%
Hazel	274	87%	270	84%	544	86%
Mono-sensitised**	72	23%	82	26%	154	24%
Poly-sensitised	242	77%	238	74%	480	76%

Notes: ** Missing for 1 subject*
*** Mono-sensitised defined as skin prick test positive to birch, alder or hazel*
Reference: *TT-04 CSR (4)*

The 2021 publication Nolte et al. analysed the subjects of the TT-04 trial who were allergic to oak pollen, specifically 86% of birch-sensitised patients who were allergic to oak pollen. (5)

Wurtzen et al., 2020 analysed the blood samples that were collected in the TT-04 trial (N= 397). Serum IgE and IgG4 specific to birch, and birch homologous tree pollens from alder, hazel, hornbeam, beech, and chestnut were measured by ImmunoCAP. The majority of the birch allergic patients had serum IgE binding to multiple related trees in the birch homologous group, including alder (99%), hazel (96%), hornbeam (96%), and beech (95%), indicating a high level of cross-reactivity with these allergens and therefore an increased likelihood of birch pollen-sensitised patients also reacting to the different tree pollen species. (6)

i. Do patients only have to have a positive test of sensitisation to one member of the birch homologous group (skin prick test and/or specific IgE)?

To be eligible for 12 SQ-Bet treatment patients are required to have a clinical history of symptoms and a positive test of sensitisation to one member of the birch homologous group (*Betula verrucosa* (birch), *Alnus glutinosa* (alder), *Carpinus betulus* (hornbeam), *Corylus avellana* (hazel), *Quercus alba* (oak) and *Fagus sylvatica* (beech)). This test of sensitisation can be a skin prick test and/or a specific IgE response. (7) Due to the high level of cross-reactivity, 12 SQ-Bet treatment is relevant for allergy towards all the members of the birch homologous group.

ii. Are there any clinical implications of which tree species the patient has a positive test to, e.g., in terms of severity?

The onset of a patient's AR symptoms is dependent on the specific tree species to which they are allergic. The different tree species within the birch homologous group have different flowering patterns, influencing the timing, duration, and, depending on pollen levels, the severity of a patient's AR symptoms. The tree pollen season can commence as early as December in Europe, with hazel and alder trees pollinating from December to April. (3, 8, 9) Following on from the alder season are the ash, birch, and oak pollen seasons, which finish in June. If a patient is sensitised to more than one tree species, which is often observed due to the high levels of cross-reactivity, they will experience AR symptoms for an extended period of the year. (3, 9-11) There is no clinical evidence to suggest that disease severity varies between the tree pollen species.

B 3. Priority question. The scope and DP define the population as *"adults with moderate to severe AR or allergic conjunctivitis (…) despite the use of symptom-relieving medication".* The company also states that the line of therapy is second line. However, the British Society for Allergy and Clinical Immunology (BSACI) algorithm shows that there are several forms of this medication and three lines of therapy (separated by failure).

a) Please clarify where in the care pathway ITULAZAX 12 SQ-Bet SLIT would be used in clinical practice in relation to the algorithm.

12 SQ-Bet is to be used for the treatment of AR in patients with a seasonal allergy to tree pollen whose symptoms persist despite use of symptomatic pharmacotherapy.

12 SQ-Bet is intended to be used as an add-on to standard therapy for AR rather than a replacement for an existing symptom-relieving medication in the treatment pathway. This positioning is in line with the BSACI and ARIA guideline recommendations for allergen immunotherapy (AIT). Clinical experts have also confirmed this positioning of 12 SQ-Bet (see appendix J6).

B 4. Priority question. The TT-04 trial includes patients with and without asthma (controlled/partly controlled).

a) Please clarify the nature of the population in the DP and in clinical practice who would be eligible for ITULAZAX 12 SQ-Bet SLIT in terms of presence of asthma and its degree of control.

Asthma frequently occurs alongside AR and, therefore, 12 SQ-Bet may be used in clinical practice in patients with moderate to severe AR who also have concomitant allergic asthma. In the TT-04 trial population, AR patients with concomitant asthma must have had their asthma controlled prior to initiation of treatment with 12 SQ-Bet, as 12 SQ-Bet is contraindicated for patients who have experienced a severe asthma exacerbation within the last 3 months and/or have had uncontrolled asthma within the last 3 months. Furthermore, 12 SQ-Bet is contraindicated for participants with reduced lung function (FEV1 < 70% of predicted value after adequate pharmacological treatment). Additionally, patients who experience an acute respiratory tract infection should have 12 SQ-Bet treatment initiation postponed until the infection has resolved. (7)

Systematic review

B 5. Table 1 in Appendix B (“Limitations” eligibility criteria) indicates that non-English language publications without an English abstract were excluded from the SLR.

a) Please provide the number of relevant studies omitted from the systematic literature review (SLR) because of being published in non-English language without an English abstract.

The company can confirm that no articles within the Clinical efficacy and safety SLR, Economic evaluations, cost and resource use SLR, and HRQoL and utilities SLR

were excluded at title and abstract screening on the basis of a publication language restriction (non-English language publication with a non-English abstract). Further searching of full publication screening decisions and exclusion reasons across all three SLRs revealed that three articles were excluded from the HRQoL screening library primarily based on publication language and additionally due to a lack of extractable relevant outcomes for the review population of interest being available in the abstract. These included:

- Shiomori T, Udaka T, Hashida K, Fujimura T, Hiraki N, Ueda N, Suzuki H. Evaluation of quality of life in patients with allergic rhinitis. Journal of UOEH. 2007 Jun 1;29(2):159-67.

- Maksimović N, Janković SM, Tomić-Spirić V, Marinković JM. Health-related quality of life assessment in patients with allergic rhinitis. Srpski arhiv za celokupno lekarstvo. 2005;133(5-6):223-8.

- Ogino T, ISHII H, ABE Y, NONAKA S, HARABUCHI Y, UEHARA M, KANASEKI N. Evaluation of Patient Satisfaction with Treatment for Birch Pollinosis. PRACTICA OTORHINOLARYNGOLOGICA-KYOTO-. 2006;99(10):835.

b) Please clarify the impact of excluding studies published in non-English language without an English abstract on the estimates in the submission.

The company understand the EAG's concerns considering the very minimal possibility of the introduction of the so-called 'Tower of Babel' bias. However, as English language is the primary scientific language for peer-reviewed scientific publications and grey literature by large, by only including articles published in the English language or with leniency including non-English language publications with an English language abstract discussing relevant outcomes and results, reviews are just as able to capture and summarise all available and relevant information in response to review questions. The Cochrane Handbook likewise acknowledges that the exclusion of non-English language studies is unlikely to significantly change the conclusions of the review, (12) conclusions that were further drawn in a meta-epidemiological study by Nussbaumer-Streit B et al., 2020. (13) Therefore, we anticipate the exclusion of three non-English language studies with no relevant

outcomes published in their abstract for the population of interest, to have no material impact on the conclusions of the HRQoL and utilities review.

Clinical effectiveness evidence

B 6. Priority question. Please provide further details on why some of the studies presented in Table 4 of the company submission (CS) are not included in the economic model or presented in detail in the clinical effectiveness results, e.g., TT-02.

Phase 3 RCTs are regarded as the gold standard of clinical evidence. Therefore, the Phase 3 RCT, TT-04, was presented in detail in the CS and included in the economic modelling as the trial is the primary and most robust evidence base for 12 SQ-Bet. Additionally, the trial's population and design align with the scope of the appraisal, with the trial's timelines specifically covering the birch pollen season, providing the most accurate and reliable reflection of 12 SQ-Bet's effectiveness when evaluated within the appraisal population. Consequently, the Phase 2 trials, TT-03 and TT-02, were described in the CS but were not used to inform the economic modelling, having been superseded in terms of robust estimation of treatment effect, generalisable to clinical practice by the Phase 3 TT-04 trial.

B 7. Priority question. The TT-04 trial includes patients with or without asthma (controlled/partly controlled). Please clarify the generalisability of the TT-04 trial in terms of the presence of asthma and degree of control.

Over 80% of patients with allergic asthma (AA) have comorbid AR, and correspondingly, AR is a strong risk factor for asthma development. (1, 14, 15). Although it is not included in the licensed indication for 12 SQ-Bet, 12 SQ-Bet can provide some clinical benefit to an AR patient's comorbid asthma symptoms. As discussed in the CS, the TT-04 trial explored the efficacy of 12 SQ-Bet on asthma symptoms for the subgroup of trial participants with comorbid controlled/partly controlled asthma as an exploratory endpoint. The TT-04 trial demonstrated the clinical benefit of 12 SQ-Bet, providing relief to not only patients' AR but also their comorbid AA symptoms. This is consistent with SLIT treatment for AA caused by

other allergens such as house dust mite, where treatment was shown to reduce the risk of exacerbations in comparison with SoC alone. (16)

The TT-04 trial inclusion criteria regarding asthma subjects are in line with the licensed indication and the summary of product characteristics (SmPC) for 12 SQ-Bet, with comorbid asthma subjects required to have controlled or partly controlled asthma to be eligible for the trial. In line with the contraindications for 12 SQ-Bet, patients were excluded from the trial if they had a severe asthma exacerbation within the last 3 months and if they had a clinical history of uncontrolled asthma (defined according to the GINA 2015 guidelines) within 3 months prior to trial screening. Patients were also excluded if they had reduced lung function (FEV1 < 70% of predicted value after adequate pharmacological treatment). Consequently, the TT-04 trial inclusion criteria with respect to asthma control are consistent with the target patient population for the appraisal.

B 8. Priority question. TT-04 participants were free to use specific standard of care (SoC) medications for AR and conjunctivitis. The CS states: *"in the TT-04 trial subjects were instructed to freely initiate treatment with antihistamine tablets and/or eyedrops according to their symptoms and could initiate additional treatment with nasal corticosteroids if their symptoms persisted. Symptom-relieving medication was dispensed to the subjects at visit 4 and 5 and was used according to the dosage instructions outlined in Table 8"*.

a) **Please provide evidence to support the applicability of these treatments and their doses to SoC in UK clinical practice, referring to responses to questions B1 to B4 in terms of the nature of the condition and line of therapy.**

The company provided specific SoC medications that constitute the majority of SoC treatment in clinical practice to TT-04 participants. Subjects were able to use as much or as little as needed, based on the severity of their symptoms. TT-04 subjects were provided with oral antihistamine tablets (desloratadine tablets, 5 mg), nasal corticosteroid spray (mometasone, 50 µg/dose), and antihistamine eye drops (olopatadine eye drops, 1 mg/mL). In 2024, an advisory panel of nine UK clinical

experts in allergy management confirmed that oral antihistamine tablets, nasal corticosteroid sprays, and antihistamine eye drops are representative of the typical SoC medication for AR patients (see Appendix J2). This was further supported by findings from a 2025 Delphi panel comprising three consultant allergists and immunologists, along with two GPs with a specialist interest in allergy (see Appendix J6).

The inclusion of SoC medication in the trial supports the positioning of AIT in the AR treatment pathway, with 12 SQ-Bet anticipated to be used in addition to the background SoC. The TT-04 trial demonstrated that 12 SQ-Bet also has a beneficial effect on AR with concomitant asthma. Clinical experts have confirmed that the medications provided in the TT-04 trial are representative of those used in clinical practice to treat concomitant AR and AA (see Appendix J2). Therefore, the trial is reflective of a real-world setting as patients with AR and AA who are treated with 12 SQ-Bet would also receive the SoC treatments provided in the trial alongside their 12 SQ-Bet treatment.

b) Were any medications that are also SoC excluded or prohibited?

As discussed in the company's response to B.8.a), TT-04 trial participants were provided with specific SoC medications that are representative of the typical SoC in UK clinical practice. These treatments were provided to replicate the background SoC symptomatic treatments that patients would receive in clinical practice alongside 12 SQ-Bet treatment rather than to provide all potential treatment options to trial participants, as doing so could interfere with the ability of the trial to effectively assess 12 SQ-Bet as a treatment option for AR patients. Leukotriene receptor antagonists (LTRA), ipratropium bromide, intranasal decongestants, and systemic corticosteroids were prohibited in the TT-04 trial, all of which are infrequently used in clinical practice in the UK for the management of AR. This was validated by an online survey that was conducted in 2024 with 46 UK healthcare professionals. Of these, 48% were allergy or immunology consultants; 13% were ear, nose, and throat (ENT) or respiratory consultants; with the remainder being GPs, nurses, or other healthcare professionals working in the UK. This represents a large proportion of the UK community of allergy clinicians. In this survey, 100% of responders believed that the exclusion of LTRA, ipratropium bromide, and systemic corticosteroids from both

study arms of an AR trial would not bias results in the context of UK clinical practice (see appendix J3). Additionally, clinical experts in a Delphi panel unanimously agreed that oral antihistamines, nasal corticosteroid spray, and antihistamine eye drops are reflective of the SoC in UK clinical practice (see Appendix J6).

c) What might be the implications of and deviation from SoC on effectiveness?

A Delphi panel conducted in 2025 confirmed that oral antihistamines, nasal corticosteroid spray, and antihistamine eye drops, which comprised SoC medications provided to TT-04 trial participants, were reflective of standard UK clinical practice (see appendix J6). As such, there are no anticipated implications on the generalisability of clinical evidence to UK practice.

The trial included symptomatic medications that were reflective of the SoC for UK clinical practice and, hence, a replication of the background SoC symptomatic treatments that patients would receive in clinical practice alongside 12 SQ-Bet treatment. Other symptomatic medications were prohibited from the trial to improve the standardisation between study arms and reduce potential confounding due to differences in the SoC medication use. Furthermore, as referenced in the company's responses to B.8.a) and B.8.b), an online survey was conducted in 2024 with 46 UK healthcare professionals, representing a significant proportion of the UK allergy clinician community. All respondents agreed that excluding LTRA, ipratropium bromide, and systemic corticosteroid from both study arms of an AR clinical trial would not introduce bias within the context of UK clinical practice (see appendix J3). Additionally, as combined medication scores are often a key endpoint of clinical trials for AR, a standardised set of symptomatic medications is essential for reliably determining treatment efficacy. It is also important to note that the makeup of the SoC freely available for TT-04 participants was consistent for both study arms, with either 12 SQ-Bet or placebo being added to the same symptomatic medications.

Notably, immunotherapy trials such as TT-04 are often faced with the issue of a placebo effect increasing the efficacy of symptomatic medications. Furthermore, patients were trained on how to use symptomatic medications at touchpoints during TC2, at the start of the tree pollen season (TPS). This would've likely improved adherence to and optimisation of symptomatic medications throughout the TPS

which may not be realised in clinical practice. As a result, the SoC treatments available in the TT-04 trial are likely to overestimate the efficacy of treatment with background SoC while potentially underestimating the incremental treatment benefit of 12 SQ-Bet.

Overall, the concomitant medications and prohibited medications included in the TT-04 trial are not anticipated to have any impact on the estimated efficacy of 12 SQ-Bet as a treatment for AR, and indeed, the efficacy of SLIT tablets and tree AIT is also supported by real-world evidence collected in the UK and internationally.

B 9. Priority question. The CS states that "*the European Medicines Agency (EMA) definition for the birch homologous group also includes chestnut trees*". However, chestnut pollen was excluded due to a lack of correlation in IgE and immunoglobulin subtype 4 (IgG4) reactivity.

a) Did the trial measure clinical responses (symptoms) to chestnut pollen, or was this based solely on laboratory findings?

The TT-04 trial included patients with a positive skin prick test to birch extract and/or a positive specific IgE result against species Bet v1, the major allergen of the birch homologous group. The majority of these birch allergic patients had serum IgE binding to multiple related trees in the birch homologous group, including alder (99%), hazel (96%), hornbeam (96%), and beech (95%), indicating a high level of cross-reactivity with these allergens. Only 14% of these patients had serum IgE binding to chestnut pollen, indicating a lower likelihood that birch-sensitive patients would also react to chestnut pollen. (6) Clinical response to chestnut pollen was not explicitly measured as part of the trial; however, the trial did not exclude patients based on their sensitisation to chestnut pollen. Due to the low level of immunological cross-reactivity, chestnut pollen is not included in the licensed indication for 12 SQ-Bet or in the scope of this appraisal.

b) Is it possible that some birch-sensitive patients still react to chestnut pollen despite a lack of IgE correlation?

As stated in the company's response to B.9.a), the majority of birch allergic patients in the TT-04 trial had serum IgE binding to multiple related trees in the birch

homologous group, including alder (99%), hazel (96%), hornbeam (96%), and beech (95%), indicating a high level of cross-reactivity with these allergens. However, no significant cross-reactivity between the birch and chestnut was found, with only 14% of birch-sensitive patients having a serum IgE binding to chestnut pollen, indicating a lower likelihood that birch-sensitive patients would also be allergic to chestnut pollen (i.e., be sensitised and experience symptoms following exposure). (6) Therefore, while it's possible that birch-sensitive patients will be allergic to chestnut pollen, this is much less likely than for other tree species in the birch homologous group.

c) Should chestnut-sensitised patients be considered non-responders to 12 SQ-Bet?

All patients included in the TT-04 trial had a positive skin prick test to birch extract and/or a positive specific IgE result against species Bet v1, with 14% of these patients having serum IgE binding to chestnut pollen. (6) This low level of cross-reactivity should be interpreted as patients with birch sensitisation having a lower likelihood of also reacting to chestnut pollen compared to other tree pollen species in the birch homologous group, rather than considering chestnut-sensitised patients as 'non-responders'.

It is important to note that patients would not be initiated on treatment with 12 SQ-Bet based on their sensitisation to chestnut pollen alone as they would also have to have a positive skin prick test and/or specific IgE response to a member of the birch homologous group, as defined in the licensed indication (Betula verrucosa (birch), Alnus glutinosa (alder), Carpinus betulus (hornbeam), Corylus avellana (hazel), Quercus alba (oak), and Fagus sylvatica (beech)), as well as a clinical history of symptoms. (7)

B 10. Priority question. Why did the TT-04 trial exclude oak, beech, and chestnut pollen from the efficacy analysis despite their inclusion in the birch homologous group, and how does this impact the real-world effectiveness of 12 SQ-Bet for UK patients exposed to multiple tree pollens?

In the TT-04 trial, the tree pollen species included in the efficacy analysis were selected to prioritise the most important tree species and to include both early and

late pollinating tree species to ensure the whole tree pollen season was covered, hence why oak was also included as a late pollinating species.

Nolte et al., 2021 (5) conducted a post-hoc analysis of the TT-04 trial focused on the oak pollen season. Only 1% of participants in the TT-04 trial were IgE mono-sensitised to birch pollen, while 87% were also sensitised to oak pollen. This analysis was reported in the CS in Section 2.6.7. Overall, the Nolte et al., 2021 study showed that treatment with 12 SQ-Bet leads to significant improvements in rhinoconjunctivitis outcomes during the oak pollen season. This demonstrates the efficacy of 12 SQ-Bet in birch pollen-induced AR over the course of the TPS and extending through the oak pollen season. This study further supports the clinical relevance of immunological cross-reactivity between birch and oak pollen allergens.

Couroux et al., 2019, reported the results of a Phase 2 study in which patients were treated with 12 SQ-Bet and exposed to birch pollen using an environmental exposure chamber designed to reduce the variability of allergen exposure seen in clinical trials. There was strong correlation between birch and beech IgE (r=0.91) and IgG4 (r=0.81) titres, demonstrating immunological cross-reactivity between birch and beech pollen. (17) This immunological cross-reactivity was further demonstrated in the study by Wurtzen et al., 2020, which reported that 95% of birch allergic patients in the TT-04 trial had serum IgE binding to beech. (6) This indicates that the treatment-induced immune modulation observed with 12 SQ-Bet also affects the immune response to beech pollen.

As discussed in the company's response to B.8., the TT-04 trial included patients with a positive skin prick test to birch extract and/or a positive specific IgE result against species Bet v1, the major allergen of the birch homologous group. Immunological analysis demonstrated that only 14% of the birch-sensitised patients included in the TT-04 trial had serum IgE binding to chestnut pollen, indicating a low likelihood that birch-sensitive patients would also react to chestnut pollen. (6) Clinical response to chestnut pollen was not explicitly measured as part of the trial; however, the trial did not exclude patients based on their sensitisation to chestnut pollen. Due to the low level of immunological cross-reactivity, chestnut pollen is not included in the licensed indication for 12 SQ-Bet, or in the scope of this appraisal. The exclusion of chestnut from the efficacy analysis of TT-04 does not have any impact on the

assumed real-world effectiveness of 12 SQ-Bet in UK clinical practice as patients would not be initiated on treatment based on their sensitisation to chestnut pollen alone as they would also have to have a positive skin prick test and/or specific IgE response, and a clinical history of symptoms, to a member of the birch homologous group as defined in the licensed indication (Betula verrucosa (birch), Alnus glutinosa (alder), Carpinus betulus (hornbeam), Corylus avellana (hazel), Quercus alba (oak) and Fagus sylvatica (beech)). (7)

B 11. Priority question. Was a subgroup analysis conducted to assess whether patients polysensitised to oak and beech pollen experienced a different treatment response compared to those sensitised only to birch, alder, and hazel, and if not, how does this impact the generalisability of the trial results to a UK population?

This subgroup analysis was not conducted. The TT-04 trial included a mixture of poly- and mono-sensitised patients, of which a large proportion were polysensitised (76%). More specifically, a large proportion of the TT-04 population also had specific IgE binding to oak (87%) and beech (95%) pollen. (5, 6) Polysensitisation is highly prevalent in the UK patient population; therefore, the trial results and population of the TT-04 trial are generalisable to a UK patient population.

B 12. Priority question. The CS states that randomisation was performed in September and October of 2016 all subjects received at least 16 weeks of treatment (mean 224 days) before the start of the tree pollen season (TPS) in 2017, and total treatment duration varied between 6.5 and 9.5 months. There therefore seems to be a large amount of variability in the duration of treatment, including pre-TPS treatment.

a) **Please provide the distribution of total and pre-TPS treatment in centiles.**

The company have undergone further analysis of the TT-04 trial results to provide the distribution of total and pre-TPS treatment. The distribution of these categories has been provided in Table 2.

Table 2: Summary of the distribution of pre-seasonal and total treatment duration in days

	Placebo (N=314)	Active 12 DU (N=320)	Total (N=634)
Pre-seasonal treatment duration (days)			
Mean (SD)	146 (30)	139 (42)	142 (36)
Median	153	152	153
Min - Max	1 - 194	1 - 194	1 - 194
P1 - P99	10 - 184	1 - 186	5 - 185
P5 - P95	99 - 178	21 - 179	31 - 178
P25 - P75	134 - 163	133 - 162	134 - 163
Total treatment duration (days)			
Mean (SD)	230 (48)	218 (68)	224 (59)
Median	239	239	239
Min - Max	1 - 282	1 - 279	1 - 282
P1 - P99	10 - 280	1 - 276	5 - 279
P5 - P95	99 - 268	21 - 267	31 - 267
P25 - P75	225 - 253	221 - 252	223 - 252

Abbreviations: N, number of subjects in FAS; SD, standard deviation.
Notes: Pre-seasonal treatment is defined as the time from first exposure to IMP to the first day of the tree pollen season.

b) Please perform an analysis of the effectiveness of the intervention as a function of both total and pre-TPS duration.

The additional analysis results of the TT-04 trial for the average TCS during the BPS and TPS based on pre-seasonal and total treatment duration 'above' or 'at or below' the median are presented in Table 3, Table 4, Table 5 and Table 6. As evidenced by these results this additional subgroup analysis was consistent with the results for the full trial population which were reported in the company submission. There is no significant difference between the pre-seasonal or total treatment duration 'above median' and the 'at or below median' groups during both the BPS and TPS, supporting that subjects with less time on treatment do not experience a reduced treatment benefit with 12 SQ-Bet, as long as patients initiate treatment 16 weeks prior to the start of the TPS, consistent with the design of TT-04 and the SmPC for 12 SQ-Bet.

Notably, even if variations in clinical effectiveness were observed based on the duration of pre-treatment and total treatment duration, any differences would only be applicable to the first pollen season and would be insignificant by the second pollen season. Additionally, variations in treatment durations before the start of the TPS, beyond the recommended 16-week treatment initiation period prior to the TPS with

12 SQ-Bet, are expected in UK clinical practice, as patients will have differing treatment initiation timelines. Therefore, the results of the TT-04 trial presented in the company submission are reflective of real-world UK clinical practice.

Table 3: Analysis of average TCS during the BPS based on total treatment duration

Trial arm	n	Adjusted mean [CI]	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
Average TCS during the BPS in subjects with total treatment duration above median (FAS)					
Placebo	155	[redacted]	-	-	-
12 SQ-Bet	154	[redacted]	[redacted]	[redacted]	[redacted]
Average TCS during the BPS in subjects with total treatment duration at or below median (FAS)					
Placebo	137	[redacted]	-	-	-
12 SQ-Bet	129	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BPS, birch pollen season; FAS, full analysis set; n, number observed; TCS, total combined score.

Table 4: Analysis of average TCS during the TPS based on total treatment duration

Trial arm	n	Adjusted mean [CI]	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
Average TCS during the TPS in subjects with total treatment duration above median (FAS)					
Placebo	156	[redacted]	-	-	-
12 SQ-Bet	154	[redacted]	[redacted]	[redacted]	[redacted]
Average TCS during the TPS in subjects with total treatment duration at or below median (FAS)					
Placebo	140	[redacted]	-	-	-
12 SQ-Bet	130	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; n, number observed; TCS, total combined score; TPS, tree pollen season.

Table 5: Analysis of average TCS during the BPS based on pre-seasonal treatment duration

Trial arm	n	Adjusted mean [CI]	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
Average TCS during the BPS in subjects with pre-seasonal treatment duration above median (FAS)					

Trial arm	n	Adjusted mean [CI]	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
Placebo	150	[redacted]	-	-	-
12 SQ-Bet	147	[redacted]	[redacted]	[redacted]	[redacted]
Average TCS during the BPS in subjects with pre-seasonal treatment duration at or below median (FAS)					
Placebo	142	[redacted]	-	-	-
12 SQ-Bet	136	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BPS, birch pollen season; FAS, full analysis set; n, number observed; TCS, total combined score.

Table 6: Analysis of average TCS during the TPS based on pre-seasonal treatment duration

Trial arm	n	Adjusted mean [CI]	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
Average TCS during the TPS in subjects with pre-seasonal treatment duration above median (FAS)					
Placebo	154	[redacted]	-	-	-
12 SQ-Bet	148	[redacted]	[redacted]	[redacted]	[redacted]
Average TCS during the TPS in subjects with pre-seasonal treatment duration at or below median (FAS)					
Placebo	142	[redacted]	-	-	-
12 SQ-Bet	136	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; n, number observed; TCS, total combined score; TPS, tree pollen season.

B 13. Priority question. The final scope issued by the National Institute for Health and Care Excellence (NICE) restricts the population to adults, whereas the study population in key trial TT-04 includes "*adults aged 18–65 years and adolescents aged 12–17 years (in Poland)*". While in the subgroup analysis, the company indicated that there was no statistical difference in treatment effect between adults and adolescents, the adolescent population was limited and only recruited at Polish sites.

a) **Please clarify whether this affects the robustness of the findings for the adult population as defined by NICE.**

The inclusion of a small cohort of adolescent patients in the TT-04 trial would not have affected the results of the trial as shown in subgroup analysis of the primary endpoint (presented in the company's response to B.13.c). This has been validated by a survey conducted by the company, and completed by 46 UK clinicians, with 61% of them being allergy, ENT, or respiratory consultants, where only 2% of respondents believed that a similar or equivalent response to SLIT treatment would not be observed between adult and adolescent patients (see Appendix J3). It was further validated in an advisory board, where all participants believed that SLIT treatment would perform equivalently in adolescent and adult patients (see Appendix J2).

Additionally, the TT-06 trial, a Phase 3 RCT conducted in children and adolescents with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch homologous group, demonstrated similar efficacy of 12 SQ-Bet in this population as was observed in the TT-04 trial. (18) Overall, there is no evidence to suggest that the efficacy of 12 SQ-Bet differs between the adult and adolescent populations or that the inclusion of a small cohort of adolescent patients in the TT-04 trial would impact the robustness or generalisability of findings.

b) **Please clarify what the effect of excluding those over 65 years might be.**

Clinical experience of 12 SQ-Bet in patients aged 65 years and older is limited and the exclusion of this age group from the TT-04 trial may have reduced the detection of adverse events (AEs) specific to the elderly population. However, the MT-04 Phase 3 RCT for 12 SQ-HDM, a SLIT treatment with a similar mechanism of action albeit a different allergen, and identical manufacturing and standardisation technology as 12 SQ-Bet, included patients over 65 years of age and did not identify any significant safety concerns in the adult population. (16) However, no specific subgroup analysis was conducted for elderly patients. Overall, based on the review of the quality, safety and efficacy of 12 SQ-Bet, the Medicines and Healthcare products Regulatory Agency (MHRA) approved 12 SQ-Bet for use in adult patients with no upper age limit specified.

c) Please perform all effectiveness analyses excluding adolescents.

The TT-04 trial included a pre-specified subgroup analysis of the primary endpoint, the average TCS during the BPS, with respect to the adults (18-65 years) and adolescents (12-17 years) age groups (see Table 7). The estimated absolute differences were 1.94 for adolescents and 3.16 for adults, corresponding to 31% and 41% reductions relative to placebo. For both subgroups the estimated relative treatment difference was higher than the minimal clinically relevant difference of 20% that was pre-specified for this trial based on recommendations from the World Allergy Organisation (19). This difference also exceeds the US Food and Drug Administration (FDA) criteria to demonstrate the efficacy of AIT which states a minimum difference of 15% versus placebo must be observed. (20) An analysis comparing the treatment effect in the adolescent and adult populations did not show any statistical difference in treatment effect between the adolescents and adults (p=0.5417, Table 7).

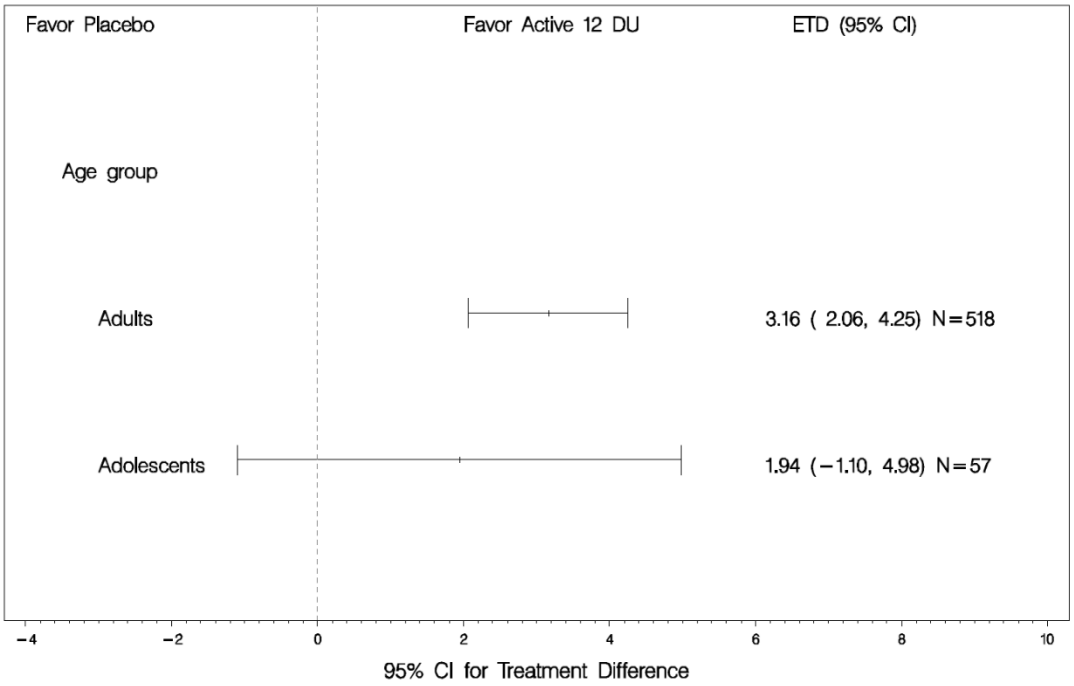
Table 7: Subgroup analysis in the TT-04 trial with respect to age group – Average TCS during the BPS (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% Relative to placebo [95% CI]	p-value
Average TCS during the BPS – Adolescents (FASBPS)					
Placebo	32	6.30	-	-	-
12 SQ-Bet	25	4.36	1.94 [-1.10, 4.98]	30.80 [-23.26, 63.63]	NA
Average TCS during the BPS – Adults (FASBPS)					
Placebo	260	7.76	-	-	-
12 SQ-Bet	258	4.60	3.16 [2.06, 4.25]	40.68 [28.92, 50.86]	NA
Test for interaction between age group and treatment effect					0.5417

Notes: *The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable. The interaction between age group and treatment is tested using an F-test in the LME model. The null hypothesis in the F-test is that treatment effect is the same in the two age groups.*
Abbreviations: *BPS, birch pollen season; CI, confidence interval; FASBPS, full analysis set birch pollen season; NA, not applicable; TCS, Total Symptom Score.*
References: *TT-04 CSR. (4)*

The forest plot for TCS over BPS for the adult and adolescent subgroups is presented in Figure 1.

Figure 1: Forest plot for TCS over BPS for the adult and adolescent subgroups in TT-04



Abbreviations: *CI, confidence interval; ETD, Estimated treatment difference.*
Reference: *TT-04 CSR (4)*

A subgroup analysis of average TCS during the TPS with respect to the age groups adults (18-65 years) and adolescents (12-17 years) was also conducted in the TT-04 trial and is presented in Table 8.

Table 8: Summary of the average TCS in age subgroups during the TPS (FASBPS)

Treatment group	Placebo	12 SQ-Bet (N=283)	Overall (N=575)
Adolescents			
N	32	25	57
Mean (SD)	6.42 (5.21)	5.23 (4.28)	5.90 (4.82)
Median	5.46	3.62	4.62
p25%-p75%	3.05 – 8.42	2.22 – 7.82	2.36 – 7.82
p5%-p95%	0.09 – 18.27	0.55 – 12.71	0.41 – 15.89
Min-Max	0.08 – 21.80	0.41 – 15.89	0.08 – 21.80
Adults			
N	260	258	518
Mean (SD)	7.74 (6.07)	5.15 (5.30)	6.45 (5.84)
Median	6.61	3.79	4.78
p25%-p75%	2.68 – 12.24	1.23 – 7.33	1.89 – 9.46
p5%-p95%	0.05 – 17.95	0.00 – 16.63	0.00 – 17.47
Min-Max	0.00 – 33.53	0.00 – 38.86	0.00 – 38.86

Abbreviations: *N, number of subjects (FAS); n, number of subjects with observations; SD, standard deviation; P25%, 25% percentile; P75%, 75% percentile; P5%, 5% percentile; P95%, 95% percentile; TPS, Tree pollen season.*
Reference: *TT-04 CSR (4)*

Overall, there was no meaningful difference between the adult and adolescent subgroups in the TCS during the BPS or TPS. This finding has also been validated in an advisory board and online survey with UK allergy clinicians with experts stating they believed that SLIT tablet treatment would perform equivalently in adolescent and adult patients (see appendix J2 and J3).

d) Please perform all effectiveness analyses for UK patients only.

The TT-04 trial was conducted at 57 trial sites across Europe, including locations in Sweden, Finland, Denmark, Poland, Germany, the Czech Republic, France, and Russia. As the trial was not conducted in the UK, analysis of UK patients is not possible. However, the TT-04 results are deemed to be generalisable to the UK population, as underlined by the MHRA approval.

As discussed in the CS, the timing of the birch homologous group pollen seasons can vary from year to year and between countries. However, similar pollen seasons are seen across Western, Central, and Northern Europe for the trees within the birch homologous group. Therefore, pollen seasons representative of the UK pollen season would have been captured in the TT-04 trial, with the included trial sites being representative of the region and capturing any potential variations. Other aspects of the TT-04 trial design and its relevance to the UK were also validated with clinical experts. Notably, UK clinical experts confirmed that the SoC medications provided as part of the trial, which patients were free to use, are representative of the typical SoC for patients in UK clinical practice (see Appendix J2 and J6).

Additionally, the baseline characteristics of the TT-04 trial population were compared to the baseline characteristics of 746 adult patients with moderate to severe SAR included in a UK-based cross-sectional study investigating the burden and unmet need of AR. (21) The two populations were comparable in terms of age, sex, ethnicity, and asthma prevalence, as summarised in Table 9. Overall, given the similarities in the distribution of prognostic and demographic factors, it is anticipated that the observed efficacy in the TT-04 trial would be generalisable to a UK population.

Table 9: Baseline characteristics of TT-04 compared to a UK cross-sectional study

	TT-04	UK cross-sectional study (Price et al., 2015)
Mean age (SD)	36.1 (13.6)	42.1 (11.8)
Sex (% female)	53	67.4
Ethnicity (%)		
White	97	89.3
Asian	1	5.5
Black	<1	3.4
Other	1	1.9
Asthma diagnosis (%)	44	35.8

Abbreviations: *SD, standard deviation*
References: *TT-04 CSR (4); Price et al., 2015 (21)*

B 14. Priority question. Limited information on the REACT study were provided in the CS. Please provide the following:

a) A list of all specific types of allergen immunotherapy (AIT) with numbers of patients prescribed each.

In the REACT study, AIT was administered via subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT) drops, and SLIT tablets (including GRAZAX® (grass SQ SLIT tablet) and ACARIZAX® (HDM SQ SLIT tablet)). The study included AIT treatments for tree pollen, house dust mites, grass and 'others' allergens. Both native allergen and allergoid AIT formulations were included in the analysis. (22)

In the study cohort, 36,927 subjects were treated with SCIT, 4,816 with SLIT drops, and 3,754 with SLIT-tablets. 11,713 subjects were treated with grass AIT, 7,774 were treated with HDM AIT, 11,897 were treated with tree AIT, and 9,726 were treated with a different form of AIT. (22) A summary of the treatment patterns for subjects in the study is presented in Table 10. A breakdown of the patient numbers included in the different subgroups of the REACT study is presented in Figure 2.

Table 10: Treatment AIT medication patterns in the REACT study

	Main N=46,024		Pre-existing asthma N=14,614		No asthma N=27,137	
Treatment patterns[#]						
Monotherapy	44,450	97%	14,094	96%	26,225	97%
Co-administration	337	0·7%	104	0·7%	203	0·7%

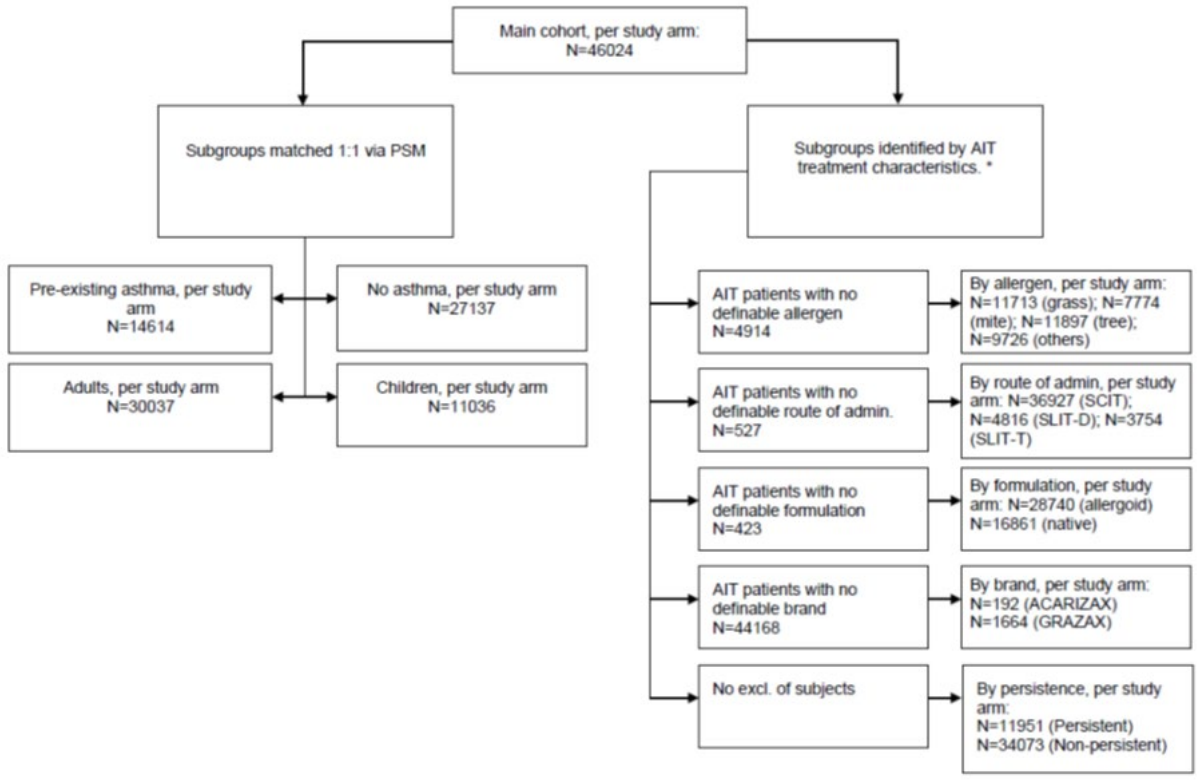
	Main N=46,024		Pre-existing asthma N=14,614		No asthma N=27,137	
SLIT-t + SLIT-t	7	0·02%	2	0·01%	5	0·02%
SLIT-t + SCIT	41	0·09%	13	0·09%	25	0·09%
SLIT-t + SLIT-d	32	0·07%	11	0·08%	19	0·07%
SLIT-d + SCIT	11	0·02%	4	0·03%	4	0·02%
Switch based on allergen	873	1·9%	281	1·9%	507	1·9%
Switch based on route of administration	251	0·5%	83	0·6%	143	0·5%

Notes: *# Categorical variables are presented as n %; Monotherapy: index-AIT prescriptions for one allergen only; Co-administration ≥ one prescription for a non-index AIT (based on allergen), in patients who have not discontinued the index-AIT. Any overlap between a new, non-index AIT and the index-AIT must last beyond 90 days (or until the end of follow-up if remaining follow-up time is <90 days), before it is recorded as a co-administration. For the analysis of co-administration of AIT, only pre-specified combinations factoring in the route of administrations were reported. In addition to the above, co-administration for SCIT was also captured, when as at least one prescription for a non-index-AIT prescription (without time requirements) and a least one procedure code for two AIT injections given on the same day was recorded >90 days after initiation of index-AIT. The time period of >90 days after initiation was needed to mitigate faster up-dosing regimen that may require more than one SCIT injections/day. Switch based on allergen / route of administration): a non-index AIT prescription within 90 days after the index-AIT was prescribed the last time and if no overlap of >90 days was recorded (co-administration).*

Abbreviations: *AIT, allergen immunotherapy; SLIT-t, sublingual immunotherapy tablet; SCIT, subcutaneous immunotherapy; SLIT-d, sublingual immunotherapy drops.*

Reference: *Fritzsching et al., 2022 supplementary information Table S4 (22)*

Figure 2: Flow chart for the identification of sub cohorts and subgroups in the REACT study



Notes: *In the pre-existing asthma cohort, 4,635 subjects could not be matched and were therefore lost from both the AIT-group and controls. Similarly, in the no asthma cohort 3,911 subjects, 6,091 children, and 3,183 adults*

*were not matched and therefore lost. *No PSM; treated patients were separated based on the treatment characteristic; the corresponding matched controls are not shown here. Pre-existing asthma: At least one asthma diagnosis or two prescriptions of SABA/ICS within the pre-index year. Children <18 years. Persistence: ≥ two index-AIT prescriptions in two consecutive follow-up (FU-years).*
***Abbreviations:** AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT-D /SLIT-T, sublingual immunotherapy drops/tablets; ICS, inhaled corticosteroids; SABA, short-acting beta2-agonists; PSM, propensity score matching.*
***References:** Fritzsching et al., 2022 supplementary information Figure S3 (22)*

b) Mean treatment duration for each type of treatment.

This data was not reported in the REACT study; however, the duration of treatment with any AIT is presented in Table 11.

Table 11: The duration of treatment with any AIT in the REACT study

	Main N=46,024		**Pre-existing asthma N=14,614**		**No asthma N=27,137**	
Duration of treatment with any AIT (days)						
	Mean	SD	Mean	SD	Mean	SD
Duration until first discontinuation	216	118	218	120	215	116
Total duration of days on any AIT	826	473	851	479	812	470

***Abbreviations:** AIT, allergen immunotherapy; SD, standard deviation*
***Reference:** Fritzsching et al., 2022 supplementary information Table S4 (22)*

c) The numbers of patients who received each treatment type with moderate to severe AR or allergic conjunctivitis or both caused by pollen from the birch homologous group or the closest subgroup to this.

The breakdown of subjects by treatment type in the REACT study is presented in the company's response to B.14.a). No further breakdown on the number of patients receiving each treatment type within the tree AIT subgroup is reported.

d) All outcomes for each of the treatments, including for those with moderate to severe AR or allergic conjunctivitis or both caused by pollen from the birch homologous group or the closest subgroup to this.

The REACT study was presented in the CS to support the long-term effectiveness of AIT treatments for patients with AR with or without AA, including those sensitised to tree pollen, in a real-world setting. The individual patient data from this study is not available to inform post-hoc analysis. However, an analysis was performed to assess

the primary endpoint, the change in prescriptions from pre-index year to year 3, for the different types of AIT. This analysis is presented in Table 12.

Table 12: REACT subgroup analysis on the change from pre-index year to year 3 in AR prescriptions by AIT modality

	Rx/ subject	SD	Change from pre-index	95% CI	Rx/ subject	SD	Change from pre-index	95% CI
Grass AIT	**AIT N=7,817**				**Control N=7,817**			
AR Rx*	0·597	1·3342	-0·513	-0·563;-0·465	0·654	1·649	-0·372	-0·427;-0·317
Tree AIT	**AIT N=8,426**				**Control N=8,426**			
AR Rx*	0·554	1·245	-0·358	-0·399;-0·316	0·541	1·401	-0·344	-0·391;-0·297
HDM AIT	**AIT N=5,224**				**Control N=5,224**			
AR Rx*	0·663	1·445	-0·527	-0·591;-0·464	0·698	1·614	-0·400	-0·468;-0·332
Other AIT	**AIT N=7,395**				**Control N=7,395**			
AR Rx*	0·634	1·377	-0·448	-0·499;-0·396	0·632	1·536	-0·358	-0·413;-0·303
Native allergens	**AIT N=12,216**				**Control N=12,216**			
AR Rx*	0·584	1·331	-0·454	-0·492;-0·416	0·610	1·559	-0·357	-0·399;-0·314
Allergoids	**AIT N=19,623**				**Control N=19,623**			
AR Rx*	0·624	1·352	-0·462	-0·493;-0·431	0·639	1·536	-0·392	-0·426;-0·359
SCIT	**AIT N=25,962**				**Control N=25,962**			
AR Rx*	0·599	1·326	-0·443	-0·469;-0·417	0·633	1·564	-0·388	-0·418;-0·358
SLIT drops	**AIT N=3,576**				**Control N=3,576**			
AR Rx*	0·672	1·416	-0·529	-0·608;-0·450	0·573	1·399	-0·359	-0·432;-0·285
SLIT tablets	**AIT N=2,223**				**Control N=2,223**			
AR Rx*	0·638	1·443	-0·510	-0·604;-0·416	0·646	1·460	-0·309	-0·404;-0·213
Persistent >2-year AIT	**AIT N=9,840**				**Control N=9,840**			
AR Rx*	0·658	1·358	-0·495	-0·540;-0·450	0·648	1·566	-0·361	-0·409;-0·314
Non-persistent <2-year AIT	**AIT N=22,272**				**Control N=22,272**			
AR Rx*	0·587	1·323	-0·442	-0·470;-0·414	0·620	1·534	-0·387	-0·419;-0·356

Notes: **continuous variables are reported as mean ± standard deviations (SD); prescriptions are reported as Rx/subject; children < 18 years of age, adults ≥ 18 years of age; HDM: house dust mite; persistent subjects: ≥ two index-AIT prescriptions in two consecutive follow-up years; non-persistent subjects < two index-AIT prescriptions in two consecutive follow-up years.*
Abbreviations: *AIT, allergen immunotherapy; AR, allergic rhinitis; CI, confidence interval; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy.*
Reference: *Fritzching et al., 2022 supplementary information Table S20 (22)*

B 15. Please provide details on the randomisation process and how patients were recruited to placebo or treatment groups.

The randomisation list was generated by a trial-independent statistician by using random sampling (block size, 4). To randomise a subject, the investigator allocated the lowest randomisation number at the site to the subject. Two sets of sealed envelopes contained treatment allocation (1 at the trial site and one at the sponsor). The sequence was not accessible to trial personnel until database lock and trial unblinding. In case of a medical emergency, the code could be broken for a particular subject if treatment knowledge was necessary for optimal treatment.

B 16. Please describe how allocation concealment was ensured.

Subjects, investigative staff, and sponsors were blind to treatment allocation. Two sets of sealed envelopes contained treatment allocation (one at the trial site and one at the sponsor). The sequence was not accessible to trial personnel until the database lock and trial unblinding. In case of a medical emergency, the code could be broken for a particular subject if treatment knowledge was necessary for optimal treatment.

Adverse events

B 17. Priority question. The discontinuation rate due to adverse events (AEs) was higher in the treatment group. Please provide a full breakdown of the nature and severity of these events for both groups.

A breakdown of all AEs that led to discontinuation in the 12 SQ-Bet treatment group in the TT-04 trial is provided in Table 13. All AEs were deemed to be possibly related to the investigational medicinal product (IMP).

Table 13: AEs leading to discontinuation in the 12 SQ-Bet treatment group of the TT-04 trial

Subject	AE preferred term	Severity	Outcome	Treatment duration (days)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subject	AE preferred term	Severity	Outcome	Treatment duration (days)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subject	AE preferred term	Severity	Outcome	Treatment duration (days)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Reference: *TT-04 CSR. (4)*

A breakdown of all AEs that led to discontinuation in the placebo treatment group in the TT-04 trial is provided in Table 14.

Table 14: AEs leading to discontinuation in the placebo treatment group of the TT-04 trial

Subject	AE preferred term	Severity	Relation to IMP	Outcome	Treatment duration (days)
[redacted]					

Reference: *TT-04 CSR (4)*

Section C: Clarification on cost-effectiveness data

Treatment effectiveness and discontinuation

C 1. Priority question. Please address the following issues regarding long-term effectiveness.

a) Please clarify whether the duration of the sustained treatment benefit for patients who discontinue AIT should depend on time on treatment (e.g., it seems reasonable to assume that patients who discontinue early would experience less sustained benefit than those who were on treatment for a longer time).

It is reasonable to assume that patients who discontinue treatment early would experience a shorter sustained benefit than those who were on treatment for the full three years. The impact of time on treatment (early discontinuation) on sustained

treatment benefit is already accounted for in the model in the 'Effectiveness' sheet, wherein the proportion of patients who discontinue treatment early (in either the 1st, 2nd, or 3rd years of treatment) that continue to receive treatment benefit is defined. Given how treatment benefit is applied in the model, the proportion of patients receiving treatment benefit after early discontinuation is analogous to discontinuing patients receiving treatment benefit for a shorter period of time. This approach to modelling the impact of early treatment discontinuation on sustained treatment benefit is consistent with the approach accepted by the Committee in the previous technology appraisal for an AIT (12 SQ-HDM), TA834.

b) If a sustained benefit indeed depends on time on treatment, please include this option in the economic model.

As outlined in the company's response to C.1.a), the impact of time on treatment (early discontinuation) on sustained treatment benefit is already accounted for in the model in the 'Effectiveness' sheet, wherein the proportion of patients who discontinue treatment early (in either the 1st, 2nd, or 3rd years of treatment) that continue to receive treatment benefit is defined, consistent with the approach accepted by the Committee in TA834.

c) On page 117 of the CS, it is mentioned that "International treatment guidelines and consensus statements refer to a treatment period of three years for AIT to achieve disease modification after its cessation". Please clarify whether patients will achieve disease modification if treatment is discontinued before 3 years. Please discuss the consequences of not achieving disease modification.

The full duration of sustained treatment effect is assumed to apply to patients who complete three years of treatment. During an advisory board, it was noted that patients who discontinue AIT treatment early may still receive treatment benefit following treatment cessation (Appendix J5), which would be indicative of achieving disease modification. Two out of three clinicians said that half of patients who discontinue may still receive benefits, while one clinician said this would be a small number of patients; therefore, in the base case it is assumed that 50% of patients who discontinue treatment early (in either Year 1, Year 2, or Year 3) will continue to receive treatment benefit following treatment cessation. It follows that the remaining

patients who discontinue early do not continue to receive treatment benefit following treatment cessation, indicative of not achieving any disease modification. As outlined in the company's response to C.1.a), the proportion of patients receiving sustained treatment benefit after early discontinuation is analogous to discontinuing patients receiving treatment benefit for a shorter period of time, given how treatment benefit is applied in the model. This approach to modelling the impact of early treatment discontinuation on long-term effectiveness is consistent with the approach accepted by the Committee in TA834.

d) **Please clarify if 12 SQ-Bet treatment durations longer than 3 years are observed in clinical practice. If that's possible, please include that option in the economic model**

UK clinical practice is likely to reflect international treatment guidelines and consensus statements that refer to a treatment period of three years for AIT to achieve disease modification after its cessation. This approach of modelling three years of AIT treatment and a sustained treatment effect thereafter is consistent with that used in Pollock et al., 2023 (23), and the approach accepted by the Committee in TA834.

e) **On page 121 of the CS, it is mentioned that "it was agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade, with treatment effectiveness unlikely to completely disappear". Please clarify whether this sustained effect refers to 10 years after completing 3 full years of treatment and if the same duration of the sustained effect would be expected if patients completed only 1 or 2 years of treatment.**

As outlined in the company's response to C.1.c), it is assumed that the full sustained effect for at least 10 years following treatment cessation would apply to patients after completing 3 years of treatment and achieving disease modification. In the model, treatment waning starts at Year 15, in line with the accepted assumptions in TA834. According to clinical expert opinion from an advisory board, patients who discontinue AIT treatment early may still receive treatment benefit following treatment cessation (Appendix J5), indicating that these patients may achieve disease modification. This

is accounted for in the model 'Effectiveness' sheet, wherein the proportion of patients who discontinue treatment early (in either the 1st, 2nd, or 3rd years of treatment) that continue to receive treatment benefit is defined. Given how treatment benefit is applied in the model, the proportion of patients receiving treatment benefit after early discontinuation is analogous to discontinuing patients receiving sustained treatment benefit for a shorter period of time. This is consistent with the approach accepted by the Committee in TA834.

C 2. Priority question. Please answer the following questions regarding treatment discontinuation.

a) **Please justify the assumption that 50% of patients who discontinue treatment with 12 SQ-Bet may continue to receive treatment benefit. Please explain whether 50% is arbitrary or not.**

As outlined in the company's response to C.1., the assumption that 50% of patients who discontinue treatment with 12 SQ-Bet may continue to receive treatment benefit is informed by clinical opinion and is aligned with the accepted assumptions in TA834. During an advisory board, it was noted that patients who discontinue AIT treatment early may still receive treatment benefit. Two out of three clinicians said that half of patients who discontinue may still receive benefits (informing the 50% used in the model base case), while one clinician said this would be a small number of patients (Appendix J5). The impact of using different assumptions around the proportion of patients receiving treatment benefit following discontinuation was explored in scenario analysis presented in Table 54 of the CS. Using the most conservative assumption, assuming no patients would continue to receive treatment benefit following early discontinuation, the incremental costs and QALYs were -£1,552, and 0.09, respectively (dominant ICER), compared to -£1,852 and 0.10 in the base case.

b) **Please justify the assumption that the discontinuation due to non-AE reasons observed in the trial (4.38 %) can be applied in the second and third cycle, in light of the findings from e.g. Pfaar et al. 2023 (doi.org/10.1002/clt2.12245) and Kiel et al. 2013 (doi.org/10.1016/j.jaci.2013.03.013).**

Clinical experience in the UK is that patients are generally adherent to treatment, with those who do not experience tolerability issues generally completing the full course of treatment. Furthermore, it is important to note that access to AIT is significantly different in Germany (where Pfaar et al. conducted their study) and the UK, with AIT use being far more frequent, and more heterogeneous including multiple unlicensed treatments used by patients with milder disease. In the UK, SLIT is accessed through secondary care, at which point patients who have been referred experience a significant disease burden and are highly motivated to continue treatment. Consequently, persistence estimated by Pfaar et al. does not reflect the experience of 12 SQ-Bet use in UK clinical practice and the discontinuation rates observed in the TT-04 trial likely offer the best estimate of what would be observed in UK clinical practice.

Mortality

C 3. Please clarify from what year the UK life tables were sourced. Please include in the economic model the option to select UK life tables before COVID-19, if these are not used in the economic model.

The model has been updated with life tables from the latest version of the 'National life tables: England and Wales' dataset published by the ONS (release date: 23rd October 2024). The model now also includes the option to select life tables based on data for the years 2021-2023 or based on data for the years 2016-2018 (before COVID-19) in the model sheet "Mortality".

Adverse events

C 4. Priority question. Please address the following issues regarding AEs.

a) Please explain the difference between severity and seriousness.

Severity and seriousness are standard terms often used to describe AEs in clinical trials. Severity refers to the intensity of the event, while seriousness refers to the outcome of or action criteria associated with the event.

In the TT-04 trial, the severity of an AE was a clinical observation assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

A serious AE was any untoward medical occurrence or effect that at any dose:

- Resulted in death
- Was life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe)
- Required inpatient hospitalisation regardless of duration or prolongation of existing hospitalisation
- Resulted in persistent or significant disability or incapacity
- Resulted in a congenital anomaly or birth defect
- Was judged medically important (refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above – e.g., AEs that result in intensive medical treatment at the emergency room or at-home)

Therefore, a severe reaction does not necessarily need to be considered serious e.g., a swollen lip that is unacceptable to the patient, while a serious reaction is not necessarily related to the treatment e.g., another member of the household swallowing a patient's tablet.

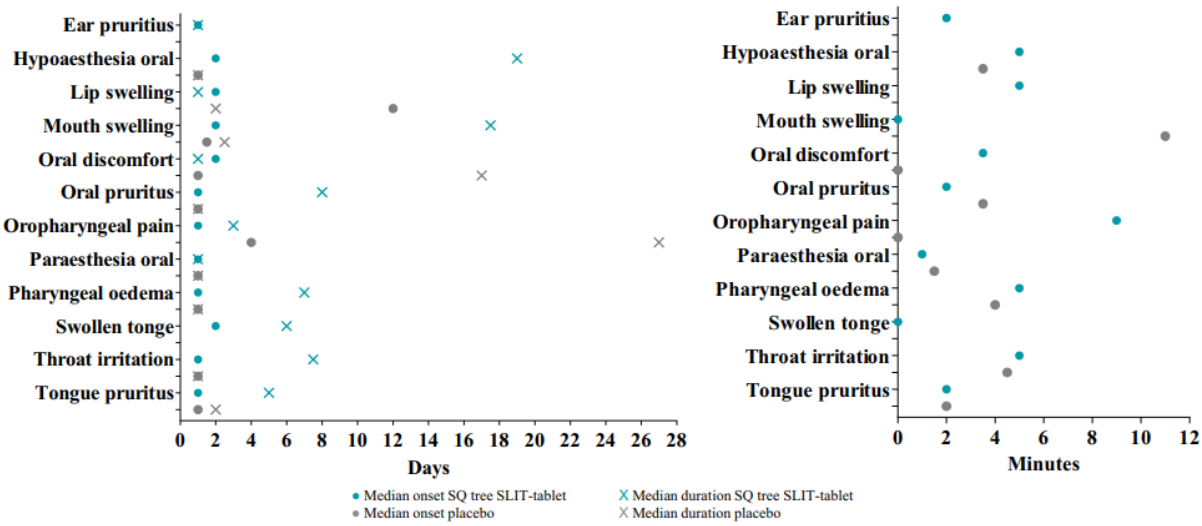
b) **Based on the values presented in Table 35 of the CS, 75% of patients in the intervention arm experienced on average more than 3 IMP (Investigational medicinal product)-related AEs. Looking at the division between severity categories, it's clear that some patients experienced multiple AEs of (possibly) different severity. Because in**

more than 18% of the cases in the intervention arm, an action was taken, the External Assessment Group (EAG) considers that this value is large enough to grant inclusion in the economic model.

i. **Please include in the model the effect of AEs in health-related quality of life (HRQoL) as well (while keeping the effect on costs). Please implement this in a multiplicative way to align with the NICE reference case.**

The model includes the option to model the effect of AEs on HRQoL in the model sheet “Adverse Events”. This is applied as a weighted QALY loss in the first model cycle only as the majority of the most frequent treatment-related AEs (TRAE) had a median onset within 1 to 12 minutes after the first IMP intake, with very few new AEs starting at a later time point (see Figure 3). In the model base case, no AE-related utility decrements (Cells L18:L25) were applied to the modelled AEs as the SLR on the HRQoL of patients with birch pollen-induced AR did not identify any utility values for the AEs associated with SLIT. Furthermore, given the reported severity and short duration of the reported TRAEs (see Figure 3), the exclusion of specific utility decrements does not have any material impact on the cost-effectiveness of 12 SQ-Bet (e.g., applying an arbitrary disutility of -0.02 for each of the most common TRAEs gives an incremental net monetary benefit (INMB) of £3,857 (total incremental QALYs = 0.1006) at a willingness-to-pay (WTP) threshold of £20,000/QALY, compared to an INMB of £3,865 (total incremental QALYs = 0.1010) with no utility decrement assumed.

Figure 3: Median onset and duration of most frequent treatment-related AEs (experienced by ≥ 5% of subjects treated with 12 SQ-Bet)



Notes: *Left, Median onset and duration of AE. Duration is given as time from onset until resolution (reoccurring AEs given from first to last day of appearance). Overlapping symbols indicate resolution on same day of occurrence. Right, Median onset of AE for AEs starting on the first day of treatment.*
Reference: *Biedermann et al., 2019 (24)*

ii. In Table 35 please clarify how to interpret the values "Temporary interrupted" and "IMP discontinued" since the values in column "e" are much larger than in column "n". Please clarify whether these data have been included in the model and how.

In the TT-04 trial, treatment could be temporarily interrupted for the following reasons:

- In case of oral surgery, including dental extraction, to allow healing of the oral cavity
- Inflammatory conditions in the oral cavity
- Upper airway viral infection in an asthmatic subject
- Other reasons if deemed necessary by the investigator

If IMP was interrupted for more than 7 days in a row, the investigator was to be contacted before restarting the treatment. Based on the length of the IMP interruption and previously experienced AEs, the investigator evaluated whether the subject should resume treatment at the clinic or at-home, or if IMP should be discontinued permanently. If IMP treatment was permanently discontinued, the subjects were discontinued from the trial.

The values in column "e" represent the number of IMP-related AEs, whereas the values in column "n" represent the number of subjects with IMP-related AEs leading

to temporary interruption of treatment or discontinuation. The values in column “e” are larger than in column “n” as each subject could experience multiple IMP-related AEs leading to temporary interruption of treatment or discontinuation.

The number of subjects who discontinued treatment (IMP discontinued) in the 12 SQ-Bet arm is included in the model to calculate the rate of discontinuation due to AEs. In total, 24 subjects out of 320 (7.5%) in the 12 SQ-Bet arm discontinued treatment due to IMP-related AEs and this is applied in the first model cycle only, as the majority of the most frequent IMP-related AEs had a median onset within 1 to 12 minutes after first IMP intake with very few new IMP-related AEs starting at a later time point. Furthermore, the majority of discontinuations due to AEs occurred within the first two months of treatment, with only one discontinuation occurring later than that, at 115 days.

c) **On page 100 of the CS, it is mentioned that “by the end of the trial 33 subjects (5%) were discontinued from the trial, 25 (8%) subjects in the 12 SQ-Bet group discontinued due to 98 AEs, while 8 (3%) subjects in the placebo group discontinued due to 15 AEs”. Please clarify whether that statement matches with the data shown in Table 35 and how. Please indicate the timing of the discontinuations as well (e.g., in what month they were observed).**

The quoted text on page 100 of the CS refers to discontinuations due to all AEs whereas Table 35 presents IMP-related AEs only. Most subjects in the 12 SQ-Bet treatment group who discontinued due to AEs did so within the first 31 days (22/25 subjects; 88%) as presented in Table 13.

d) **Please explain how an adverse event “of interest” is defined and what criteria were applied for inclusion in the economic model.**

In the TT-04 trial, AEs of interest were pre-defined based on the mode of administration (oral lyophilisate) and mechanism of action (exposing the subject to the allergen) of 12 SQ-Bet. The following were defined as AEs of interest:

- Local administration site reactions (swelling, itching, pain, redness, blister, etc.) – a potential risk when administrating a drug orally. 12 SQ-Bet is an oral

lyophilisate for sublingual use and rapidly disintegrates under the tongue, releasing the allergen extract on the oral mucosa.

- Systemic allergic reactions – as 12 SQ-Bet is developed for treatment of an allergic disease by exposing the subject to the allergen, there is a risk that the immunotherapy itself can trigger a systemic allergic reaction.
- Laryngo-pharyngeal reactions – local allergic reactions such as swellings in the laryngo-pharyngeal area may put the patient as risk by leading to breathing difficulties or suffocation.

The AEs included in the model are the eight most frequently reported IMP-related AEs from the TT-04 trial.

e) **Given that the treatment duration was less than a year in the TT-04 trial, please include in the model the option to experience treatment-related adverse events (and their associated costs and quality-adjusted life year (QALY) loss) while patients are on treatment and not only during the first year. Please discuss the plausibility of this assumption.**

The model has been updated to include the option for patients to experience AEs while on treatment or in the first cycle only using the “Method for applying AEs” dropdown in the model sheet “Adverse Events”.

The majority of the most frequent treatment-related AEs in the TT-04 trial had a median onset within 1 to 12 minutes after first IMP intake, with very few new AEs starting at a later time point (see Figure 3). Therefore, as most AEs are associated with treatment initiation, it is most appropriate to assume that all AEs occur in the first model cycle only, rather than applying them in each cycle while patients are on treatment. Furthermore, it is inappropriate to apply a cycle probability of experiencing AEs for the duration that patients are on treatment based on the frequencies observed in the trial. This would likely provide an implausible overestimate of the incidence of AEs in Year 2 and Year 3 of treatment as AEs associated with treatment initiation (the majority of AEs observed in the trial) would be repeatedly incurred.

f) **The selection of AEs included in the economic model in Table 40, seems arbitrary looking at those shown in Table 36. Please explain why lip swelling or hypoaesthesia oral were not included in Table 40 for**

example, and why oral discomfort and oropharyngeal pain are not in Table 36.

The AEs included in the model are the eight most frequently reported IMP-related AEs from the TT-04 trial. Table 36 presents the severe IMP-related AEs observed in the TT-04 trial, whereas Table 40 presents the eight most frequently reported IMP-related AEs from the TT-04 trial (regardless of severity). Lip swelling and hypoaesthesia oral were not among the eight most frequently reported IMP-related AEs in the TT-04 trial hence they are not included in Table 40. No oral discomfort or oropharyngeal pain AEs in the TT-04 trial were categorised as severe and hence they are not included in Table 36.

g) **On page 125 of the CS, it is mentioned that "the model assumes that all AEs, and their associated costs and QALY loss, occur in the first model cycle only". However, on page 131 it is mentioned that "in the model base case, no AE-related utility decrements were applied to the modelled AEs". Please clarify this discrepancy. In any case, please include in the model utility decrements associated to AEs, and let the model have the option to apply those while patients are on treatment (so not only during the first year).**

As described in the company's response to C.4.b), the model includes the option to model the effect of AEs on HRQoL in the model sheet "Adverse Events". This is applied as a weighted QALY loss in the first model cycle only (as indicated in the quoted text on page 125 of the CS which describes the functionality of the model). In the model base case, no AE-related utility decrements (Cells L18:L25) were applied to the modelled AEs (as described in the quoted text on page 131 of the CS), as the SLR on the HRQoL of patients with birch pollen-induced AR did not identify any utility values for the AEs associated with SLIT. Furthermore, given the reported severity and duration of the reported TRAEs, the exclusion of specific utility decrements does not have any material impact on the cost-effectiveness of 12 SQ-Bet.

Utility decrements associated with each of the modelled AEs can be input in cells L18:L25 in the model sheet "Adverse Events". No suitable sources for utility values for the modelled AEs were identified in the SLR, nor were suitable proxies identified

in the literature. Therefore, to assess the impact of AE-related utility decrements on cost-effectiveness an arbitrary disutility of -0.02 was applied to all modelled AEs. With AEs applied in the first cycle only, this resulted in an INMB of £3,857 (total incremental QALYs = 0.1006) at a WTP threshold of £20,000/QALY, compared to an INMB of £3,865 (total incremental QALYs = 0.1010) with no utility decrement assumed. With AEs applied while on treatment, this resulted in an INMB of £3,836 (total incremental QALYs = 0.1003) at a WTP threshold of £20,000/QALY, compared to an INMB of £3,848 (total incremental QALYs = 0.1010). Overall, due to the short duration of the reported TRAEs in the TT-04 trial, the impact of AE-related utility decrements on cost-effectiveness is minimal.

As outlined in the company's response to C.4.e), the model has been updated so that it includes the option for patients to experience AEs (and any associated utility decrement) while on treatment. However, as most AEs in the TT-04 trial were associated with treatment initiation, it is most appropriate to assume that all AEs occur in the first model cycle only, rather than applying them in each cycle while patients are on treatment.

HRQoL

C 5. Please clarify the purpose of the studies identified in Section 3.4.3 of the CS and whether the company have deemed all studies irrelevant except Dick et al. 2019.

Section 3.4.3 of the CS discusses relevant studies identified by the HRQoL and utilities SLR which published health state utility values (HSUVs) that could be relevant for health economic modelling, following a relevance assessment of included studies using the NICE reference case (see Section 3.5.2 of Appendix F for further details on the NICE reference case parameters for HSUVs). As discussed, Dick et al., 2019 (25) was the only publication identified in the SLR which published utility values for ARC caused by pollen from the birch homologous group and hence deemed the only relevant study for inclusion in the economic model.

C 6. On page 132 of the CS, it is mentioned that "treatment benefit of 12 SQ-Bet is applied as a disutility to the SoC arm, with the 12 SQ-Bet arm taking on general population utilities". Please discuss the

plausibility of that assumption since looking at Figure 19 there seems to be a decline in HRQoL also for the intervention group (so lower utilities than in the general populations might be expected). Please adjust the economic model to include this observed decline in HRQoL in the intervention group as well.

As the benefit of 12 SQ-Bet is applied as a disutility to the SoC arm, with the 12 SQ-Bet arm taking on general population utilities this means that the total QALYs may not be reflective of ARC patients' but the incremental QALY gain correctly reflects the difference between 12 SQ-Bet and SoC accrued over the model time horizon. While ARC patients' would be expected to have reduced HRQoL compared to the general population (as observed in Figure 19 of the CS), applying a utility decrement to reflect this would have no impact on the incremental cost-effectiveness results as this would apply to both treatment arms, with the fixed treatment-specific utility decrement, and consequently the total incremental QALYs would remain the same.

C 7. In the economic model it is mentioned that general population utilities are derived from Ara and Brazier 2010. To align with the NICE reference case, please replace these by those derived from Hernandez Alava, M., Pudney, S., and Wailoo, A. (2022) Estimating EQ-5D by age and sex for the UK. NICE DSU Report. 2022

The general population utilities derived from Hernandez Alava, M., Pudney, S., and Wailoo, A. (2022) Estimating EQ-5D by age and sex for the UK. NICE DSU Report. 2022 have been added into the model. These can be selected using the dropdown "Age- and sex- adjusted utilities source" in the model sheet "HRQoL".

Resource use and costs

C 8. Priority question. The CS states: "Additionally, in line with the NICE final scope, to account for a requirement of a positive test for birch pollen sensitisation, the cost of a diagnostic blood test is included in the administration costs of treatment (£2.75, National Schedule of NHS costs, DAPS05). In the model, administration costs are applied to all patients in the 12 SQ-Bet arm in cycle 0 only". At the point in the care pathway where they

might be eligible for the intervention, what percentage of patients receive the test in current clinical practice? Please apply the test cost to this percentage in the comparator arm and 100% of those tested in the intervention arm.

The cost of diagnostic testing has been added into the model and the proportion of patients receiving the diagnostic test is input in the "Costs" sheet. There is uncertainty around the percentage of patients receiving the test in current clinical practice; therefore, different scenarios are presented in Table 15 to demonstrate the impact of different assumptions on cost-effectiveness (100% of the intervention arm are tested in all scenarios). Overall, the different assumptions for what proportion of patients receive the test in current clinical practice and hence the proportion of the comparator arm being tested have little impact on cost-effectiveness.

Table 15: Diagnostic testing in comparator arm scenarios

Proportion of comparator arm being tested	Incremental costs	Incremental QALYs	ICER
0%	-£1,845.46	0.10	Dominant
25%	-£1,846.14	0.10	Dominant
50%	-£1,846.83	0.10	Dominant
75%	-£1,847.52	0.10	Dominant
100%	-£1,848.21	0.10	Dominant

Abbreviations: *ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year*

C 9. Please clarify whether data on medication use derived directly from the integrated clinical trial report for TT-04 (page 133 of the CS) refers to the data shown in Table 44, and whether these are the same as in Pollock et al. 2023.

Table 44 in the CS presents the symptom-relieving medication resource use by treatment arm in the TT-04 trial, as reported in Pollock et al., 2023. (23) However, it was not reported in the publication how these values were calculated (e.g., whether they were calculated using daily medication scores or if data from the BPS or TPS were used). Therefore, for the CS model it was deemed most appropriate to derive data on medication use directly from the integrated clinical trial report for TT-04. The mean daily doses of each pharmacotherapy within the BPS and TPS are derived directly from the integrated clinical trial report and multiplied by 137 days to calculate the annual dose (aligned with the length of the full dataset from Dick et al., 2019 (25)), as it is assumed that pharmacotherapy is only required during the pollen season.

C 10. Please discuss any potential concerns regarding 12 SQ-Bet treatment compliance in daily practice and how they could impact the economic model results. Please include treatment compliance in the economic model.

Clinical experience in the UK is that patients are generally adherent to treatment, with those who do not experience tolerability issues generally completing the full course of treatment. 12 SQ-Bet is accessed in secondary care, at which point patients who are referred are experiencing a significant disease burden and are highly motivated to adhere to treatment. Therefore, it is likely that the compliance in the TT-04 trial (95.9% (4)) is reflective of what would be observed in UK clinical practice.

The treatment-specific utility difference derived from Dick et al., 2019 (25) is based on the TT-04 trial; therefore, the modelled treatment effect already inherently accounts for treatment compliance. Consequently, adding treatment compliance in the model would only impact costs, which would be reduced by 4.1%, and therefore the model base case provides a conservative scenario in this context. Furthermore, exploring additional scenarios around treatment compliance below that which was observed in the TT-04 trial would have little material impact on the ICER, as the modelled costs and benefits would be reduced proportionally.

C 11. Please compare the costs associated with the management of patients in primary and secondary care, and the anticipated reduction in healthcare resource utilisation (Table 48), with those considered in technology appraisal (TA) 834.

The costs associated with the management of patients in primary and secondary care are applied in a similar way to TA834, in a treatment-specific manner, with the baseline annual average number of visits modelled in the established clinical management arm and a relative reduction in the number of visits applied in the 12 SQ-Bet arm, reflecting the improvement in disease control in these patients. The annual average number of visits is multiplied by the unit cost per GP surgery consultation (primary care) or consultant-led outpatient attendance (secondary care) using the same sources for these costs as in TA834. Therefore, any differences in management costs compared to those considered in TA834 are due to differences in

the estimates for the average annual number of visits to primary and secondary care and the relative risk reduction associated with AIT treatment.

In TA834, the annual average number of primary care visits for the AR population, 1.7, was informed by clinical expert opinion derived in a Delphi panel. The relative reduction in GP visits associated with 12 SQ-HDM, 4.92%, was informed by data collected in the MT-06 trial. The annual average number of secondary care visits in TA834, 2.66, was derived from an assessment of Hospital Episode Statistics data for the average number of episodes per patient between 2016-2021 in each hospital setting (elective day case, elective inpatient, emergency, outpatient) for the overall allergy patient cohort at a national level. The relative reduction in secondary care visits for the AR population, 73.53%, was informed by an observational, retrospective study conducted in Spain which reported the healthcare resource use for patients treated with SCIT with HDM-induced AA and/or AR. (26)

No data was collected in the TT-04 trial on healthcare resource utilisation. Furthermore, the study used for the relative reduction in secondary care visits in TA834 was not deemed applicable to this appraisal, as it was conducted in Spain, in a different patient population, and patients were treated with SCIT as opposed to SLIT. Therefore, the company conducted a probabilistic Delphi panel comprising three consultant allergists and two GPs with a specialist interest in allergy and experience with AIT, to derive clinically informed estimates for the healthcare resource utilisation (number of visits to primary and secondary care) of patients with birch pollen-induced AR and the anticipated healthcare resource utilisation for patients treated with 12 SQ-Bet (Appendix J6). As reported in Table 48 in the CS, for patients treated with symptomatic pharmacotherapy, the median number of visits to a GP was judged to be 2.61; for patients receiving the average treatment effect of 12 SQ-Bet, the median number of GP visits was judged to be 1 (relative risk reduction: 61.7%). For patients treated with symptomatic pharmacotherapy, the median number of visits to secondary care was judged to be 1.93; for patients receiving the average treatment effect of 12 SQ-Bet, the median number of secondary care visits was judged to be 0.75 (relative risk reduction: 61.1%).

The annual average number of primary and secondary care visits and the relative risk reduction with 12 SQ-Bet and 12 SQ-HDM used in the CS and in TA834 are

presented in Table 16. Overall, the data for secondary care utilisation is comparable to TA834, with slightly more conservative estimates for the baseline annual outpatient visits and the relative risk reduction with 12 SQ-Bet applied in the CS. The larger discrepancy in the values for primary care is likely explained by the fact that the Delphi panel informing the value used in TA834 included patients with mild disease, who would be expected to visit the GP less frequently compared to those with moderate to severe disease. On the other hand, participants in the probabilistic Delphi panel informing the estimates used in the CS considered only patients with moderate to severe birch pollen-induced AR (the population relevant to this appraisal). It is also important to note that in MT-06, the TCS was significantly reduced by 1.21 (p=0.029), corresponding to a relative difference of 13% in the 12 SQ-HDM group compared to placebo. (27) In TT-04, the TCS was significantly reduced by 3.02, corresponding to a relative difference of 40% in the 12 SQ-Bet group compared to placebo (p<0.0001). (4) While the populations are not directly comparable due to the different causative allergens, 12 SQ-Bet led to a greater relative reduction in TCS in TT-04 compared to 12 SQ-HDM in MT-06, indicating that a greater relative reduction in healthcare resource utilisation would also be expected.

Table 16: Primary and secondary care resource utilisation in the CS and TA834

	CS	TA834
Primary care		
Annual GP visits (SoC)	2.61	1.7
Relative risk reduction with 12 SQ-Bet/12 SQ-HDM	61.7%	4.92%
Secondary care		
Annual outpatient visits (SoC)	1.93	2.66
Relative risk reduction with 12 SQ-Bet/12 SQ-HDM	61.1%	73.53%

Abbreviations: *CS, company submission; GP, general practitioner; SoC, standard of care;*
Reference: *Appendix J6.*

Model results

C 12. Table 50 indicates that the same standard errors (SE) has been chosen for all input parameters in the model. This seems an arbitrary choice which does not conform to best practices (SE's for each parameter should be informed separately, ideally based on trial or other source of data). This is especially clear in those parameters

informed by the Delphi panel (three participants only) for which the SE would be expected to be much higher than 10%. Please correct this in the economic model and re-run the DSA and PSA.

The model has been updated where parameter uncertainty was available but not used. The SE for mean age, primary and secondary care visits/relative reductions, and utility gain in each of the pollen seasons were available; for other parameters, a SE of 10% of the input value is assumed.

The PSA was re-run and the results for 2,000 iterations are presented in Table 17. The incremental costs and QALYs from the probabilistic analysis are comparable with the updated deterministic results (Table 18). The updated PSA scatter plot is shown in Figure 4. The ICER in the remained cost-effective with a dominant ICER in 86% of the iterations, and a probability of cost-effectiveness of 100% at a WTP threshold of £20,000/QALY.

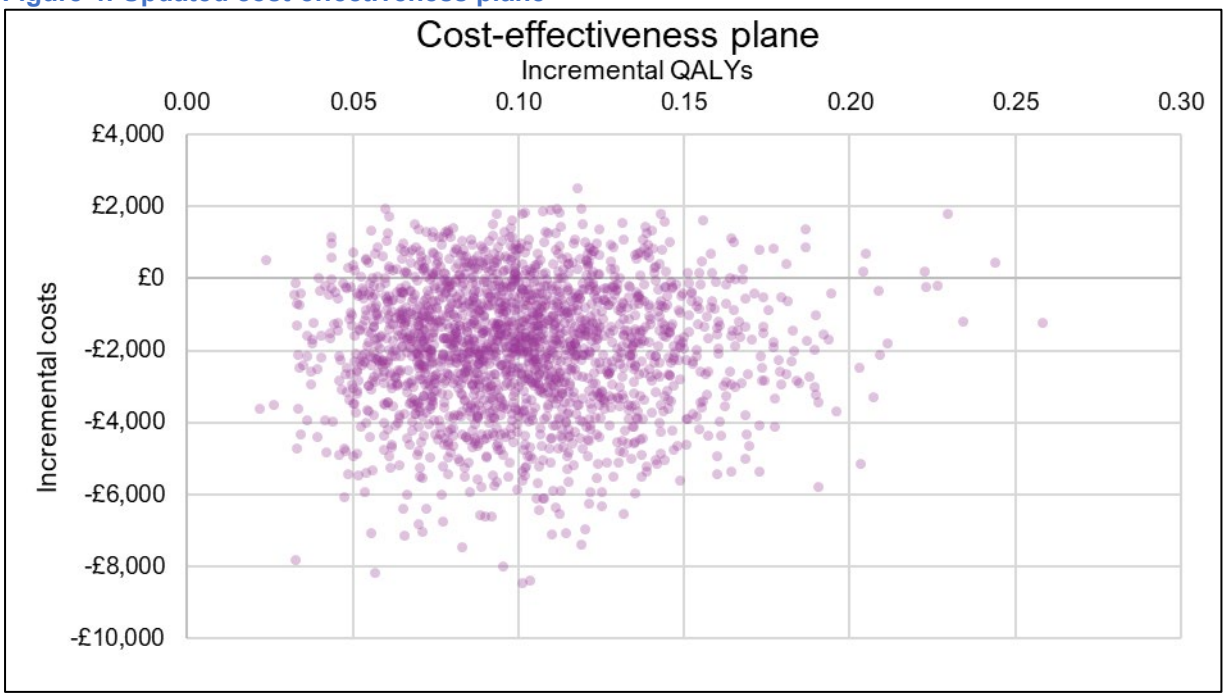
The DSA was also re-run, and the inputs with the greatest impact on the INMB are presented in descending order as a tornado plot in Figure 5. In none of the varied parameters did the ICER or INMB exceed a WTP threshold of £20,000/QALY. The cost-effectiveness of 12 SQ-Bet is most sensitive to changes in secondary care costs as well as the treatment-specific utility difference associated with the treatment benefit 12 SQ-Bet.

Table 17: Updated PSA results

Parameter	12 SQ-Bet	SoC	Incremental	ICER
Total costs (£)	£9,322	£11,209	-£1,886	12 SQ-Bet dominant
Total life years	22.58	22.58	0.00	
Total QALYs	19.32	19.21	0.10	

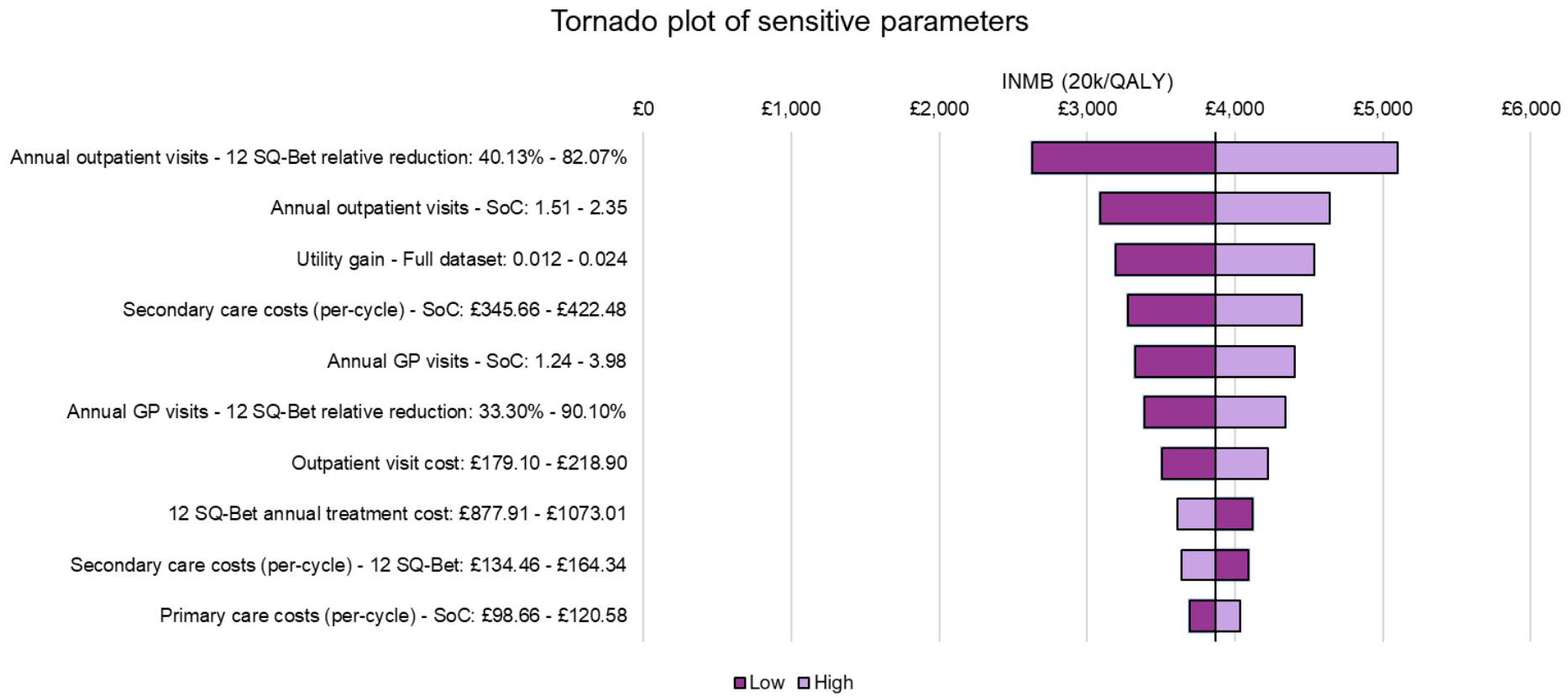
Abbreviations: *ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.*

Figure 4: Updated cost-effectiveness plane



Abbreviations: *QALY, quality-adjusted life year;*

Figure 5: Updated tornado plot of sensitive parameters in DSA



Abbreviations: *INMB, incremental net monetary benefit; QALY, quality-adjusted life year; SoC, standard of care.*

Model implementation

C 13. Priority question. There appear to be programming errors in the model engine, in the calculation of column W. When the percentage of patients discontinuing per year is set to e.g. 50% (sheet Effectiveness, cells E12:G12), column W shows values larger than 1, which leads to columns referring to number of patients on treatment (e.g. X, Y) to be negative. Please correct this error and provide a new set of results.

The coding in column W of the model engine has been amended. This has a minimal impact on the model results in the base case, presented in Table 18, with an INMB of £3,865 at a WTP threshold of £20,000/QALY. Please note that the updated base case results presented in Table 18 also reflect other model changes requested by the EAG in previous questions, most notably updated life tables and general population utilities.

Table 18: Updated base case deterministic results

Parameter	12 SQ-Bet	SoC	Incremental	ICER
Total costs (£)	£9,408	£11,253	-£1,845	12 SQ-Bet dominant
Total life years	22.58	22.58	0.00	
Total QALYs	19.31	19.21	0.10	

Abbreviations: *ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.*

C 14. When opening the model, a warning is given that the workbook is linked to two other Excel files. Please remove any links to other files, ensure that the model is still working, and highlight any changes made.

The model was reviewed for links to external files which were identified in the Name Manager and subsequently removed. This had no impact on the model functionality.

C 15. The cells “Proportion to discontinuing” and in the column “Treatment waning” in the model sheet “Effectiveness” are hardcoded. Please explain the rationale for having these formulas in these cells.

The proportion discontinuing row in the model sheet “Effectiveness” represents the proportion of patients discontinuing due to reasons other than AEs in the TT-04 trial. In the 12 SQ-Bet arm, the reasons for discontinuation (excluding AEs) were listed as: ‘Other’ (5 patients), and ‘Withdrawal By Subject’ (9 patients). (4) These values were

added together and divided by the number of patients in the full analysis set: (5+9)/320 = 4.38%.

The treatment waning column in the model sheet "Effectiveness" represents the change in treatment effect over time. The treatment waning assumptions and approach to modelling the long-term effectiveness of 12 SQ-Bet are consistent with the approach accepted by the Committee in TA834. In the base case, to reflect the improving treatment effect observed in the REACT study (22), the proportion of patients in the 12 SQ-Bet arm receiving treatment benefit increases by 2.5% in each model cycle up to Year 10 (reflected by the -2.5% in cell G24). Treatment waning starts at 15 years, and by Year 20, 80% of patients in the 12 SQ-Bet arm will have lost treatment benefit. The formulae in cell G26 calculates the rate of waning between Year 15 to Year 20 required for 80% of the patient population to have lost the treatment benefit by Year 20 (validated in column P of the model engine, where the waning proportion = 0.8 at Year 20). All model assumptions with respect to the long-term efficacy beyond the end of the trial period are consistent with the preferred base case assumptions specified by the Committee in TA834.

Validation

C 16. Priority question. In Section 3.14 of the CS the company explained that the TECH-VER checklist was used to validate their model (and the results of these validation efforts are included in the economic model). The purpose of this tool is to validate the computerised model (i.e., verification); however, other validation aspects (such as validating the conceptual model, input data or model results) are also relevant. Please provide details on the efforts conducted regarding these other validation aspects. This could be presented for example (but not necessarily) with the help of AdViSHE (https://advishe.wordpress.com/author/advishe/).

Validation of the computerised model was performed using the TECH-VER checklist, the results of which are included as a sheet in the model.

The conceptual model was validated by comparing the modelling approach with the previously published cost-utility analysis of 12 SQ-Bet by Pollock et al., 2023. (23) The model structure is aligned to that described in Pollock et al., 2023 with costs and benefits applied in a treatment-specific manner, and with Dick et al., 2019 (25) used as the source of treatment-specific utility differences in both cases. Furthermore, Pollock et al., 2023 also assumed that 12 SQ-Bet would be taken daily for the first three years, in line with the European Academy of Allergy and Clinical Immunology (EAACI) recommendation of three years of AIT treatment, with the treatment effect persisting beyond treatment cessation. Any differences in the modelling approach can be largely attributed to the Pollock et al., 2023 study being conducted from the Swedish Societal perspective and using a shorter time horizon of 10 years, whereas the CS model was constructed to align with the NICE reference case. The conceptual model was also validated by ensuring that the assumptions in the model are aligned to those accepted by the Committee in TA834, particularly assumptions around the duration of treatment, impact of early discontinuation on treatment effect, and long-term effectiveness.

All clinical data included in the model was sourced directly from the TT-04 trial where appropriate. Importantly, while there is some uncertainty around some of the model inputs due to a lack of available data e.g., long-term effectiveness, the base case assumptions are informed by UK clinical expert opinion and consequently are inherently consistent with expectations. Furthermore, the impact of different model assumptions and variations in model inputs on the model results was extensively tested in scenario analyses to assess the robustness of modelled results. Notably, it is inappropriate to compare the model results to those reported in Pollock et al., 2023, as this study used a shorter time horizon and was conducted from the Swedish Societal perspective.

Section D: Textual clarification and additional points

D 1. Please note that the net monetary benefit (NMB) should be *incremental* (INMB). Please change this in the text and also in the figures where appropriate.

This has been updated where appropriate.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Betula verrucosa (Itulazax 12 SQ-Bet) for treating moderate to severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen [ID6462]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses (ARNS)
3. Job title or position	Lead nurse – Airways and ARNS committee member
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	ARNS – non- profit organisation – supporting and educating nurses and other health care professionals in the UK
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	For treating moderate to severe allergic rhinitis, conjunctivitis or both caused by tree pollen.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in exacerbations, reduction in hospitalisations, reduction in corticosteroid use and improved quality of life in patients.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	I believe there is already standard treatment available which can be very effective. The unmet need is through education and correct knowledge of how to administer treatments and individualised treatment plans for symptomatic patients

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Standard treatments such as antihistamines, eye drops, nasal corticosteroids, nasal douching, in some patients under specialist allergy centres there is desensitisation treatment and anti-allergy injections in severe cases.
9a. Are any clinical guidelines used in the	NICE- Rhinitis guidelines 2024, BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis 2017,). ARIA guideline 2019: treatment of allergic rhinitis.

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are local and national guidance which varies depending on geographical areas and local prescribing guidelines and criteria. This is just my experience from in the UK.
9c. What impact would the technology have on the current pathway of care?	It would be placed at the end of the current pathway as a add on therapy for patients who are uncontrolled on current available treatments.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be used as a add on therapy.
10a. How does healthcare resource use differ between the technology and current care?	This treatment is given via a different route of administration, it is unclear how long it would need to be used for.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	I would suggest in Specialist clinics or at least secondary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Costing for education of staff, costing for medication and staff time.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I understand it may benefit patients who have tried conventional readily available treatment and are still symptomatic despite education and adherence to treatment.
11a. Do you expect the technology to increase length of life more than current care?	NO
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – you would hope so.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who are more atopic and have heightened sensitivities and/or failed on previously available treatments. Because of its easy of use non -adherent people may find it easier to take regularly.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	It would be easy to use if patient can take the treatment independently at home. I am unable to comment if extra monitoring is required.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I presume it will have guidance to be used as a additional treatment when a patient is symptomatic despite conventional treatments available.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	There are a variety of similar treatments for consideration for various sub-groups which causes of severe rhinitis and treatments such as for example house dust mites and other atopy . I think to have a significant impact having a treatment that can improve health for a mixture of allergies and group them together such as House dust mite and grass would have more of a significant impact as often patients who are atopic with allergic rhinitis may have multiple allergies which trigger their disease.
16a. Is the technology a 'step-change' in the management of the condition?	I would suggest it is an additional step.

16b. Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not to my knowledge.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Symptom reduction, cost savings and adherence where not fully covered. There is mention about hospital reduction, however it is not clear the diagnosis and the evidence is weak.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Unable to comment.
18d. Are there any adverse effects that were not apparent in clinical	NO

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I'm unsure on the data on hospital admissions- were the patients admitted because of rhinitis, which I find hard to believe as the cause of a admission or was this a treatable trait acknowledged in these patients. It states In 2022-23, there were 2,132 admissions and 2,140 finished consultant episodes (FCE) for allergic rhinitis due to pollen in England and a further 290 admissions and 278 finished consultant episodes for 'allergic rhinitis.
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	No comment

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Treatment for consideration as a add on treatment • Costs versus benefit implications • Patient education • Data -limited • Limited to patients with tree pollen allergy only

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

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Single Technology Appraisal

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society of Allergy and Clinical Immunology (BSACI)
3. Job title or position	Consultant Allergist at [redacted], BSACI member
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BSACI is the UK's professional and academic society which represents the specialty of allergy at all levels. Its aim is to improve the management of allergies and related diseases of the immune system in the United Kingdom, through education, training and research
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	None
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. To alleviate symptoms of moderate-severe allergic rhinoconjunctivits caused by Silver Birch pollen and other cross-reactive tree pollens (the major causes of Springtime hay fever in the UK) 2. In addition, the treatment may, in common with other forms of allergen immunotherapy, induce long-lasting allergen tolerance and disease modification (Durham SR et al. J Allergy Clin Immunol. 2012 Mar;129(3):717-725; Hamelmann E et al. Allergy 2024;79:1018-1027; Fritzsching et al. Lancet Regional Health- Europe 2022:13:10027).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	For context a landmark World Allergy Organization task force report on standardisation of allergen immunotherapy clinical trials stated, 'the minimal clinically relevant efficacy should be at least 20% higher than placebo' (Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. Allergy. 2007;62 Suppl 85:17-25. doi: 10.1111/j.1398-9995.2007.01549. x. PMID: 17927674). The combined symptom-medication score (CSMS) is the standard outcome measure used internationally in allergen immunotherapy trials. The pivotal Phase III Itulazax trial (Biedermann T et al. J Allergy Clin Immunol 2019;143:1058-66) showed a 40% reduction vs placebo in CSMS, reflecting highly significant reductions in symptoms, and an almost 50% reduction in use of standard pharmacotherapy (antihistamines, nasal steroids, eye drops). This is an extraordinary effect size for a multicentre international trial where the readout is inherently noisy, being entirely dependent on variable natural pollen exposure across wide geographic areas. Futhermore, allergen immunotherapy trials typically see a 30-40% CSMS improvement in placebo-treated patients, thought to be due to variable pollen levels and an associated regression to the mean effect, as well as from a pure placebo-effect. Hence there is a high bar for achieving a positive outcome in such trials and a very large or consistent change needed from baseline/pre-treatment symptom burden. This trial also showed a halving of 'severe' symptom days despite availability of standards medication to all participants. By any standards, this a clinically significant reponse.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Absolutely. A large proportion of patients with allergic rhinitis are uncontrolled and/or unsatisfied with currently available treatments – a recent study in Belgium found 60% of sufferers have suboptimal control (Scheire et al. Journal of Allergy and Clinical Immunology In Practice 2024;12:1865-1876), the situation is very likely to be the same in the UK. Moreover, use of medications with adverse impacts such as systemic corticosteroids and over-use of nasal and systemic decongestants was high – a picture we see reflected in clinical practice in the UK. Patients suffer symptoms which greatly affect quality of life, impair sleep and adversely affect work and academic achievement (Walker and Avant's Analysis) Silver birch is the archetypal spring tree pollen in Northern Europe, being highly cross-reactive with other common indigenous tree pollens. Spring hay fever is catching up in frequency with summer (grass pollen-induced) hay fever and a major cause of seasonal allergic rhinitis.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Oral antihistamines and intranasal corticosteroids are the mainstay of treatment, alongside saline nasal rinses; some patients will see further benefit from combined intranasal steroid plus intranasal antihistamine, where available. Other treatments – leukotriene receptor antagonists, nasal ipratropium bromide spray, intranasal decongestants – are merely adjunctive treatments with either minimal effect or appropriate for short term use only. Allergen avoidance is largely impossible as the pollens are highly abundant and ubiquitous throughout the UK. Many patients self-treat via pharmacies or see their GPs, a minority are referred to allergy clinics where allergen immunotherapy but availabilty is highly restricted, with limited provision to only a small proportion of patients, exacerbated by the paucity of allergy services, lack of funding and geographical differences in access to allergy services. Perhaps linked to this, we encounter significant number of patients resorting to unlicensed depot steroid injections in the private sector.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The BSACI guideline provides an algorithm which places allergen immunotherapy, such as Itulazax, as a final step in management, once other treatments (intranasal steroids and combination intranasal steroid + intranasal antihistamine) have failed to provide adequate symptom control. Other guidelines, such as the EAACI and EUFOREA guidelines, consider using allergen immunotherapy at an early stage because of disease-modifying

	effects of this class of treatment, including persistence of benefit after stopping treatment (allergen tolerance), and possible reduction in new-onset asthma. Scadding GK et al. BSACI rhinitis guidelines. Clin Exp Allergy 2017;47:856-889 Roberts G et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy 2018;73:4:756-798 Hellings PW et al. EUFOREA treatment algorithm for allergic rhinitis. Rhinology 2020; 58;6:618 – 622
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	For seasonal allergic rhinitis, the pathway of care would typically be GP to allergist/immunologist if a service is available; in some areas, limited allergy services may be provided by ENT, respiratory or dermatology specialists. There are considerable regional differences across the UK, given the relatively low numbers of allergy/immunology specialist clinics. Access to allergen immunotherapy, including Itulazax, is very low in the UK compared to much of Europe. We do not think there is significant difference of opinion in treating severe allergic rhinitis between these different specialist clinicians. In my experience, all would recommend allergen immunotherapy for patients with severe symptoms uncontrolled by intranasal steroids/intranasal steroid + intranasal histamine. Access to treatment is the main barrier, rather than differences in management approach.
9c. What impact would the technology have on the current pathway of care?	The pathways would likely remain similar, though access for patients would undoubtedly be improved as funding is a clear barrier to treatment currently.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Some allergy/immunology centres already use Itulazax, but numbers are very limited by resources. It is given to patients with severe spring hay fever with confirmed Silver Birch pollen allergic sensitisation who have failed to gain adequate symptom control despite good compliance with intranasal corticosteroids or combined intranasal corticosteroid + intranasal antihistamine. It will be used in the same way but technology approval by NICE would allow improved access to the treatment for many patients who are currently unable to access it. Some centres provide subcutaneous allergen immunotherapy injections with tree pollen products. Itulazax will provide an alternative to this with a better safety profile, better evidence of efficacy and reduced administration costs (see below).

10a. How does healthcare resource use differ between the technology and current care?	Itulazax is initially given under supervision, typically in a nurse-led allergy/immunology clinic, with the patient observed for one hour afterwards. After that initial dose, further doses can be taken at home with remote monitoring (telephone/video clinics) over the next 3 years (typically after 3 months initially, extending to 6 monthly contact). Current care consists of either standard pharmacotherapy – intranasal steroids etc. – or, in specialist clinics, subcutaneous immunotherapy (SCIT). Compared to subcutaneous treatment, Itulazax involves far fewer resources – subcutaneous treatment requires 12-40 clinic visits over 3 years, depending on the product used – and is far safer, with severe allergic reactions being exceedingly rare, in contrast to subcutaneous treatment which carries a risk of systemic allergic reaction in approximately 1 in every 100-1,000 injections. There is no evidence of any difference in efficacy between the two modes of treatment. Sublingual treatment is more environmentally friendly and more efficient of patient time (Cardel L-O et al. Scientific Reports 2024;14:1575). In clinics where the alternative option is subcutaneous immunotherapy, the technology will reduce healthcare resource use.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment should be initiated and monitored in specialist allergy/immunology clinics in secondary care; or specialist ENT, dermatology or respiratory clinics, if the treating consultant has knowledge and experience in use of allergen immunotherapy.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	If restricted to the above specialist clinics, little, if anything, beyond what already exists. If more patients are seen, then perhaps an increase in allergy nurse specialist posts in these clinics.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. In well-selected patients, inadequately controlled with or unable to tolerate optimum standard care,wewould anticipate a clear improvement in symptoms and quality of life. In fact, in many patients, the treatment can be life-changing during the pollen season.
11a. Do you expect the technology to increase length of life more than current care?	No

11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, without doubt.wewould expect a very significant improvement in quality of life during the spring months in those receiving Itulazax (with benefit seen between January/February and May, particularly in peak season in March and April).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment will only be effective in individuals with allergic sensitisation to Silver Birch pollen. Patients reporting spring hay fever symptoms without sensitisation to Silver Birch pollen are not anticipated to gain benefit and should not receive Itulazax.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The only equivalent comparator is subcutaneous Silver birch/tree pollen allergen immunotherapy which is given to patients on a named-patient basis at specialist allergy/immunology clinics by regular injection. All injections are given in clinic, typically with a one-hour observation period afterwards. Itulazax treatment will be easier than this for both patients and healthcare professionals as only the first dose of treatment need be taken in clinic, under supervision. Thereafter, daily doses can be taken at home. This is more convenient for patients and a reduced workload for healthcare professionals (not to mention being much safer with much lower risk of systemic allergic reactions). Compared to standard treatment for allergic rhinitis with intranasal steroids, the treatment is simple to take, so, whilst it is an additional treatment, the addition is not burdensome. There are no interactions with other medicines. A proportion of patients will suffer local allergic side effects (itching, swelling beneath the tongue etc.), and a few (<5%) will find these intolerable and stop treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	All patients must be tested for evidence of Silver Birch pollen IgE sensitisation prior to starting treatment. This is usually a standard test in patients referred to specialist allergy/immunology clinics for allergic rhinitis and may also be tested for in ENT, dermatology and respiratory clinics treating rhinitis, asthma or eczema.

include any additional testing?	Patients must have: 1. shown good compliance with, or had intolerable side effects from, or other reason not to take, standard therapies; 2. been counselled on how to take sublingual immunotherapy and possible side effects and reasons to withhold treatment; 3. have an FEV1 of at least 70% predicted if suffering with asthma. Treatment would be stopped in the event of intolerable side effects (e.g. severe oral itching/swelling not responding to antihistamines and not declining over time) or a severe systemic allergic reaction caused by Itulazax (exceptionally rare).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There is evidence that use of allergen immunotherapy in patients with allergic rhinitis can reduce the risk of them developing asthma. The data is predominantly derived from studies in children and adolescents (see Valovirta et al J Allergy Clin Immunol. 2018;141(2):529-538 as an example). It may also reduce asthma medication use and exacerbations, extrapolating from allergen immunotherapy more generally (Fritzsching et al. Lancet Regional Health- Europe 2022:13:10027).wesuspect this prevention of asthma development would not be picked up in the QALY calculations
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Itulazax has proven efficacy beyond that already provided by standard care. Treatment is associated with the production of allergen-specific IgG4 and IgGA antibodies which have been shown to be instrumental in achieving allergen tolerance and necessary for the long-term benefits seen from allergen immunotherapy.wewould anticipate this treatment, as has already been demonstrated for the equivalent grass pollen allergy tablet, Grazax, to provide a lasting effect after completion of treatment. It may also reduce new-onset asthma and/or reduce asthma severity, as has been observed in studies of allergen immunotherapy more generally.
16a. Is the technology a 'step-change' in the	No, if you consider that allergen immunotherapy is provided by some allergy and immunology clinics already, but yes given that allergen immunotherapy access is patchwork and divided by postcode. It is provided by only a limited number of specialist allergy/immunology clinics on a named patient basis, with funding often provided by

management of the condition?	departmental budgets, meaning limited numbers of patients can access treatment. More widespread access to this technology would democratise access to optimal treatment.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. There is a huge unmet need in Allergy due to the limited clinic resources/specialists in the UK. Patients with Silver birch/tree pollen hay fever have very little access to allergen immunotherapy, in contrast with similar patients in Europe and North America. This technology will improve access to specific treatment with long lasting benefits.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The technology is very safe – no fatalities or life-threatening adverse reactions have been reported, to my knowledge, including in our own service. Conversely, most patients experience local itching within the mouth but this is not bothersome in the majority, it is short lived (approx. 15 mins), with most resolving within 2-4 weeks of initiating the treatment. In many cases this can addressed by administering half a tablet for the first few weeks, then stepping up to a full tablet. A small proportion of patients will find these symptoms intolerable and discontinue treatment (after which, symptoms resolve with no lasting side effects).

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Intranasal steroids and oral antihistamines are the mainstay of treatment and will be prescribed to the vast majority of sufferers by their GP and/or specialist. The only notable difference from current practice is the use of combined intranasal steroid and antihistamine sprays, though it should be noted that these are not universally available (some CCGs will not prescribe them). Other treatments not used in the clinical trial (anti-leukotrienes, ipratropium bromide nasal spray, intranasal decongestants) have very minimal additional effect and are rarely used in clinical practice. (Intranasal decongestant use beyond a few days should be actively discouraged due to the risk of developing rhinitis medicamentosa).
18a. If not, how could the results be extrapolated to the UK setting?	I believe the results are applicable to the UK setting without extrapolation, the trial population is entirely representative of UK patients.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	For rhinitis, the combined symptom-medication score is by far the most important outcome in allergen immunotherapy trials, as was recorded in the published study. This allows consistency and comparison between

	clinical trials. The rhinitis quality of life questionnaire (RQLQ) is also helpful from a clinical monitoring perspective but is seldom used as a primary outcome in rhinitis trials for practical reasons.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No surrogate outcomes were used. Evidence suggests three years treatment with allergen immunotherapy is required for long-term efficacy so this cannot be judged from this study over one season. However, aswehave mentioned above, the generation of allergen specific IgG4 and IgGA antibodies is consistent with the development of allergen tolerance and we anticipate that use of this treatment for 3 years would produce a sustained clinical benefit for at least 2 years thereafter and potentially much longer, as seen in at least four phase 3 clinical trials of other allergen tablets produced by the same manufacturer and used at similar doses.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There have been a few reports of eosinophilic oesophagitis (EOE) occurring in patients taking sublingual immunotherapy, though none thatweam aware of relating specifically to Itulazax. EOE is usually controlled with PPIs or swallowed corticosteroids but may require stopping the sublingual immunotherapy in some patients, but in practice we have found this to be very uncommon.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real-world evidence suggests allergen immunotherapy in general reduces use of standard medication for rhinitis up to a period of 10 years and reduces asthma exacerbations and hospitalisation, though this data is for immunotherapy in general and not specific to Itulazax. (See Fritzsching et al. Lancet Regional Health- Europe 2022:13:10027).

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	I believe that NICE approval for this technology would have a positive effect on equality of access to allergen immunotherapy. As it currently stands, with allergen immunotherapy being available only in specialist centres on a named patient basis, patients with knowledge of how to navigate the system and how to push for treatment tend to end up getting access to allergen immunotherapy, whereas those with less knowledge and savvy lose out. A clear NICE appraisal could help democratise access.
21b. Consider whether these issues are different from issues with current care and why.	As above.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Allergic rhinitis is a major cause of reduced quality of life and productivity; Silver Birch/tree pollen induced allergic rhinitis is a common cause of debilitating hay fever. • Patients with allergic rhinitis are often dissatisfied with available treatments, reporting poor symptom control; they may resort to using treatments with poor long term side effect profiles, including systemic corticosteroids. • Itulazax has a clear, meaningful benefit in patients with spring hay fever over and above that provided by standard therapy. • Itulazax is a very safe treatment, considerably safer than the only current comparator, subcutaneous tree pollen immunotherapy, with extremely low risk of systemic allergic reactions. • Itulazax is a more convenient and less resource-intensive treatment than subcutaneous allergen immunotherapy. •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Betula verrucosa (Itulazax 12 SQ-Bet) for treating moderate to severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen [ID6462]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)
3. Job title or position	Programme Manager- Clinical
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes – [redacted] (completing sections 1-5) A specialist in the treatment of people with this condition? Yes – [redacted] (Completing sections 6 -22)
5a. Brief description of the organisation (including who funds it).	The BSI-CIPN is a professional network hosted within the British Society for Immunology, a learned society. The BSI-CIPN is an integrated and impactful professional network for individuals working within clinical immunology. The network includes over 160 professionals working in the clinical immunology field, including clinical immunologists, allergists, healthcare scientists, pharmacists and specialist nurses. The BSI-CIPN is funded through the British Society for Immunology, which has a range of income streams which can be viewed in our 2024 annual report here. The BSI-CIPN also has some ringfenced funding as a result of a merger with the UK Primary Immunodeficiency Network in 2022.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve disease control and quality of life in people with moderate to severe allergic rhino-conjunctivitis due to birch pollen and homologues, unresponsive to symptom-relieving medication.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Sufficient improvement in allergic rhino-conjunctivitis symptoms such that disease is controlled or can be adequately controlled with symptom relieving medication, and daily activities and/or sleep are not affected.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need. Currently, there is no national policy for allergen immunotherapy for birch or tree pollen. Itlulazax and other immunotherapy products (Pollinex and various unlicensed products) are available in the UK market, but there is a postcode lottery with significant variability in whether these treatments can be accessed or are commissioned, depending on where someone lives.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Allergic rhino-conjunctivitis is mostly treated in primary care with referral to specialist allergy clinics when there are significant uncontrolled symptoms. Measures include allergen avoidance and symptom-relieving medication (which includes intranasal steroids, antihistamines, leukotriene receptor antagonists if there is concomitant asthma, combination intranasal steroids and antihistamine sprays, short courses of oral steroids for severe uncontrolled symptoms). For patients who continue to have significant uncontrolled symptoms affecting daily activities and/or sleep despite the above, allergen immunotherapy (both sublingual and subcutaneous) can be offered in specialist care, although availability and eligibility vary throughout the UK.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007) - https://pubmed.ncbi.nlm.nih.gov/30239057/ NICE CKS on Allergic Rhinitis - https://cks.nice.org.uk/topics/allergic-rhinitis/management/management/
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Professionals would generally agree on the above pathway of care, although its implementation can be variable in real life practice.
9c. What impact would the technology have on the current pathway of care?	If approved, it should help to reduce the postcode lottery in treatment and improve accessibility to sublingual immunotherapy for birch/tree pollen. It would help standardise what treatments patients can access nationally for birch/tree pollen sublingual immunotherapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is likely to used in the same way as current care in NHS clinical practice, where the technology is available at a local/regional level.

10a. How does healthcare resource use differ between the technology and current care?	Healthcare resource use is likely to be the same where the technology is currently available on the NHS. Where the technology is not available, use of the technology would be expected to reduce the amount of symptom-relieving medication used as well as consultations.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be initiated in secondary care/specialist allergy clinics. It may be possible for shared care with primary care for ongoing prescription of the technology, depending on local arrangements.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment would be needed to introduce the technology where there are existing allergy services. Given the limited number of allergy services in the UK and long waiting times, better and equitable access to the technology would require investment to improve access to allergy services in general, so that patients living a long distance from allergy services are not disadvantaged.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, in areas of the UK where the technology is not currently available.
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, in areas of the UK where the technology is not currently available.
12. Are there any groups of people for whom the technology would be more or less effective (or	Not aware of any specific groups.

appropriate) than the general population?	

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Technology is already part of current care in some parts of the UK. Where technology is not available in the UK, usage should not be more difficult for healthcare professionals. Patients will need to be able to commit to a course of treatment for several years if they wish to use the technology.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The SPC recommends that treatment should not be continued if there is no improvement during the first year of treatment. Additional tests are not required, although the patient will require re-assessment.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Technology can potentially improve work or academic performance due to improved health and better disease control.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Technology is already in use in some parts of the UK depending on local/regional arrangements. In areas of the UK where there is no or limited access to allergen immunotherapy, the technology has the potential to make a significant impact for patients where symptom-relieving medication alone is inadequate to control disease.
16a. Is the technology a 'step-change' in the management of the condition?	Technology is already in use in some parts of the UK depending on local/regional arrangements. In areas of the UK where there is no or limited access to allergen immunotherapy, the technology would represent a step-change in the management of the condition.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology would address the unmet need where patients do not have access to allergen immunotherapy for significant uncontrolled allergic rhino-conjunctivitis, unresponsive to symptom-relieving medication
17. How do any side effects or adverse effects of the technology affect the management of the	The commonest side effect is local allergic symptoms when the technology is used – this can be managed with antihistamines and often resolves/improves as treatment goes on.

condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Short-term effect on quality of life, symptoms, medication usage – these were measured in the trials. Long-term efficacy – not measured in trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Trial publication has cited that long-term outcomes have been described in similar products – this would not be an unreasonable assertion that Itulazax could be similar.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	Real-world data is limited, but available data would suggest that there is longevity of effect.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any equality issues that would affect this specific technology. There is variable access to allergy services in the UK depending on where a person lives, which could affect access to this technology.
21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Itulazax (and other allergen immunotherapies) are an important treatment step up for patients with uncontrolled allergic rhino-conjunctivitis affecting daily activities and/or sleep, where symptom-relieving medication are inadequate • There is significant variation in the availability and accessibility of Itulazax in the UK, resulting in a postcode lottery, where some patients can, and some cannot access this technology • National guidance would be beneficial to standardise access to this therapy in the UK • •

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About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologists
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	
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The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve disease control and quality of life in people with moderate to severe allergic rhino-conjunctivitis due to birch pollen and homologues, unresponsive to symptom-relieving medication.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Sufficient improvement in allergic rhino-conjunctivitis symptoms such that disease is controlled or can be adequately controlled with symptom relieving medication, and daily activities and/or sleep are not affected.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need. Currently, there is no national policy for allergen immunotherapy for birch or tree pollen. Itlulazax and other immunotherapy products (Pollinex and various unlicensed products) are available in the UK market, but there is a postcode lottery with significant variability in whether these treatments can be accessed or are commissioned, depending on where someone lives.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Allergic rhino-conjunctivitis is mostly treated in primary care with referral to specialist allergy clinics when there are significant uncontrolled symptoms. Measures include allergen avoidance and symptom-relieving medication (which includes intranasal steroids, antihistamines, leukotriene receptor antagonists if there is concomitant asthma, combination intranasal steroids and antihistamine sprays, short courses of oral steroids for severe uncontrolled symptoms).

	For patients who continue to have significant uncontrolled symptoms affecting daily activities and/or sleep despite the above, allergen immunotherapy (both sublingual and subcutaneous) can be offered in specialist care, although availability and eligibility vary throughout the UK.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007) - https://pubmed.ncbi.nlm.nih.gov/30239057/ NICE CKS on Allergic Rhinitis - https://cks.nice.org.uk/topics/allergic-rhinitis/management/management/
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Professionals would generally agree on the above pathway of care, although its implementation can be variable in real life practice.
9c. What impact would the technology have on the current pathway of care?	If approved, it should help to reduce the postcode lottery in treatment and improve accessibility to sublingual immunotherapy for birch/tree pollen. It would help standardise what treatments patients can access nationally for birch/tree pollen sublingual immunotherapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is likely to used in the same way as current care in NHS clinical practice, where the technology is available at a local/regional level.
10a. How does healthcare resource use differ between the technology and current care?	Healthcare resource use is likely to be the same where the technology is currently available on the NHS. Where the technology is not available, use of the technology would be expected to reduce the amount of symptom-relieving medication used as well as consultations.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be initiated in secondary care/specialist allergy clinics. It may be possible for shared care with primary care for ongoing prescription of the technology, depending on local arrangements.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment would be needed to introduce the technology where there are existing allergy services. Given the limited number of allergy services in the UK and long waiting times, better and equitable access to the technology would require investment to improve access to allergy services in general, so that patients living a long distance from allergy services are not disadvantaged.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, in areas of the UK where the technology is not currently available.
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, in areas of the UK where the technology is not currently available.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not aware of any specific groups.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Technology is already part of current care in some parts of the UK. Where technology is not available in the UK, usage should not be more difficult for healthcare professionals. Patients will need to be able to commit to a course of treatment for several years if they wish to use the technology.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The SPC recommends that treatment should not be continued if there is no improvement during the first year of treatment. Additional tests are not required, although the patient will require re-assessment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Technology can potentially improve work or academic performance due to improved health and better disease control.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Technology is already in use in some parts of the UK depending on local/regional arrangements. In areas of the UK where there is no or limited access to allergen immunotherapy, the technology has the potential to make a significant impact for patients where symptom-relieving medication alone is inadequate to control disease.
16a. Is the technology a 'step-change' in the management of the condition?	Technology is already in use in some parts of the UK depending on local/regional arrangements. In areas of the UK where there is no or limited access to allergen immunotherapy, the technology would represent a step-change in the management of the condition.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology would address the unmet need where patients do not have access to allergen immunotherapy for significant uncontrolled allergic rhino-conjunctivitis, unresponsive to symptom-relieving medication
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The commonest side effect is local allergic symptoms when the technology is used – this can be managed with antihistamines and often resolves/improves as treatment goes on.

Sources of evidence

18. Do the clinical trials on the technology reflect	Yes

current UK clinical practice?	
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Short-term effect on quality of life, symptoms, medication usage – these were measured in the trials. Long-term efficacy – not measured in trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Trial publication has cited that long-term outcomes have been described in similar products – this would not be an unreasonable assertion that Itulazax could be similar.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real-world data is limited, but available data would suggest that there is longevity of effect.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any equality issues that would affect this specific technology. There is variable access to allergy services in the UK depending on where a person lives, which could affect access to this technology.
21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Itulazax (and other allergen immunotherapies) are an important treatment step up for patients with uncontrolled allergic rhino-conjunctivitis affecting daily activities and/or sleep, where symptom-relieving medication are inadequate • There is significant variation in the availability and accessibility of Itulazax in the UK, resulting in a postcode lottery, where some patients can, and some cannot access this technology • National guidance would be beneficial to standardise access to this therapy in the UK • •

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Question	Expert 1	Expert 2	Expert 3	Expert 4
Is it appropriate to consider the eligible population as one combined population (moderate-to-severe allergic rhinitis AND conjunctivitis)? How should this eligible population be defined?	Yes. The characteristic symptoms diagnostic of tree pollen allergy are itching/sneezing, watery discharge and associated eye symptoms during the relevant pollen season (Feb-May). They may also get blockage which is common but that is a symptom shared by all rhinitis causes, not just allergic) but 50% of the eye symptoms result from the nasolacrimal reflex due to associated nasal inflammation and 50% from actual pollen exposure in the eye. This is why the eye symptoms respond to nasal steroid sprays – dampening nasal inflammation inhibits reflex eye symptoms. It is rare to see hay fever sufferers with isolated nasal symptoms and no eye symptoms (< 10%) and even rarer to see those with isolated eye	I am not entirely sure I understand the question precisely, but of course, there will be patients who have debilitating moderate-to-severe allergic rhinitis and patients who have allergic rhinoconjunctivitis. In my view, either should be eligible for this treatment. Also, there is a small % of patients with severe allergic conjunctivitis with minimal nasal symptoms who would benefit, some of whom need steroid eye drops or have developed complications from allergic eye disease like keratoconus. Overall, these should be patients who have symptoms that impact on functioning and quality of life. This could be measured with a validated tool such as the RQLQ during the peak of the pollen season, for example. Eligibility should be	Yes. It is essentially one condition, seasonal allergic rhinoconjunctivitis. Patients simply differ in the extent to which they have more predominant nasal or eye symptoms. I would define this population as individuals who have symptoms which affect daily life (work, sleep, activities) and/or reduce quality of life despite use of reasonable standard medication (typically intranasal corticosteroids).	Yes, I think it would be reasonable to consider the eligible population as one combined population - allergic rhinitis and conjunctivitis very often overlap. Unless there is enough data to do a separate analysis? In standard practice, people are usually recommended for immunotherapy if they have symptoms which interfere with usual daily activities or sleep despite appropriate pharmacotherapy and/or avoidance - it would seem reasonable to define the eligible population as that group of patients.

	symptoms (<5% in my estimation). The eligible population should have moderate-severe allergic rhinoconjunctivitis (ARIA classification) during tree pollen season with inadequate response to usual anti-allergic drugs.	considered in those whose symptoms persist despite adherence to optimised medical therapy, which should consist at a minimum of a non-sedating long-acting antihistamine once daily and a steroid nasal spray started before the season, also daily use of antihistamine eye drops such as olopatadine.		
In what line of therapy would betula verrucosa be used? Would it be used at multiple lines? Would it be used alongside any other treatments?	Betula verrucosa is indicated in moderate severe allergic rhino conjunctivitis when modern non-sedating antihistamines and an adequate trial of an intranasal corticosteroid over 1 month have not provided adequate symptom relief. I personally recommend a trial of a combination intranasal steroid and antihistamine nasal spray (Dymista, Ryaltris) but some GPs are not allowed to prescribe the combination nasal sprays.	This should be third-line therapy after nasal steroids are added to oral antihistamines. In patients with significant allergic eye symptoms, it may be considered fourth-line, after the addition of olopatadine to oral antihistamines and intranasal steroids. I do not factor in leukotriene receptor antagonists, as these are not licensed for the treatment of allergic rhinitis.	It would be used for patients who fail to control symptoms with intranasal corticosteroids or combined intranasal corticosteroid plus intranasal antihistamine +/- anti-allergy eye drops if predominant eye symptoms despite regular use or those who have adverse effects/contraindications to intranasal corticosteroids. It would be used as a final step. It should be used alongside the above treatments, at least initially, accepting that the need for these standard treatments may reduce as the effect of the Itulazax kicks in.	Itulazax (and other immunotherapies) are usually used as above - in patients who have moderate to severe symptoms which interfere with usual daily activities or sleep despite appropriate pharmacotherapy and/or avoidance. So this would be after pharmacotherapy (antihistamines, nasal sprays, eye drops etc) have been tried. It is usually used alongside standard pharmacotherapy as well - where standard pharmacotherapy can treat any residual symptoms.

	I would recommend a one month trial AND would check and reinforce the need for REGULAR use of the spray and ensure the CORRECT technique of using nasal spray before agreeing to prescribe Betula. It is not a substitute for pharmacotherapy and should be used in combination but attempts can be made to reduce/withdraw intranasal steroids and use oral antihistamines and eye drops only prn.			
Use of immunotherapy: What proportion of people with allergic rhinoconjunctivitis after inadequate response to pharmacological treatment currently receive pollinex trees or other immunotherapy treatments in the NHS? In what treatment line are	In a primary care survey, 40-60% of allergic rhinoconjunctivitis sufferers reported inadequate response to antihistamines and intranasal corticosteroids. I suspect the failure rate would drop to 10% if the sufferers were advised to take the sprays even when asymptomatic during the pollen season and also taught the	Estimate 1-5%. These treatments are used for patients who have debilitating hay fever, i.e. symptoms that impact functioning and quality of life despite use of antihistamines and nasal steroids. Currently service provision is extremely limited and patients treated is far exceeded by numbers	It is difficult to give a precise answer but it is likely to be a small proportion of patients who make it to specialist allergy-immunology services and receive allergen immunotherapy. We use immunotherapy about 100-fold less than countries such as Germany and it is unlikely that the severity of allergic rhinitis is any lower here. I would estimate less than 5%, perhaps much less. Allergen immunotherapy	As far as I'm aware, there is no good data to be able to be certain about this. The rate of people in specialist care receiving immunotherapy after inadequate pharmacological treatment will be high, but this is because this is select population that have already been filtered out before they get to the specialist clinic. There is a far larger pool of patients with allergic rhinoconjunctivitis that may not get to secondary care

immunotherapy treatments used?	correct use of the spray. Another legitimate population for immunotherapy is patients who gets side effects of antiallergic drugs – nasal bleeding for intranasal steroids (5-8% of users) or drowsiness even with the modern antihistamines that rarely may occur. Also effective in treating co-morbid seasonal asthma symptoms. So my guess is an unmet need in 10% of the overall Betula and tree pollen allergic patient population are in need of immunotherapy. I never prescribe pollinex tree because this product, although registered in the mid seventies, does not have strong evidence for efficacy. Unfortunately Alutard SQ that was available on a named patient basis and highly effective as been withdrawn from the UK	who fall into above category.	would be the final step in treatment of allergic rhinitis.	(or even primary care) despite inadequate response. If there is any information on sales data of the available immunotherapy products in the UK, that may give better information on this question. In terms of treatment lines, as above, immunotherapy would usually be used after standard pharmacotherapy has failed.

	market. There are no registered sublingual drop tree pollen preparations registered in UK.Other immunotherapy products available in UK on a named pt basis are Allergovit and Pollinex Quattro – both are subcutaneous allergoids with some evidence of efficacy although there is still a significant risk of allergic general reactons to the allergoids. Also no head to head comparisons with the subcutaneous gold standard Alutard SQ.The product with the strongest portfolio of evidence is Betulava fast-dissolving tablets, MHRA approved and registered in UK.			
What is your expectation of the clinical efficacy of betula verrucosa compared with pollinex trees or other immunotherapy treatments?	There are no head to head comparisons. Indirect comparisons suggest Betula is at least as effective and definitely safer and more convenient for patients as	Although Pollinex for trees is licensed, there are no published data from randomised controlled clinical trials showing that subcutaneous immunotherapy with Pollinex Trees is effective. It	I would expect at least equivalent efficacy given the treatment effect size seen in TT-04. Importantly, the safety profile is much improved compared to injection immunotherapy products such as Pollinex. It is also important	This is difficult to be certain as there are no head-to-head comparisons, and limited trial and long-term data, so difficult to give a definitive answer to this. The other immunotherapy products work with the same mechanism of action - so one

	the sublingual tablets are self-administered.	is a very old legacy product. Moreover, in my view, based on analysis of published data, it is not a strongly immunogenic product and I have little faith in its efficacy. It is not something I have ever or would ever use (I have 30 years of experience in investigating immunotherapy and its mechanisms). Pollinex Quattro is a different formulation and unlicensed; again, there is a poor evidence base for efficacy. This is also true of other subcutaneous tree immunotherapy products which are unlicensed but used occasionally in the UK such as Allergovit. There is no product widely available for which there is a similar expectation of clinical efficacy as Itulazax.	to note that Pollinex is unlicensed.	would expect some effect from the other products as well, which are potentially comparable to Itulazax.
Generalisability of trial results: Are the TT-04 results generalisable to people sensitised specifically to	There are no head to head comparisons. Indirect comparisons suggest Betula is at least as effective and definitely safer and more	Yes. The main allergen molecules (PR-10 proteins) in beech and birch pollen are molecularly highly similar to birch major allergen Bet v1, the main	We do not see patients who are exclusively sensitised to oak and/or beech trees - the pollen of both these species are highly cross-reactive with silver birch pollen, meaning that a patient	Yes, one would expect that Itualazax to have an effect against the other tree species, due to cross-reactivity in the pollen. In standard clinical practice, the decision to offer

oak and beech pollen tree species?	convenient for patients as the sublingual tablets are self-administered. • If not, what is the expected clinical efficacy of betula verrucosa in people sensitised specifically to oak and beech pollen tree species? I would expect efficacy of Betula to include oak and beech allergic patients, both in and extending outside the birch pollen season.	constituent of Itulazax—to the extent that patients who are sensitised to birch pollen will usually be co-sensitised to oak and beech on skin prick testing. In fact, most allergists do not even skin test for these pollens for this reason. People specifically sensitised to oak and beech tree species but not birch are not an entity routinely encountered in clinical practice. The TT-04 trial population is anticipated to also include patients with this profile. • If not, what is the expected clinical efficacy of betula verrucosa in people sensitised specifically to oak and beech pollen tree species? In my view, the results of TT-04 would be generalisable to those trees since I have every expectation that the immune response generated against Itulazax will also be cross-reactive	sensitised to one species is sensitised to the others and, inevitably, will have symptoms on exposure to the other pollen species. So, yes, the results of TT-04 are generalisable to people sensitised to oak and beech because these people are also all birch sensitised. Given the very high cross-reactivity, treatment with one species will have protective effects against all	immunotherapy is not usually based on investigations to that level of tree pollen specificity, due to the cross-reactivity between the tree species.

		immunologically with tree pollen from these species, on the basis that the IgE response is also extremely cross-reactive. There are some tree pollens which are entirely distinct from birch, and an example of this would be plane trees. Plane tree pollen allergy is clinically relevant in only a small minority, and most allergists would (and should!) double-check this when assessing patients or include it as part of their routine diagnostic workup, since pollination coincides with the birch season.		
Adverse events: Would the adverse events associated with betula verrucosa lead you to recommending another treatment to an eligible patient?	I would anticipate common but not bothersome local side effects in 30% of patients during first days weeks after starting treatment with resolution within 2-4weeks. The studies would suggest a drop out rate of around 5-8% due to local side effects which is comparable with the drop out rate from intranasal steroids due to	I have significant experience using Itulazax in my private practice, with over 50 patients personally initiated on treatment. Local oral reactions occur in the majority and are expected, but most are very mild and of no clinical significance. It is very important to be familiar with this and inform and reassure the patient before and during dosing, also to explain that these	If you mean, would I avoid giving Itulazax to a patient in the first instance, because of concerns about the side effect profile, the answer is no, the benefit of Itulazax over alternatives (i.e. injection immunotherapy for tree pollen allergy) is the greatly reduced risk of systemic reactions/anaphylaxis - a much more serious concern than the local side effects seen with sublingual immunotherapy such	Yes, particularly if there are significant uncontrollable oral side effects with Itulazax, subcutaneous immunotherapy may be recommended to get around this.

	nose bleeds if used regularly. In such a patient I may recommend cautious subcutaneous birch immunotherapy, provided they did not have moderate-severe or uncontrolled asthma.	side effects abate with time. Symptoms typically start after 2-3 mins and are improving by 10-15 mins. Very occasionally, oral and pharyngeal itching may be uncomfortable. I have had only a few patients who felt this was sufficient unpleasant to suspend treatment. Most are highly motivated to continue. I emphasise these responses were not dangerous, but felt uncomfortable for the patient. Generally, I find these local adverse reactions can be managed successfully by reducing to a quarter or half tablet for a few weeks and then stepping up the dose gradually as local reactions reduce. I appreciate that this is not part of the recommendation given by the manufacturer, but I have found it a very effective practical approach when local symptoms are significant.	as Itulazax. On the other hand, if I have a patient on Itulazax who develops troublesome local symptoms (oral itch and swelling most commonly) that do not respond to antihistamines or diminish over time, the yes, I would stop and either rely on standard pharmacotherapy or consider the option of injection immunotherapy (though in the knowledge that they may be more at risk of side effects with this form of treatment too).	
Resource use:	Yes definitely compared to subcutaneous	Yes, in my view.	Treatment with Itulazax requires fewer secondary care visits than	In centres where Itulazax or other immunotherapy treatments

Would the use of betula verrucosa lead to reduced GP visits and secondary care visits compared to established clinical management and immunotherapy treatments?	immunotherapy due to need for specialist in clinic administration for SCIT. There is also the likelihood of reduced visits due to reduced need for anti allergic drugs. Importantly the proven longterm benefits for several years after stopping pollen immunotherapy would represent substantial cost savings (proven for grass pollen and cedar tree pollen fast dissolving tablets, and my view is this strong data is generalisable to tree pollen immunotherapy)		injection immunotherapy treatments because, aside from the first tablet, the medication is taken at home. Injection immunotherapy requires multiple visits to secondary care, for over an hour at a time, with monitoring and access to emergency treatment given the possibility of anaphylaxis. Depending on the exact injection immunotherapy product, patients will require somewhere between 20 and 40 visits to an allergy/immunology department over 3 years. So, the time and labour saving made here is large. We typically undertake virtual consultation follow ups with patients on Itulazax on a 3-6 month basis to monitor effects and ensure compliance. Visits to the GP would not necessarily change if the comparison is with equivalent patients already treated in allergy clinics - these patients would not normally need to see their GP as well. However, allergen immunotherapies such as Itulazax have a persistent	are already being used, this would not be expected to make a difference to the number of visits, as the product is already in use. In centres where there is currently no immunotherapy available, this may make a difference.

			benefit beyond the treatment period, meaning treated patients are likely to have improved symptoms for some years after completion of the treatment and therefore less likely to need to consult their GP during this period than patients treated with medications without a disease-modifying effect.	
If so, please quantify the expected reduction for GP and secondary care visits.	The reduction compared to Subcutaneous treatment for secondary care would be dramatic due to no need for attendance for injections (70%), accepting need for clinic adherence checks 3 monthly by phone for Betula tablet treatment. I would predict a reduction in GP visits due to reduced need for rescue medication in the Betula population of around 50% (a guess, but data available from RCTs?)	I would expect a 70 to 80 percent reduction in visits, although it should be acknowledged that to facilitate adherence to sublingual immunotherapy it is important to have some follow-up visits, although this can be done remotely. I also believe that there is considerable scope for developing technologies to facilitate this, such as apps which can also incorporate scoring of symptoms. This is not an area of technology that has yet been exploited in the field of allergy.	- 2 visits plus virtual consults versus up to 40 clinic visits of over an hour with careful monitoring and access to resuscitation equipment and services; harder to quantify with regards to GP visits.	This is difficult to quantify. In centres not currently providing immunotherapy, additional visits will be required to assess the patient, initiate treatment and follow up when immunotherapy is started. If no immunotherapy is available, these patients would previously potentially not have been seen in secondary care at all, as there would potentially have been limited things to offer. This will potentially be offset with fewer GP visits as their allergic rhinoconjunctivitis is better controlled but there is limited data to accurately quantify how many fewer visits this would be. Additionally, patients with severe allergic

				rhinoconjunctivitis may just put up with things rather than consulting the GP if they have been told that there is nothing more that can be done beyond pharmacotherapy.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Allergic rhinitis, conjunctivitis (tree pollen, moderate, severe) - betula verrucosa (Itulazax 12 SQ-Bet) [ID6462]

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 9 April 2025

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number STA 17/42/42.

Declared competing interests of the authors: None.

Acknowledgements: We gratefully acknowledge the expert clinical advice input from Dr Sujoy Khan, Consultant Immunologist & Allergist, Hull University Teaching Hospitals NHS Trust.

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Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Wolff R, Corro Ramos I, Patel M, Tian X, Poleij M, Anagnostopoulos S, Stirk L, Armstrong N, Al M. Allergic rhinitis, Conjunctivitis (tree pollen, moderate, severe) - betula verrucosa (Itulazax 12 SQ-Bet) [ID6462]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2025.

Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the company's definition of the decision problem as well as the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Marten Poleij and Stavros Anagnostopoulos acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mubarak Patel, Xiaoyu Tian and Nigel Armstrong acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance.

Abbreviations

AA	Allergic asthma
ACT	Asthma control test
AdViSHE	Assessment of the Validation Status of Health-Economic decision models
AE	Adverse event
AHPS	Alder and hazel pollen season
AIT	Allergic immunotherapy
AR	Allergic rhinitis
AR/C	Allergic rhinitis with, or without conjunctivitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BMI	Body mass index
BPS	Birch pollen season
BSACI	British Society for Allergy and Clinical Immunology
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CER	Cost-Effectiveness Analysis Registry
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CON	Confidential
COVID-19	Coronavirus disease 2019
CQ	Clarification question
CS	Company submission
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
DMS	Daily medication score
DP	Decision problem
DSS	Daily symptom score
EAACI	European Academy of Allergy and Clinical Immunology
EAG	External Assessment Group
ECM	Established clinical management
eMIT	Electronic market information tool
EQ-5D	European Quality of Life-5 Dimensions
ESHPM	Erasmus School of Health Policy & Management
EU	European Union
EUFOREA	European Forum for Research and Education in Allergy
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FASAPPLE	The apple challenge analysis set
FASASTHMA	Subjects in FAS with a medical history of asthma
FASBPS	Subjects in FAS with observations in the birch pollen season
FDA	Food and Drug Administration
FE	Fixing errors
FEV	Forced expiratory volume
FV	Fixing violations
GEE	Generalised estimating equation
GINA	Global Initiative for Asthma
GP	General Practitioner
HDM	House dust mite
HERC	Health Economics Research Center
HRQoL	Health-related quality of life
HSUV	Health state utility value

HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IgE	Immunoglobulin E
IgG4	Immunoglobulin G subtype 4
IMP	Investigational Medicinal Product
iMTA	Institute for Medical Technology Assessment
Inc.	Incremental
INCS	Intranasal corticosteroids
INMB	Incremental net monetary benefit
ISPOR	Professional Society of Health Economics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IWLM	Important worsening of larger magnitude
KSR	Kleijnen Systematic Reviews Ltd
LME	Linear mixed effect
LTRA	Leukotriene receptor antagonists
LYG	Life years gained
Max	Maximum
Min	Minimum
MIW	Minimally important worsening
MJ	Matters of judgement
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	Netherlands
ONS	Office for National Statistics
OPS	Oak pollen season
OR	Odds ratio
PBM	Preference-based measure
PP	Per protocol
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCPath	Royal College of Pathologists
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RR	Relative risk
SAR	Seasonal allergic rhinitis
SAS	Safety analysis set
SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLIT	Sublingual immunotherapy
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SPT	Skin prick test
SQ	standardised quality

STA	Single Technology Appraisal
TA	Technology Appraisal
TCS	Total combined score
TPS	Tree pollen season
TRAE	Treatment-related adverse event
UK	United Kingdom
VAS	Visual analogue scale
VBA	Visual Basic for Applications
WAO	World Allergy Organisation
WHO	World Health Organization
WTP	Willingness-to-pay

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1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost-effectiveness (CE). A summary is in presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (DP), 3 (clinical effectiveness) and 4 (CE) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1 provides a summary of key issues identified in the EAG report.

Table 1.1: Summary of key issues

ID6462	Summary of issue	Report Sections
1	Definition of population of interest is ambiguous.	2.1
2	Omission of immunotherapy as a comparator.	2.3 and 3.1.1
3	Generalisability of trial findings to patients in England and Wales.	3.3.1.6
4	Adverse events, [redacted].	3.3.2
5	There is uncertainty in some key parameters estimated from clinical experts.	4.2.6 and 4.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the following:

- Correcting the errors concerning the implementation of the long-term effectiveness found in the model provided in response to the clarification letter.
- Assuming higher discontinuation rates (due to other reasons) than those observed in the TT-04 trial. In particular, the EAG assumed that 8% of patients would discontinue treatment for other reasons in year 1, and 10% would discontinue treatment after 2 and 3 years.
- For the proportion of patients receiving benefit after discontinuation, the EAG assumed an estimate based on the responses from the three clinical experts consulted by the company (instead of just two). For the clinician who said this proportion would be a small number of patients, the EAG arbitrarily assumed 5%, resulting in a total of 35% of patients receiving treatment benefit after discontinuation.
- Selecting life tables (before coronavirus disease 2019 [COVID-19]) based on 2016-2018.
- Using adverse event (AE)-related utility decrements for the first year of treatment. An arbitrary disutility of -0.02 for each of the AEs was assumed for the EAG base-case.

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by slightly increasing total QALYs by relieving symptoms during the pollen season.

Overall, based on the company's base-case results, the technology is modelled to affect costs by:

- Reducing the number of visits to primary and secondary care and their associated costs
- Increasing costs due to treatment acquisition and administration
- Slightly increasing costs due to experiencing treatment-related adverse events (TRAEs) and slightly reducing symptomatic pharmacotherapy costs

The model is robust to changes in all the assumptions tested by the company and the EAG. The EAG considers that large effect on the ICER is observed for "extreme" or implausible scenarios only. When this has been observed, the modelling assumptions that have the greatest effect on the ICER are:

- Resource use disease management
- Discontinuation rates due to AEs

1.3 The decision problem: summary of the EAG's key issues

The DP addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is ambiguity regarding the definition of the population of interest (Table 1.2) and immunotherapy has been omitted as a relevant comparator (Table 1.3).

Table 1.2: Key issue 1. Definition of population of interest is ambiguous

Report Section	**2.1**
Description of issue and why the EAG has identified it as important	There are few issues with the definition of the population of interest: • In the CS, AR is defined as moderate-to-severe based on several criteria based on the ARIA guideline. Details on these criteria are limited thus the population is not clearly defined. • The final scope issued by NICE defines the population of interest as adults with AR *or* allergic conjunctivitis whereas the CS used the term AR referring to allergic rhinoconjunctivitis as a combined condition. • The birch homologous group includes a range of entries, not all of which are included in the efficacy analysis presented in the CS. • The line of therapy is unclear. According to the company, ITULAZAX 12 SQ-Bet is used in second line, however, treatment might be at a later line of treatment.
What alternative approach has the EAG suggested?	Clearer definitions of the population of interest and line of treatment would decrease the ambiguity as well as the heterogeneity of included participants.
What is the expected effect on the CE estimates?	The expected effect on the CE estimates is uncertain.

Report Section	2.1
What additional evidence or analyses might help to resolve this key issue?	Clearer definitions of the population of interest and line of treatment would decrease the ambiguity as well as the heterogeneity of included participants.
AR = allergic rhinitis; ARIA = Allergic Rhinitis and its Impact on Asthma; CE = cost-effectiveness; CS = company submission; EAG = External Assessment Group; NICE = National Institute for Health and Care Excellence	

Table 1.3: Key issue 2. Omission of immunotherapy as a comparator

Report Sections	2.3 and 3.1.1
Description of issue and why the EAG has identified it as important	The comparator, as defined in the final scope issued by NICE, is ECM, which includes Pollinex trees, as a form of SCIT. However, the CS omits any form of immunotherapy. The clinical expert consulted by the EAG notes that 30 to 40% of patients with moderate-to-severe AR, conjunctivitis, or both, caused by tree pollen would receive immunotherapy in clinical practice which is in line with the submission by RCPath.
What alternative approach has the EAG suggested?	Evidence on immunotherapy should be identified and compared to ITULAZAX 12 SQ-Bet. An ITC could inform a comparison with any form of immunotherapy that is currently used in clinical practice in England and Wales and the results should be reflected in the CEA.
What is the expected effect on the CE estimates?	The expected effect on the CE estimates is uncertain.
What additional evidence or analyses might help to resolve this key issue?	Evidence on immunotherapy should be identified and compared to ITULAZAX 12 SQ-Bet. An ITC could inform a comparison with any form of immunotherapy that is currently used in clinical practice in England and Wales and the results should be reflected in the CEA.
AR = allergic rhinitis; CE = cost-effectiveness; CEA = cost-effectiveness analysis; CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; RCPath = Royal College of Pathologists; SCIT = subcutaneous immunotherapy	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG is concerned about the generalisability of the TT-04, the main source of evidence presented in the CS, to patients in England and Wales (Table 1.4). Furthermore, the EAG wants to highlight a higher rate of AEs in the treatment group (Table 1.5).

Table 1.4: Key issue 3. Generalisability of trial findings to patients in England and Wales

Report Section	3.3.1.6
Description of issue and why the EAG has identified it as important	Lack of subgroup analyses for patients sensitised specifically to oak and beech pollen tree species which are highly relevant in the UK. There were also concerns with the reliance on immunological markers rather than clinical outcomes to support generalisability.
What alternative approach has the EAG suggested?	To perform subgroup analyses for patients sensitised specifically to oak and beech pollen tree species.
What is the expected effect on the CE estimates?	The expected effect on the CE estimates is uncertain.

Report Section	3.3.1.6
What additional evidence or analyses might help to resolve this key issue?	To perform subgroup analyses for patients sensitised specifically to oak and beech pollen tree species.
EAG = Evidence Assessment Group; CE = cost-effectiveness; UK = United Kingdom	

Table 1.5: Key issue 4. Adverse events, [redacted]

Report Section	3.3.2
Description of issue and why the EAG has identified it as important	There are more AEs in the intervention arm compared to the placebo arm. Some of these AEs led to discontinuation in the 12 SQ-Bet treatment group, [redacted].
What alternative approach has the EAG suggested?	None. However, the EAG wanted to highlight the issue for consideration by the committee.
What is the expected effect on the CE estimates?	The expected effect on the CE estimates is uncertain.
What additional evidence or analyses might help to resolve this key issue?	None. However, the EAG wanted to highlight the issue for consideration by the committee.
AE = adverse event; AR = allergic rhinitis; EAG = Evidence Assessment Group; CE = cost-effectiveness	

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

A full summary of the CE evidence review conclusions can be found in Section 6.4 of this report. The EAG's summary and detailed critique can be found in Section 4, the company's CE results are presented in Section 5, and the EAG's amendments to the company's model and results are in Section 6. The key issues in the CE evidence are discussed in Table 1.6.

Table 1.6: Key issue 5: There is uncertainty in some key parameters estimated from clinical experts

Report Sections	**4.2.6 and 4.2.8**
Description of issue and why the EAG has identified it as important	Relative risks for the reduction on the number of GP and secondary care visits associated to 12 SQ-Bet compared to ECM were estimated by a panel of experts. The clinical expert consulted by the EAG confirmed the expectation of a reduction in healthcare resource utilisation associated with the management of patients in primary and secondary care for patients treated with 12 SQ-Bet compared to those who are not treated with 12 SQ-Bet for at least 5-6 years following a 3-year course of SLIT, but did not provide an estimate of the expected number of primary and secondary care visits with and without 12 SQ-Bet. The EAG considers that a reduction in resource utilisation is expected but how much is uncertain. The impact of changing these parameters on the model results is expected to be large.
What alternative approach has the EAG suggested?	The EAG: • Incorporated additional expert opinion • Explored new scenario analyses
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Additional data to validate and/or replace estimates provided by the clinical experts.
CE = cost-effectiveness; EAG = External Assessment Group; ECM = established clinical management; GP = General Practitioner; SLIT = sublingual immunotherapy	

1.6 Summary of the EAG's view

The step-by-step changes made by the EAG to derive its base-case can be seen in Table 1.7. Overall, all changes included in the EAG base-case had a minimal impact on the model results and did not affect the company's general conclusions regarding CE.

Table 1.7: Individual impact of EAG preferred assumptions

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY)**
CS base-case					
12 SQ-Bet	9,486	19.34	-1,853	0.1012	Dominant
ECM	11,339	19.24			
Company base-case after clarification					
12 SQ-Bet	9,408	19.31	-1,846	0.1010	Dominant
ECM	11,253	19.21			
EAG change 1 – 8% of patients discontinue treatment for other reasons in year 1, and 10% in year 2 and 3					
12 SQ-Bet	9,502	19.31	-1,751	0.0946	Dominant
ECM	11,253	19.22			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG change 2 – 35% of patients receive treatment benefit after discontinuation					
12 SQ-Bet	9,494	19.31	-1,759	0.0991	Dominant
ECM	11253	19.22			
EAG change 3 – life tables based on 2016-2018 (before COVID-19)					
12 SQ-Bet	9,440	19.38	-1,885	0.1014	Dominant
ECM	11,294	19.28			
EAG change 4 – AE-related utility decrement (-0.02) for each of the AEs for the first year of treatment					
12 SQ-Bet	9,408	19.32	-1,846	0.1014	Dominant
ECM	11,253	19.21			
EAG's base-case					
12 SQ-Bet	9,710	19.38	-1,585	0.0907	Dominant
ECM	11,294	19.29			

Based on the model submitted following the clarification.[47]

AE = adverse event; COVID-19 = coronavirus disease 2019; CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	Adults with moderate-to-severe AR or allergic conjunctivitis or both caused by pollen from the birch homologous group despite the use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (SPT and/or specific IgE).	Adults with moderate-to-severe AR or allergic conjunctivitis or both caused by pollen from the birch homologous group despite the use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (SPT and/or specific IgE).	N/A	The wording for final scope issue by NICE and the DP defined in the CS are identical. However, the EAG discusses the definition of the population in Section 2.1.
Intervention	ITULAZAX 12 SQ-Bet SLIT as an add-on to standard therapy.	ITULAZAX 12 SQ-Bet SLIT as an add-on to standard therapy.	N/A	No specific comment.
Comparator(s)	ECM without ITULAZAX 12 SQ-Bet SLIT, such as Pollinex trees.	ECM without ITULAZAX 12 SQ-Bet SLIT.	ECM consists of symptomatic pharmacotherapy.	There are relevant differences which are discussed in Section 2.3.
Outcomes	The outcome measures to be considered include: • combined symptom and medication score • rhinoconjunctivitis symptom scores • complications of allergic rhinoconjunctivitis • medication usage • adverse effects of treatment • HRQoL	The outcome measures to be considered include: • combined symptom and medication score • rhinoconjunctivitis symptom scores • complications of allergic rhinoconjunctivitis • medication usage • adverse effects of treatment • HRQoL	N/A	No specific comment.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Special considerations including issues related to equity or equality	None stated.	None stated.	N/A	No specific comment.

Based on Table 1 of the CS[1]

AR = allergic rhinitis; CS = company submission; DP = decision problem; EAG = External Assessment Group; ECM = established clinical management; HRQoL = health-related quality of life; IgE = immunoglobulin E; N/A = not applicable; NICE = National Institute for Health and Care Excellence; SLIT = sublingual immunotherapy; SPT = skin prick test

2.1 Population

Both, the final scope issued by the National Institute for Health and Care Excellence (NICE) and the decision problem (DP) defined in the company submission (CS), define the population of interest as *"adults with moderate to severe AR or allergic conjunctivitis or both caused by pollen from the birch homologous group despite the use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (skin prick test and/or specific IgE)"*.[1, 2]

EAG comment: The External Assessment Group (EAG) noted that the definition of the population in this project includes some elements which might be relevant for the decision-making of the committee, namely 1. the meaning of 'moderate-to-severe' allergic rhinitis (AR), 2. distinguishing between AR and allergic conjunctivitis, 3. the underlying allergenic tree pollen, and 4. the line of treatment.

1. Meaning of 'moderate-to-severe' AR

   According to the CS, *"AR is classified as moderate to severe when one or more of the following items are present: troublesome symptoms, sleep disturbance, impairment of school or work, or impairment of daily activities, leisure, and/or sport"*.[1] In the request for clarification (Question B1), the EAG asked the company to provide objective criteria for the aforementioned symptoms.[3] In response to the request for clarification, the company reiterated the above definition, which is based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline,[4] and noted that *"there are no additional details on the objective criteria for these items as they are based on a patient's evaluation"*.[5] Objective criteria would have been helpful in defining the population more clearly.

2. Distinguishing between AR and allergic conjunctivitis

   In the request for clarification (Question B2), the EAG asked the company to define the proportions in each of AR and allergic conjunctivitis likely to be found in clinical practice.[3] In response to the request for clarification, the company noted that *"allergic rhinitis and allergic conjunctivitis are often concomitant diseases with a strong epidemiology correlation and similar pathophysiological mechanisms (…) with the two terms used interchangeably. Throughout the CS, the term 'AR' is used to refer to allergic rhinoconjunctivitis as a combined condition"*.[5] The committee should be aware that AR might refer to allergic rhinoconjunctivitis as a combined condition.

3. Underlying allergenic tree pollen

   According to the CS, the *"appraisal is concerned with AR induced by pollen from the birch homologous group (Betula verrucosa (birch), Alnus glutinosa (alder), Carpinus betulus (hornbeam), Corylus avellana (hazel), Quercus alba (oak) and Fagus sylvatica (beech))"*.[1] The company were therefore asked to provide the proportions of patients who are allergic to each tree pollen species in clinical practice.[3] However, the company only provided a breakdown from the TT-04 trial, which did not include the United Kingdom (UK). In response to Question B10, the company confirmed that in the included trial, TT-04, *"the tree pollen species included in the efficacy analysis were selected to prioritise the most important tree species and to include both early and late pollinating tree species to ensure the whole tree pollen season was covered, hence why oak was also included as a late pollinating species"*, this is discussed further in Section 3.3.16.[5]

4. Line of therapy

   The scope and DP define the population as *"adults with moderate to severe AR or allergic conjunctivitis (...) despite the use of symptom-relieving medication"*.[1, 2] The company also states that the line of therapy is second line. However, the British Society for Allergy and Clinical Immunology (BSACI) algorithm shows that there are several forms of this medication and three lines of therapy (separated by failure).[1] Therefore, the EAG asked the company to clarify where in the care pathway ITULAZAX 12 SQ-Bet sublingual immunotherapy (SLIT) would be used in clinical practice in relation to the algorithm.[3] In response, the company did not provide a more precise positioning than when: *"...symptoms persist despite use of symptomatic pharmacotherapy"*.[5]

Overall, the ambiguity and heterogeneity of the definition of the population of interest, particularly in terms of the definition of severity, mix of tree pollen species to which patents are allergic and uncertain place in the care pathway imply a key issue.

2.2 Intervention

Both, the final scope issued by the NICE and the DP defined in the CS, define the intervention of interest as *"ITULAZAX 12 SQ-Bet SLIT as an add-on to standard therapy"*.[1, 2]

EAG comment: The EAG does not have specific comments.

2.3 Comparators

The comparator in the NICE scope is established clinical management (ECM), which includes Pollinex trees, as a form of subcutaneous immunotherapy (SCIT). However, the company's DP omits any form of immunotherapy as comparator in ECM, confining ECM to what is observed in the key trial i.e., *"symptomatic pharmacotherapy"*.[1]

EAG comment: No evidence is presented for a comparison with SCIT and, as detailed in Section 3.1.1, searches in the submission were unnecessarily restrictive and could have excluded potentially relevant records on the clinical effectiveness of subcutaneous treatments. However, the EAG clinical expert notes that 30 to 40% of patients with moderate-to-severe AR, conjunctivitis, or both, caused by tree pollen would receive immunotherapy in clinical practice. This is supported by the submission from the Royal College of Pathologists (RCPath), which states that *"Itlulazax and other immunotherapy products (Pollinex and various unlicensed products) are available in the UK market,.."*.[6]

This is therefore a key issue, which would be resolved by an indirect treatment comparison (ITC) to inform a comparison with any form of immunotherapy that is currently used in clinical practice in England and Wales. The cost-effectiveness analysis (CEA) should also incorporate immunotherapy used in clinical practice in England and Wales as a comparator.

2.4 Outcomes

Both, the final scope issued by the NICE and the DP defined in the CS, provide an identical list of outcomes of interest.[1, 2]

EAG comment: The EAG does not have specific comments.

2.5 Other relevant factors

No special considerations were stated in the NICE final scope or addressed in the DP in the CS.[1, 2]

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[1] Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health [CADTH]) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[7] The EAG has presented only the major limitations of each search strategy in the report.

Appendix B of the CS details the systematic literature review (SLR) conducted to identify relevant clinical evidence on the efficacy and safety of therapies associated with managing birch pollen-induced seasonal allergic rhinitis (SAR).[8] Searches were conducted in May to July 2024.

EAG comment:

- Searches were undertaken to identify clinical evidence on the efficacy and safety of therapies associated with managing birch pollen-induced SAR. The CS, Appendix B and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[1, 5, 8]
- The following databases were searched from inception on 27 May 2024: Embase, MEDLINE, the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL). Full searches were reported.
- Key conference proceedings were searched in July 2024 for international conferences for the last 3 years via the MEDLINE and Embase searches. In addition, the European Forum for Research and Education in Allergy (EUFOREA) proceedings were hand-searched.
- Two clinical trials registries (www.ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform [WHO ICTRP]), six Health Technology Assessment (HTA) bodies' websites, and multiple additional sources were hand-searched to identify relevant publications in July 2024. Bibliographies of systematic reviews and meta-analyses and other selected studies were reference checked.
- No date or language limits were applied to the searches.
- The database searches for the clinical effectiveness SLRs combined a facet for SAR with facets containing search terms for the comparator treatments/placebo. This was further combined using the Boolean operator 'AND' with terms for both immunotherapy and for SLIT. Animal-only studies were excluded, and no date limit was applied.

  Population
  AND
  Comparators
  AND
  Immunotherapy/allergens
  AND
  Sublingual/Itulazax
- The EAG has concerns that this approach to the structure of the search was unnecessarily restrictive and could have excluded potentially relevant records on the clinical effectiveness of subcutaneous

treatments. A more cautious approach might have been to combine the population facet with facets for the comparators or SLIT, as was the case in the CE searches in Appendix E:[9]

Population
AND
Comparators OR Sublingual immunotherapy

- All searches were transparent and reproducible, and contained a good range of search terms, synonyms and subject headings.
- The EAG notes that although validated filters created by the Scottish Intercollegiate Guidelines Network (SIGN) were used to limit the results to clinical trials, these were not appropriate or necessary for the searches of the CENTRAL and CDSR databases. CENTRAL is a pre-filtered database of randomised controlled trials (RCTs), and CDSR is a systematic reviews database.
- A typographical error for betula verrucosa was included in the strategies ('Betula verrcose') but given the range of synonyms and indexing terms used, and extensive range of resources covered, this is unlikely to have affected the recall of the literature searches.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.1.

Table 3.1: Eligibility criteria used in the search strategy for RCT and non-RCT evidence

Category	Inclusion criteria	Exclusion criteria
Population	Participants (children >5 years of age, adolescents 12-17 years of age, and adults 18+ years of age) with birch group or Fagales group tree pollen allergies confirmed by SPT and/or specific IgE: • Birch (Latin: *betula verrcose*) • Alder (Latin: *alnus glutinosa*) • Oak (Latin: *quercus alba*) • Hazel (Latin: *corylus avellana*) • Hornbeam (Latin: *carpinus betulus*) • Beech (Latin: *fagus sylvactica*) Adults, adolescents, and children with symptoms of SAR/hay fever or seasonal allergic rhinoconjunctivitis with birch pollen induced-sensitivity	• Healthy volunteer studies • Animal studies • Patients with AA without SAR • Patients with perennial AR (allergen: HDM; Latin: d*ermatophagoides pteronyssinus*)
Intervention	ITULAZAX 12 SQ-Bet SLIT-tablets	Studies that do not report on the intervention of interest and a listed comparator

Comparator	• Placebo
	• Oral/nasal/eye drop antihistamines
	  • Acrivastine
	  • Antazoline with xylometazoline nasal spray
	  • Azelastine†
	  • Cetirizine
	  • Chlorphenamine maleate tabs
	  • Desloratadine
		Interventions not recommended or marketed for the treatment of SAR

Category	Inclusion criteria	Exclusion criteria
	• Fexofenadine • Hydroxyzine • Levocetirizine • Lodoxamide eye drops • Loratadine • Olopatadine eye drops • Sodium cromoglicate eye drops • Nasal steroid sprays • Beclomethasone • Budesonide • Ciclesonide • Fluticasone • Mometasone • Triamcinolone • Nasal decongestant sprays • Xylometazoline • Oxymetazoline • Sodium chloride	
Outcomes	Efficacy outcomes: • Daily/total symptom score (ocular, nasal) • Daily/total medication score (antihistamines, corticosteroids) • Total symptom and medication scores Safety outcomes TRAEs	Studies not reporting any of the outcomes listed in the inclusion criteria will be excluded due to a lack of outcomes of interest
Study design	RCT (any phase and design). Five current reviews will be used for citation searching[††]	• Non-randomised prospective controlled clinical studies or single arm trials • Observational studies (including prospective and retrospective studies, registries, etc.) • Preclinical and Phase 1 studies • Trial protocols • Non-human studies • In vitro, ex-vivo studies • Case reports • Editorials, notes, comments • Narrative reviews
Limitations	English language publications or non-English language publications with an English abstract	Non-English language publications without an English abstract
Based on Table 1 of Appendix B of the CS.[8]		

Category	Inclusion criteria	Exclusion criteria
Notes: † This preparation is used as a nasal spray/eye drops formulation †† During the title/abstract and full publication screening phase, all reviews were screened and the most relevant were included to be used for hand searching, these have not been ultimately excluded from the SLR. AA = allergic asthma; AR = allergic rhinitis; CS = company submission; HDM = house dust mite; IgE = immunoglobulin E; RCT = randomised controlled trial; SAR = seasonal allergic rhinitis; SLIT = sublingual immunotherapy; SPT = skin prick test; TRAEs = treatment-related adverse events		

EAG comment: The SLR study selection criteria limited inclusion to English language publications or non-English language publications with an English abstract. The company was asked to provide the number of relevant studies omitted from the review because of being published in non-English language publications without an English abstract and to consider the impact of the exclusion of such studies on clinical effectiveness estimates (clarification question [CQ] B5).[3]

In response, the company stated that, *"three articles were excluded from the HRQoL* [health-related quality of life] *screening library primarily based on publication language and additionally due to a lack of extractable relevant outcomes for the review population of interest being available in the abstract"* and further, *"we anticipate the exclusion of three non-English language studies with no relevant outcomes published in their abstract for the population of interest, to have no material impact on the conclusions of the HRQoL and utilities review"*.[5] All three references did provide an English language abstract but did not report outcomes related to the intervention of interest thus the EAG agreed with the exclusion of these studies.

3.1.3 Critique of data extraction

The company provided the following description of the data extraction process in Section 2.5 of Appendix B of the CS: *"Data was independently extracted from each included publication into this template by a single reviewer, with validation performed by a second reviewer. Any disagreements were resolved through adjudication by a third reviewer"*.[8]

Extraction included information on the following:

- General trial information, including bibliographic details, date of publication, study objectives, study population, inclusion and exclusion criteria, study design, countries of recruitment, interventions assessed, and statistical analysis.
- Population information, including sample size, demographic data for each trial arm, and clinical baseline characteristics for each trial arm.
- Primary and secondary endpoints, including the number of patients analysed, the instruments used for assessment, descriptions of the parameters used to report outcomes, time point(s) of assessment, details of analysis, and results by trial arm.

EAG comment: The screening process is satisfactory and has followed recommended good practice in systematic reviews.

3.1.4 Quality assessment

According to Appendix B of the CS, quality assessment of the included studies in this review was conducted using the Cochrane Risk of Bias 2 tool.[8] One reviewer carried out the critical appraisals of eligible studies, and a second reviewer validated the results. Any discrepancies were resolved through adjudication by a third reviewer.

3.1.5 Evidence synthesis

The company stated that no meta-analyses were conducted for inclusion.[1] The TT-04 trial included head-to-head data with ECM as patients in both treatment arms were permitted to use selected symptom-relieving medications for AR and conjunctivitis during the trial.

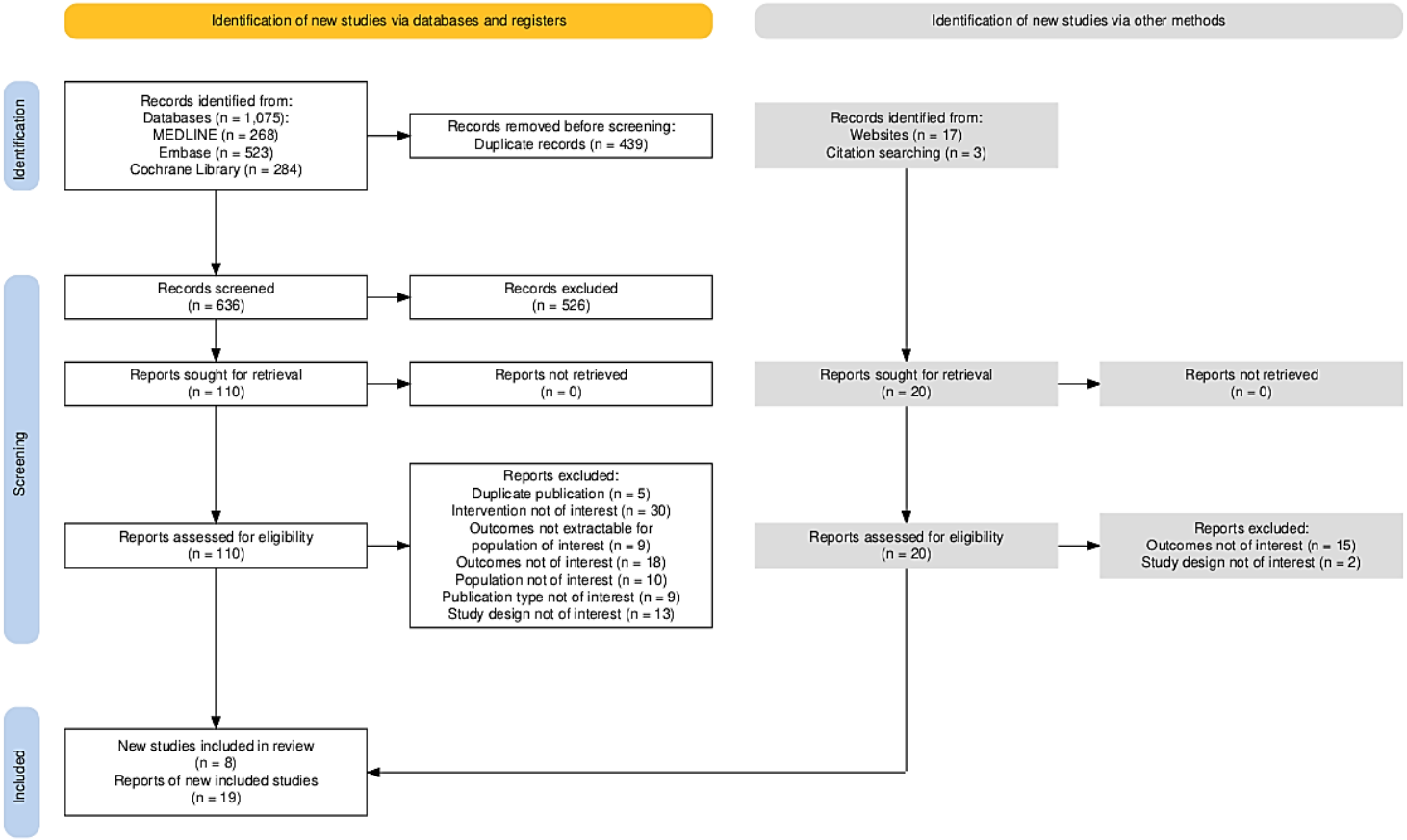
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

In Section 2.1 of the CS, the company reported that *"the electronic database search identified 1,075 citations. After removing 439 duplicates, 636 citations were screened based on title and abstract, with 110 publications considered potentially relevant and obtained for full publication review. Upon review, 16 articles from the database search were identified as eligible for inclusion in the SLR. Three additional records were identified via the grey literature search or supplementary sources. In total, 19 articles were found to report on the review questions; however, 7 of these were pooled analyses and/or literature reviews which were only used for citation tracking. Therefore, of the records identified, 12 publications reporting on 8 unique RCTs were eligible for further discussion in this SLR"*.[1]

The study retrieval process is summarised in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart detailed in Figure 3.1.

Figure 3.1: PRISMA flow diagram



Based on Figure 9 of CS[1]

CS = company submission; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

3.2.2 Summary of the included study

TT-04 was a large-scale, prospective phase 3, randomised, parallel-group, double-blind, placebo-controlled multicentre study to evaluate the efficacy and safety of 12 SQ-Bet in adult and adolescent patients with moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group.

A summary of the methodology of the TT-04 trial is included in Table 3.2.

Table 3.2: Summary of methodology of the TT-04 study

Methodology	Description
Trial design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multi-site field trial including 634 subjects with a clinically relevant history of moderate-to-severe AR and/or conjunctivitis induced by birch pollen despite having received treatment with symptom-relieving medication during the two previous TPS.
Duration of study and follow-up	Subjects were randomised in September and October 2016. All subjects received at least 16 weeks of treatment before the start of the TPS in 2017. The treatment duration with the investigational medicinal product was between 6½ months and 9½ months for subjects completing the trial. Mean duration: 224 days Median duration: 239 days P5%-P95%: 31-267 days Range: 1-282 days
Eligibility criteria	• Male or female aged 18 to 65 years at time of consent (in Poland adolescents aged 12-17 were also included) • A documented clinically relevant history of moderate-to-severe AR and/or conjunctivitis induced by birch pollen (with or without controlled/partly controlled asthma) despite having received treatment with symptom-relieving medication during the two previous TPS • An appropriate minimum level of allergic rhinoconjunctivitis symptoms induced by birch pollen during the BPS 2016 and a minimum use of antihistamines and/or nasal steroids during the screening period (i.e. an average DSS ≥6 with at least two moderate or one severe symptom and use of antihistamines and/or nasal steroids on at least four of the seven days of the screening period) • Presence of one or more of the following ARIA QoL items due to AR and/or conjunctivitis during the previous BPS: a) Sleep disturbance b) Impairment of daily activities, leisure, and/or sport c) Impairment of school or work d) Troublesome symptoms • Positive SPT response (wheal diameter ≥ 3 mm) to birch (Betula verrucosa) extract at screening • Positive specific IgE against Bet v 1 (≥IgE Class 2; 0.7 kU/L) at screening • No clinically relevant history of symptomatic (seasonal or perennial) AR and/or conjunctivitis caused by an allergen source, other than tree pollen from the birch homologous group overlapping the TPS • No severe asthma exacerbation within the last 3 months

Methodology	Description
	• No clinical history of uncontrolled asthma (by GINA definition) within 3 months prior to screening • FEV1 ≥70% of predicted value after adequate pharmacological treatment
Settings and locations	There was a total of 57 trial sites in EU (Sweden, Finland, Denmark, Poland, Germany, the Czech Republic, France) and Russia.
Trial drugs	SQ tree SLIT-tablet, 12 SQ-Bet, batch numbers 1592975, 1598079. Placebo, batch number 1592017.
Concomitant medications	Symptom-relieving medications for AR and conjunctivitis were provided as open-labelled medication and were used in addition to the IMP to which the subjects had been randomised: • Oral antihistamine tablets (Desloratadine tablets, 5 mg) • Nasal corticosteroid spray (Mometasone, 50 µg/dose) • Antihistamine eye drops (Olopatadine eye drops, 1 mg/ml)
Pre-planned subgroups	No subgroup analysis relevant to the appraisal population was performed in the TT-04 trial.

Based on Table 6 of the CS[1]
AR = allergic rhinitis; ARIA = Allergic Rhinitis and its Impact on Asthma; BPS = birch pollen season; CS = company submission; DSS = daily symptom score; EU = European Union; FEV = Forced expiratory volume; GINA = Global Initiative for Asthma; IgE = immunoglobulin E; IMP = Investigational Medicinal Product; QoL = quality of life; SLIT = sublingual immunotherapy; SPT = skin prick test; TPS = tree pollen season

EAG comment:

- The company was asked to clarify how allocation concealment was ensured.[3] The company responded that *"subjects, investigative staff, and sponsors were blind to treatment allocation. Two sets of sealed envelopes contained treatment allocation (one at the trial site and one at the sponsor). The sequence was not accessible to trial personnel until the database lock and trial unblinding. In case of a medical emergency, the code could be broken for a particular subject if treatment knowledge was necessary for optimal treatment"*.[5] The company was also asked to provide details on the randomisation process and how patients were allocated to treatment or placebo groups.[3] The company responded that *"the randomization list was generated by a trial-independent statistician using random sampling (block size, 4). To randomize a subject, the investigator allocated the lowest available randomization number at the site"*.[5] The EAG considered that the company's description of the randomisation process and allocation concealment was consistent with good practice approaches.
- In CQ B8, the company was asked to clarify the applicability of standard-of-care (SoC) medications used in the TT-04 trial to UK clinical practice, the exclusion of certain medications, and the potential implications for treatment effectiveness.[3] The company responded that the trial provided participants with oral antihistamines, nasal corticosteroid sprays, and antihistamine eye drops, which were confirmed by expert panels and clinician surveys as representative of typical SoC for AR management in the UK. The inclusion of these symptomatic treatments was intended to reflect real-world clinical practice, ensuring that 12 SQ-Bet was assessed within an appropriate treatment context.[5]

  The company also justified the exclusion of certain medications, such as leukotriene receptor antagonists (LTRA), intranasal decongestants, ipratropium bromide, and systemic corticosteroids, stating that these treatments are infrequently used in UK AR management and their omission would not introduce bias. This was supported by an online survey of UK clinicians and a Delphi panel,

both of which confirmed that the trial's approach to SoC was aligned with UK practice. The company further noted that standardising symptomatic medications across trial arms was necessary to ensure consistency and reduce potential confounding effects.[5]

Regarding the impact on treatment effectiveness, the company acknowledged that structured training on symptomatic medication use and the potential for a placebo effect in immunotherapy trials could lead to an overestimation of background SoC efficacy while potentially underestimating the incremental benefit of 12 SQ-Bet. However, they maintained that the overall design of the TT-04 trial, including the selected SoC treatments, was reflective of real-world clinical practice and unlikely to impact the estimated efficacy of 12 SQ-Bet.[5]

The EAG considered the company's response to be consistent with good clinical trial design practices. The selection of SoC medications and exclusion of certain treatments were well justified, aligning with UK clinical practice and ensuring standardisation between trial arms. While the potential impact of structured medication use training was acknowledged, the EAG agreed that the overall trial design remains relevant to assessing 12 SQ-Bet within the UK treatment pathway. However, as discussed in Section 2.1, the definition of the line of treatment is a key issue.

3.2.2.1 Eligibility criteria of the TT-04 trial

A summary of the inclusion and exclusion criteria of the TT-04 trial is provided in Table 3.3.

Table 3.3: An overview of the inclusion and exclusion criteria of the TT-04 trial

Inclusion criteria	Exclusion criteria
The study population comprised adults (aged 18–65 years, in Poland, adolescents 12-17 years were also included) with moderate-to-severe AR and/or conjunctivitis induced by tree pollen, with or without asthma (controlled/ partly controlled), despite being treated with allergy pharmacotherapy in the previous two pollen seasons	Patients were excluded if they had a clinically relevant history of AR and/or conjunctivitis caused by allergens other than tree pollen from the birch homologous group (including animal hair and dander)
The presence of at least one of the following four ARIA QoL items: sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; troublesome symptoms	Severe asthma exacerbation within the last 3 months
A positive response to a birch extract SPT	A clinical history of uncontrolled asthma within 3 months prior to screening
A positive IgE against Bet v 1 (the major allergen of birch pollen)	Reduced lung function (FEV1 < 70% of predicted value after adequate pharmacological treatment)
Based on Table 7 of the CS[1] AR = allergic rhinitis; ARIA = Allergic Rhinitis and its Impact on Asthma; CS = company submission; FEV = forced expiratory volume; IgE = immunoglobulin E; QoL = quality of life; SPT = skin prick test	

EAG comment: The company was asked to clarify (clarification Question B13) whether the inclusion of adolescents in the TT-04 trial affects the robustness of findings for the adult population, the impact of excluding patients over 65 years, and to provide effectiveness analyses excluding adolescents and UK patients only.[3]

- The company stated that the inclusion of adolescents in TT-04 does not affect the robustness of the findings for adults. Subgroup analysis of the primary endpoint (average total combined score [TCS] during the birch pollen season [BPS]) showed no statistically significant difference in treatment

effect between adults and adolescents (P=0.5417). The absolute reduction in TCS was 3.16 for adults and 1.94 for adolescents, corresponding to relative reductions of 41% and 31% respectively, both exceeding clinically meaningful thresholds.[5]
Additionally, expert opinion gathered from UK clinicians (survey and Advisory Board discussions) supported the assumption that treatment response would be similar between adults and adolescents. The TT-06 trial, which studied 12 SQ-Bet in children and adolescents, also demonstrated efficacy comparable to TT-04, further reinforcing that the adolescent population does not compromise the robustness of findings for adults.[5]

- The company acknowledged limited clinical experience in patients aged over 65 years, as this group was not included in TT-04. However, no upper age limit is specified in the regulatory approval for 12 SQ-Bet. Additionally, safety data from the MT-04 Phase 3 trial for 12 SQ-house dust mite (HDM) (a SLIT treatment with a similar mechanism of action and manufacturing technology) included patients over 65 years and did not reveal safety concerns. While no specific subgroup analysis was conducted for elderly patients, the available data suggest no significant concerns regarding efficacy or safety in this population.[5]
- Effectiveness analyses excluding adolescents show that treatment effects remain consistent. Among adults, the relative reduction in TCS was 40.68% (compared to placebo) during the BPS, with an absolute difference of 3.16 (95% confidence interval [CI]: 2.06, 4.25). The adult subgroup analysis demonstrated a clinically meaningful treatment effect exceeding regulatory thresholds (20% for World Allergy Organisation [WAO], 15% for United States Food and Drug Administration [FDA]).[5]
- As TT-04 was not conducted in the UK, effectiveness analyses for UK patients alone are not possible. However, the company argued that the trial's findings are generalisable to the UK population. The trial included sites in Western, Central, and Northern Europe, which experience similar pollen seasons to the UK. Clinical experts confirmed that the SoC medications used in TT-04 align with UK clinical practice.
  Baseline characteristics from TT-04 were also compared with a UK-based cross-sectional study, showing similar age, sex distribution, ethnicity, and asthma prevalence.[10] Given these similarities, the TT-04 results are expected to be applicable to UK patients.[5]

The EAG considers the company's justification for the inclusion of adolescents and the exclusion of elderly patients reasonable. The statistical evidence suggests no significant difference in treatment effect between adults and adolescents, and regulatory approval without an upper age limit mitigates concerns about the lack of elderly participants in TT-04. The company's argument for generalisability to UK patients is supported by comparable baseline characteristics and similar pollen exposure patterns across European trial sites. However, real-world data from UK patients may be beneficial in further confirming these findings.

3.2.2.2 Baseline characteristics of the TT-04 trial

Table 3.4 describes the baseline characteristics of the TT-04 trial as presented in the CS. The company reported that *"overall, the treatment groups were generally well balanced with respect to demographics and baseline characteristics. The mean age of the population was 36.1 years, with a range of 12 to 65 years, which is in alignment with the age limits specified in the inclusion criteria. A total of 60 adolescent subjects (9.5%) were included in the trial, of which 57 completed. All subjects had Bet v 1 specific IgE ≥ class 2 (0.7 kU/l), 43.5% reported asthma, and 66.4% had a medical history of PFS. On average, patients reported having birch pollen allergy for 15.9 years. Skin prick tests showed that all patients were sensitised to birch, and 75.7% were polysensitised (defined as sensitisation to birch, alder, hazel, and others)"*.[1]

Table 3.4: Demographic and baseline characteristics in the TT-04 study (FAS)

Treatment group	Placebo (N=314) n (%)	12 SQ-Bet (N=320) n (%)	Overall (N=634) n (%)
Allergy history			
Birch pollen allergy	314 (100%)	320 (100%)	634 (100%)
Asthma (all causes)	134 (43%)	142 (44%)	276 (44%)
PFS	209 (67%)	212 (66%)	421 (66%)
Sensitisations by SPT			
Birch	313 (>99%)*	320 (100%)	633 (>99%)
Alder	288 (92%)	293 (92%)	581 (92%)
Hazel	274 (87%)	270 (84%)	544 (86%)
Mono-sensitised**	72 (23%)	82 (26%)	154 (24%)
Polysensitised	242 (77%)	238 (74%)	480 (76%)
Impact on QoL during BPS prior to randomisation			
Impairment of daily activities, leisure and or sport	264 (84%)	278 (87%)	542 (85%)
Impairment of school or work	228 (73%)	242 (76%)	470 (74%)
Sleep disturbance	211 (67%)	212 (66%)	423 (67%)
Troublesome symptoms	299 (95%)	307 (96%)	606 (96%)
Gender			
Male	146 (46%)	152 (48%)	298 (47%)
Female	168 (54%)	168 (53%)	336 (53%)
Ethnic origin			
White	304 (97%)	314 (98%)	618 (97%)
Asian	3 (<1%)	4 (1%)	7 (1%)
Black/African American	1 (<1%)	-	1 (<1%)
Hispanic/Latino	2 (<1%)	1 (<1%)	3 (<1%)
Other	2 (<1%)	1 (<1%)	3 (<1%)
Unknown	2 (<1%)	-	2 (<1%)
Age			
Mean (SD)	35.3 (13.5)	36.8 (13.7)	36.1 (13.6)
Median	34.5	36	36
Min-Max	12.0-65.0	12.0-65.0	12.0-65.0
BMI			
Mean (SD)	24.6 (4.1)	25.0 (4.3)	24.8 (4.2)
Median	24.2	24.7	24.5
Min-Max	14.5-41.3	16.2-40.4	14.5-41.3
Smoking history			
Never	253	(81%)	252
Former	35	(11%)	39

Treatment group	Placebo (N=314) n (%)	12 SQ-Bet (N=320) n (%)	Overall (N=634) n (%)
Current	26	(8%)	29
Bet v 1 specific IgE class			
2-3	134	(43%)	137
4-6	180	(57%)	183

Based on Table 11 of the CS.[1]
* missing for one subject
** mono-sensitised defined as SPT positive to birch, alder, or hazel
BMI = body mass index; BPS = birch pollen season; CS = company submission; FAS = full analysis set; HDM = House dust mite; IgE = Immunoglobulin E; Max = maximum; Min = minimum; QoL = quality of life; SD = standard deviation; SPT = skin prick test

EAG comment: The company was asked to clarify the eligibility criteria for ITULAZAX 12 SQ-Bet SLIT treatment in patients with asthma and the generalisability of the TT-04 trial to clinical practice.[3] The company responded that ITULAZAX 12 SQ-Bet is intended for patients with moderate-to-severe AR, including those with concomitant controlled or partly controlled allergic asthma (AA). The TT-04 trial required asthma to be controlled prior to treatment initiation, excluding patients with recent severe exacerbations, uncontrolled asthma, or reduced lung function (forced expiratory volume [FEV]1 <70% of predicted value). The company further clarified that, although asthma is not included in the licensed indication for 12 SQ-Bet, the trial explored its impact on comorbid asthma symptoms as an exploratory endpoint. The trial results suggested potential benefits for comorbid asthma symptoms, aligning with SLIT treatments for other allergens, such as HDMs. The company also highlighted that the trial's inclusion criteria regarding asthma control were consistent with the summary of product characteristics (SmPC) and the licensed indication.[5] The EAG considered that the company's response regarding the trial population and asthma control criteria was consistent with good clinical practice and aligned with the intended target population for ITULAZAX 12 SQ-Bet in clinical use.

3.2.3 Statistical analysis for the TT-04 trial

Details of the statistical analysis and definitions of study groups in the TT-04 trial as presented in the CS, are summarised in Table 3.5.[1]

Table 3.5: Summary of the statistical analysis carried out in the TT-04 trial

Hypothesis objective	The primary and key secondary endpoints were controlled for multiplicity by means of hierarchical testing to ensure a maximum overall type I error rate of 5% in hypothesis testing. The null hypothesis was the hypothesis of no difference between the two treatments.
Statistical analysis	All statistical tests were two-sided and were performed using a significance level of 5% The primary efficacy endpoint, and key secondary endpoints, were analysed using a LME model, with treatment group as fixed effect and pollen region as a random effect. An LME model was also used to analyse other endpoints (secondary and exploratory): average rhinoconjunctivitis symptom VAS, productivity, asthma DSS, ACT score, and the changes from baseline in IgE and IgG4.[99] Patient-rated clinical global improvement, percentage of mild, or severe days, number of sick days, and asthma medication use, were analysed using a generalised logistic regression model. The RQLQ was analysed using a repeated measurement linear

	mixed model. Exploratory endpoints related to the apple challenge were summarised using descriptive statistics. The LME model described above was also used to analyse two other sets of data:[99, 104] 1) *post-hoc* analysis of the average TCS, DSS, and DMS data in the combined AHPS (separate to the BPS), 2) subgroup analysis of the average TCS during the BPS data for adolescent patients.
Sample size, power calculation	A sample size of 300 per treatment group was needed to have at least 90% power to detect a significant difference between active and placebo treatment in the primary endpoint. The power calculation was based on a 2-sided t test with a 5% significance level assuming use of all observed data, a 20% reduction in TCS in the active compared with placebo groups, a 10% dropout rate, and a coefficient of variation of 0.79 in both treatment groups (based on previous trial with the SQ tree SLIT-tablet (TT-03)).[98] For the post *post-hoc* analysis of the average TCS, DSS, and DMS in in the combined AHPS (separate to the BPS) 34 individuals were randomised (tree SLIT-tablet = 320; placebo = 314) and analysed during the OPS; 575 participants were in the FASBPS population that was analysed during the continuous TPS. Rubin's multiple imputation strategy was used and missing values in both treatment groups were sampled from the observed data of the end point in the placebo group.
Data management, patient withdrawals	The FAS was defined as all randomised patients in accordance with the ITT principle. The FAS was used for baseline demographics. The primary analysis was conducted on patients in the FAS who had at least one diary entry during the BPS – known as the FASBPS. The apple challenge analysis set (FASAPPLE) comprised all patients in the FAS who participated in the apple challenge and for whom data were available. The asthma analysis set (FASASTHMA) included all patients with an asthma diagnosis at randomisation with at least one observation related to an asthma endpoint and was used for the analysis of ACT score. The SAS represents the 'as treated' population regardless of randomisation and was used for all safety analyses.

Based on Table 12 of the CS.[1]
ACT = Asthma Control Test; AHPS = alder and hazel pollen season; BPS = birch pollen season; CS = company submission; DMS = daily medication score; DSS = daily symptom score; FAS = full analysis set; FASAPPLE = the apple challenge analysis set; FASASTHMA = subjects in FAS with a medical history of asthma; FASBPS = subjects in FAS with observations in the BPS; IgE = immunoglobulin E; IgG4 = immunoglobulin G subtype 4; ITT = intention-to-treat; LME = linear mixed effect; OPS = oak pollen season; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SAS = safety analysis set; SLIT = sublingual immunotherapy; SQ = standardised quality; TCS = total combined score; VAS = visual analogue scale

3.2.4 Risk of bias assessments

The Company provided the risk of bias assessment for each primary study included in the evidence base in the Appendix B of the CS (using the Cochrane RoB 2 tool).[8] The results of the assessment are shown in Table 3.6 below.

Table 3.6: Assessment of the risk of bias of individual studies using the Cochrane Risk of Bias-2 tool

Study	Random sequence generation	Assignment to intervention	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall bias
TT-04	Low	Low	Low	Unclear	Low	Unclear

Study	Random sequence generation	Assignment to intervention	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Overall bias
TT-03 (NCT02481856)	Low	Low	Unclear	Low	Low	Low
Frati, 2023	Unclear	Low	Unclear	Unclear	Unclear	High
TT-02	Low	Low	Unclear	Unclear	Low	Unclear
Smith, 2002	High	Low	Unclear	Unclear	Unclear	High
EudraCT-2013-002129-45	Low	Low	Unclear	Unclear	Low	Unclear
Birk, 2017	Unclear	Low	Unclear	High	Low	High
Rak, 2010	Unclear	Low	Unclear	Unclear	Unclear	High

Based on Table 9 of Appendix B of the CS.[8]
CS = company submission

3.2.5 Evidence synthesis

No meta-analyses were conducted for inclusion in this submission.[1]

3.3 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.3.1 Efficacy results of the TT-04 trial

The following Section will appraise the results from the TT-04 trial. This includes primary efficacy endpoints, key and other secondary endpoints, exploratory endpoints, pharmacodynamic endpoints and post-hoc analysis.

The company were asked about the proportions in each of AR and allergic rhinoconjunctivitis likely to be found in clinical practice.[3] The company responded by stating that *"the clinical evidence presented in TT-04 is relevant to allergic rhinoconjunctivitis patients, with the pivotal TT-04 trial's primary endpoint being specific to allergic rhinoconjunctivitis. Additionally, where specified, the secondary endpoints of the trial are specific to allergic rhinitis and conjunctivitis as a combined condition"*.[5] This has been discussed in Section 2.1.

3.3.1.1 Primary efficacy endpoint: Average daily allergic rhinoconjunctivitis TCS during BPS

The TCS, which the CS described as being the sum of the daily symptom score (DSS) and daily medication score (DMS), is an appropriate and optimal primary endpoint for allergic immunotherapy (AIT) trials recognised by the European Academy of Allergy and Clinical Immunology (EAACI) task force.[1] The TT-04 trial demonstrated a statistically significant improvement in TCS during the BPS, with 12 SQ-Bet showing a relative reduction of 39.59% in the full analysis set (FAS) during BPS (subjects in FAS with observations in the birch pollen season [FASBPS]) and 42.9% in the per protocol (PP) set compared to placebo ($P < 0.0001$), see Table 3.7 for a full overview.

Table 3.7: Overview of the results for TCS during the BPS in the FASBPS and PP analysis sets of the TT-04 trial

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet)	% relative to placebo [95% CI]	P-value
TCS during the BPS (FASBPS)					
Placebo	292	7.62	-	-	-
12 SQ-Bet	282	4.61	3.02 [1.99, 4.05]	39.59 [28.24, 49.51]	<0.0001
TCS during the BPS (PP)					
Placebo	247	7.63	-	-	-
12 SQ-Bet	235	4.35	3.27 [2.17, 4.38]	42.90 [31.11, 53.12]	<0.0001

Based on Table 15 of the CS.[1]
Reference: TT-04 CSR.[11]
Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; FASBPS = subjects in FAS with observations during the BPS; LME = linear mixed effect; PP = per protocol; TCS = total combined score

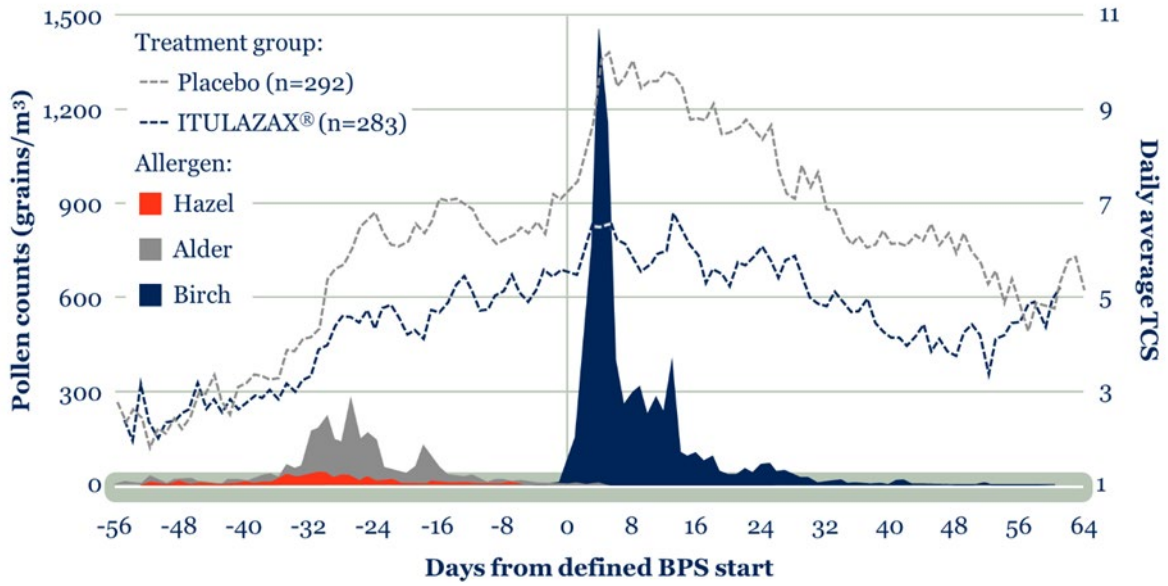
The CS[1] stated that these results exceeded the WAO's pre-specified clinically relevant difference of 20%[11-13] and the United States FDA's minimum efficacy threshold of 15% for demonstrating the effectiveness of AIT.[14]

Despite the strong relative reduction, the absolute difference in TCS was only 3.02 in the FASBPS group and 3.27 in the PP group (Table 3.7). While the relative reduction is above regulatory thresholds, the company does not justify whether an absolute reduction of ~3 is clinically meaningful for patients. Without an established minimal clinically important difference for TCS, it is unclear whether patients would perceive this reduction as a significant improvement in daily life.

The PP analysis showed the strongest relative reduction in TCS at 42.9% (Table 3.7), reinforcing the notion that higher adherence and adequate pollen exposure improves treatment outcomes. However, the PP cohort set of patients excludes non-adherent patients, those with major protocol deviations, and those with insufficient pollen exposure, making it less representative of real-world conditions. The difference in efficacy between FASBPS (39.6%) and PP (42.9%) suggests that treatment effectiveness is optimised in highly adherent patients, but real-world habitual adherence may be lower than in this clinical trial setting.

A key finding from the TT-04 trial is the early separation between 12 SQ-Bet and placebo in TCS scores, *"approximately four weeks before the onset of the BPS"*.[1] This trend coincides with the earlier alder and hazel pollen seasons (AHPS), suggesting that 12 SQ-Bet may provide early symptom relief for patients sensitised to multiple tree pollens. This separation was sustained throughout the BPS, with the most pronounced difference observed in the first 4 weeks of peak birch pollen exposure (Figure 3.2).

Figure 3.2: The average daily pollen counts and average TCS during the TPS in the TT-04 trial



Based on Figure 13 of the CS.[1]
Reference: TT-04 CSR.[11]
Notes: Data are presented for the FASBPS (all patients with ≥1 observation during the BPS; 12 SQ-Bet, n=283; placebo, n=292).
BPS = birch pollen season; CS = company submission; CSR = clinical study report; FASBPS = subjects in FAS with observations during the BPS; TCS = total combined score; TPS = tree pollen season

A major concern is the handling of missing data and the impact of treatment discontinuations. The dropout rate was higher in the treatment arm (13%) compared to the placebo arm (7%), and this was attributed to adverse events (AEs). The FASBPS excludes early dropouts who did not have observations during BPS, meaning that the primary analysis does not account for patients who discontinued treatment early, potentially inflating efficacy estimates if these patients had worse symptom control or lower adherence.

To address this, sensitivity analyses were conducted using the FAS, which includes all randomised patients regardless of treatment adherence or BPS exposure. The results of the two multiple imputation methods applied to FAS (Tables 3.8 and 3.9) showed slightly lower relative reductions (35.69% and 36.55%) compared to FASBPS (39.59%). While this suggests that the missing data did not substantially alter conclusions, the difference between FAS and FASBPS indicates that excluding early dropouts from the primary analysis may have slightly overestimated efficacy.

Table 3.8: Sensitivity analysis for TCS during the BPS using multiple imputation method 1 (FAS)

Trial arm	N Total	N Observed	N Imputed	Adjusted mean	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% relative to placebo [95% CI]	P-value
Placebo	314	292	22	7.67	-	-	-
12 SQ-Bet	320	283	37	4.93	2.74 [1.69, 3.78]	35.69 [24.25, 46.20]	<0.0001

Trial arm	N Total	N Observed	N Imputed	Adjusted mean	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% relative to placebo [95% CI]	P-value
Based on Table 16 of the CS.[1] Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable. BPS = birch pollen season; CI = confidence interval; CS = company submission; FAS = full analysis set; LME = linear mixed effect; TCS = total combined score							

Table 3.9: Sensitivity analysis for TCS during the BPS using multiple imputation method 2 (FAS)

Trial arm	N Total	N Observed	N Imputed	Adjusted mean	Absolute difference (placebo – 12 SQ-Bet) [95% CI]	% relative to placebo [95% CI]	P-value
Placebo	314	292	22	7.67	-	-	-
12 SQ-Bet	320	283	37	4.93	2.74 [1.69, 3.78]	35.69 [24.25, 46.20]	<0.0001
Based on Table 17 of the CS.[1] Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable. BPS = birch pollen season; CI = confidence interval; CS = company submission; FAS = full analysis set; LME = linear mixed effect; TCS = total combined score							

A potential concern from the EAG is that oak and beech pollen were excluded from the efficacy analysis, despite their overlap with BPS in the UK (according to Figure 1 of the CS)[1]). If UK patients are sensitised to these additional pollens, their symptoms may persist beyond the period measured in the trial, potentially limiting the generalisability of the findings.

EAG comment: In summary, the TCS endpoint is an appropriate and widely accepted measure for allergic rhinoconjunctivitis trials, and the trial demonstrated a statistically significant and clinically relevant relative improvement in symptoms compared to placebo. The early separation in TCS scores suggests that 12 SQ-Bet may provide benefits beyond birch pollen alone, possibly extending to patients sensitised to hazel and alder pollen. However, several methodological concerns remain, including the lack of justification for the absolute reduction in TCS (~3), the exclusion of early dropouts from the primary analysis (FASBPS), and the omission of oak and beech pollen from the efficacy evaluation. The differences in relative TCS reductions between FAS (35.69%–36.55%), FASBPS (39.6%), and PP (42.9%) suggest that real-world effectiveness may be lower than reported in the trial. Additionally, the role of adherence and real-world exposure to multiple tree pollens should be considered when interpreting the potential benefits of 12 SQ-Bet for UK patients.

3.3.1.2 Key secondary endpoints: Average allergic rhinoconjunctivitis DSS during the BPS and TPS; average allergic rhinoconjunctivitis TCS during the TPS

The key secondary endpoints assessed in the TT-04 trial were the average DSS during the BPS and tree pollen season (TPS), as well as the TCS during the TPS. These measures extend the evaluation of 12

SQ-Bet's efficacy beyond peak birch pollen exposure, capturing both symptom severity (DSS) and combined symptom-medication use (TCS) over a longer pollen season. All analyses showed a statistically significant improvement with 12 SQ-Bet compared to placebo (P<0.0001), reinforcing the primary efficacy findings.

3.3.1.2.1 Average allergic rhinoconjunctivitis DSS during the BPS and TPS

The DSS measures symptom severity without considering medication use, providing insight into the direct effect of treatment on allergic rhinoconjunctivitis symptoms. During the BPS, 12 SQ-Bet significantly reduced DSS compared to placebo, with an estimated absolute difference of 1.32, equating to a 36.75% relative reduction (P<0.0001). A similar trend was observed during the TPS, where 12 SQ-Bet showed an absolute difference of 0.99 and a 32.73% relative reduction (P<0.0001), see Table 3.10.[11]

Table 3.10: Overview of the DSS results during the TPS and BPS in the FASBPS analysis set of the TT-04 trial

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet)	% relative to placebo [95% CI]	P-value
Average DSS during the BPS (FASBPS)					
Placebo	292	3.60	-	-	<0.0001
12 SQ-Bet	283	2.28	1.32 [0.84, 1.81]	36.75 [25.29, 46.70]	
Average DSS during the TPS (FASBPS)					
Placebo	292	3.02	-	-	<0.0001
12 SQ-Bet	283	2.03	0.99 [0.60, 1.38]	32.73 [21.45, 42.56]	

Based on Table 18 of the CS[1]
Reference: TT-04 CSR.[11]
Notes: FASBPS refers to subjects in FAS with observations during the BPS.
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; DSS = daily symptom score; FAS = full analysis set; FASBPS = subjects in FAS with observations in the BPS; TPS = tree pollen season

These reductions exceed the WAO and United States FDA clinical relevance thresholds (20% and 15%, respectively).[11-14] However, while the relative reductions are substantial, the absolute reductions in DSS are modest. The submission does not justify whether a 1.32 or 0.99 reduction corresponds to a noticeable improvement in patient symptoms. Therefore, it is unclear whether this improvement is clinically meaningful in real-world settings.

As observed with the primary TCS endpoint, DSS separation between 12 SQ-Bet and placebo emerged approximately 4 weeks before the BPS, coinciding with the AHPS. This suggests that patients sensitised to multiple tree pollens may experience symptom relief earlier than those sensitive only to birch pollen. However, oak and beech pollen were not included in the efficacy analysis, raising concerns about whether patients with broader polysensitisation would experience the same level of benefit.

3.3.1.2.2 Average allergic rhinoconjunctivitis TCS during the TPS

The TCS reduction extended beyond the BPS into the full TPS, with 12 SQ-Bet showing an absolute difference of 2.27 and a 36.54% relative reduction versus placebo (P<0.0001), see Table 3.11.[11] These results suggest that the treatment effect persisted beyond peak birch pollen exposure, reducing both symptoms and medication use throughout the extended pollen season.

Table 3.11: Overview of the TCS results during the TPS in the FASBPS analysis set of the TT-04 trial

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet)	% relative to placebo [95% CI]	P-value
Average TCS during the TPS (FASBPS)					
Placebo	292	6.22	-	-	<0.0001
12 SQ-Bet	283	3.95	2.27 [1.44, 3.11]	36.54 [24.99, 46.62]	

Based on Table 19 of the CS.[1]
Reference: TT-04 CSR.[11]
Notes: The response variable in the analysis is: the square root of the average TCS (results were back-transformed to original scale). The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; FASBPS = subjects in FAS with observations in the BPS; LME = linear mixed effect; TCS = total combined score

Both placebo and treatment groups experienced lower overall TCS values during the TPS than during the BPS, likely due to reduced pollen concentrations as the season progressed. However, while the relative reduction in TCS is substantial (36.54%), the absolute reduction of 2.27 is not explicitly justified in terms of real-world patient benefit. Similar to DSS, the submission does not provide a minimal clinically important difference for TCS in the TPS, making it difficult to determine the clinical significance of these results.

EAG comment: The FASBPS was used for key secondary endpoint analyses, mirroring the primary analysis. Sensitivity analyses were also conducted using the FAS, which includes all randomised patients and employs multiple imputation for missing data. The consistency of results between FASBPS and FAS suggests that missing data did not substantially impact findings. However, since FASBPS excludes early dropouts (who were primarily in the treatment group due to AEs), there is still potential for selection bias.

Additionally, the PP analysis showed stronger treatment effects than FASBPS, with a relative DSS reduction of 42.9% (primary) versus 36.75% (secondary) in FASBPS. This suggests that patients who were highly adherent to the treatment and had adequate pollen exposure experienced greater symptom relief. While this supports the efficacy of 12 SQ-Bet under ideal conditions, the generalisability of the PP results to real-world patients, who may have lower adherence, remains uncertain.

3.3.1.3 Other secondary endpoints: average allergic rhinoconjunctivitis DMS; average number of mild and severe days; average rhinoconjunctivitis symptom VAS; global evaluation of efficacy; and RQLQ endpoints during the BPS and TPS

In addition to the primary and key secondary endpoints, the TT-04 trial assessed several other secondary endpoints to provide a broader evaluation of the effectiveness of 12 SQ-Bet. These included the DMS, proportion of mild and severe symptom days, visual analogue scale (VAS) for symptoms, global evaluation of efficacy, and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). These endpoints were designed to assess the impact of treatment on medication use, symptom burden, and QoL.

3.3.1.3.1 Average allergic rhinoconjunctivitis DMS during the BPS and TPS

The DMS measures the use of symptomatic medication, to manage allergic rhinoconjunctivitis symptoms. In the TT-04 trial, 12 SQ-Bet was associated with a significant reduction in medication use,

with a 49.20% relative reduction versus placebo during the BPS (absolute difference: 1.58, P<0.0001), see Table 3.12.[11] A similar effect was observed during the TPS, where DMS was reduced by 46.71% (absolute difference: 1.20, P<0.0001).[11]

Table 3.12: Overview of the DMS results during the TPS and BPS in the FASBPS analysis set of the TT-04 trial

Trial arm	No. observed (no. imputed)	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo (95% CI)	P-value
Average DMS during the BPS (FASBPS)					
Placebo	292	3.21	-	-	<0.0001
12 SQ-Bet	283	1.63	1.58 (0.94, 2.22)	49.20 (33.38, 62.41)	
Average DMS during the TPS (FASBPS)					
Placebo	292	2.58	-	-	<0.0001
12 SQ-Bet	283	1.37	1.20 (0.69, 1.72)	46.71 (30.47, 60.29)	

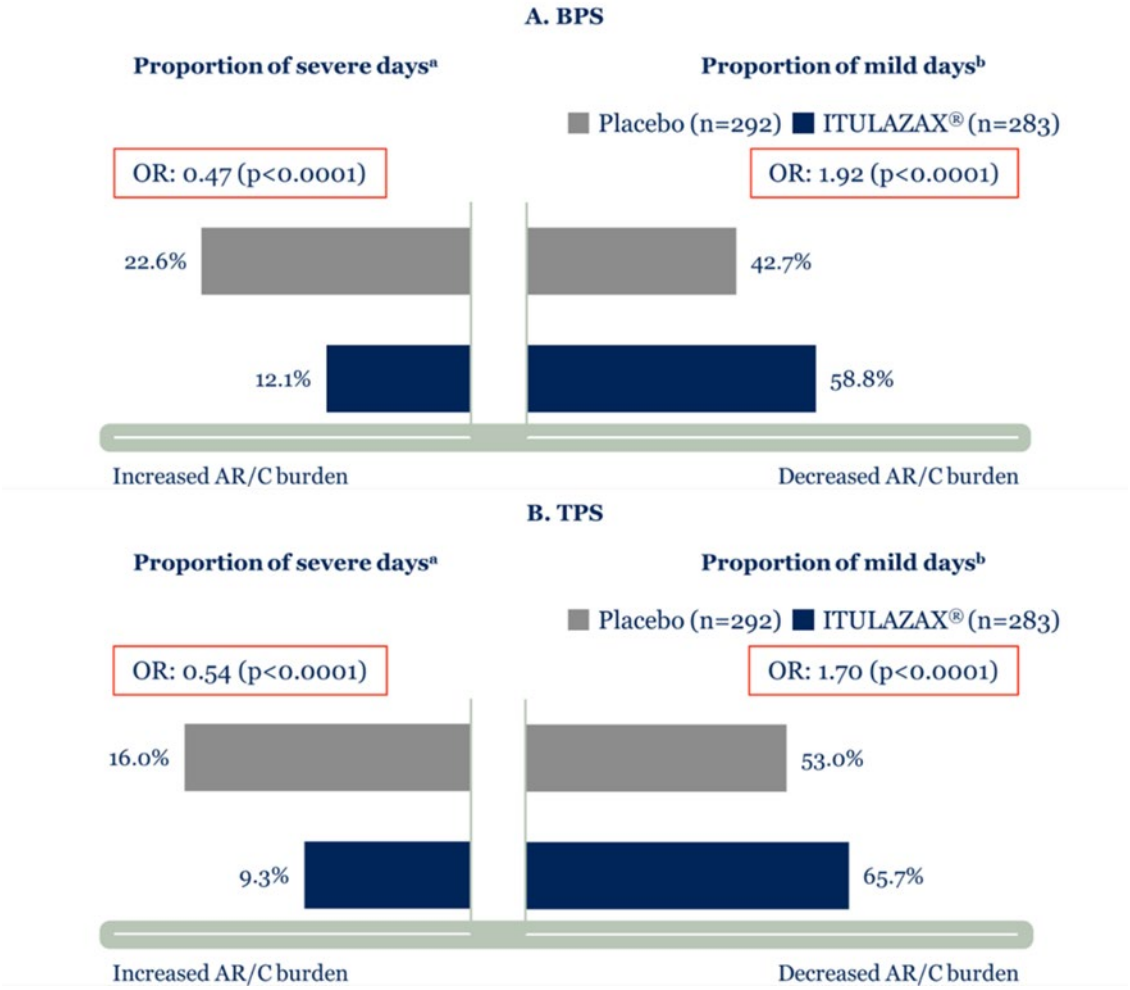
Based on Table 20 of the CS.[1]
Reference: TT-04 CSR.[11]
Notes: FASBPS refers to subjects in FAS with observations during the BPS.
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; DMS = daily medication score; FAS = full analysis set; FASBPS = subjects in FAS with observations in the BPS; TPS = tree pollen season

These results suggest that 12 SQ-Bet helped patients control their symptoms with less reliance on symptomatic medication across both the peak and extended pollen seasons. However, while the relative reductions were large, the absolute reductions were not explicitly justified as clinically meaningful. Therefore, making it difficult to determine whether a 1.58 or 1.20 reduction in medication use significantly impacts daily life.

3.3.1.3.2 Proportion of mild and severe days during the BPS and TPS

To assess daily symptom burden, the trial recorded the number of days classified as “mild” or “severe” during both the BPS and TPS. The number of severe symptom days was reduced from 5.1 days (placebo) to 2.7 days (12 SQ-Bet) during the BPS, and from 7.8 to 4.6 days during the TPS. Conversely, the odds of experiencing a mild symptom day nearly doubled with 12 SQ-Bet (odds ratio [OR] = 1.92, P<0.0001), while the odds of experiencing a severe symptom day were halved (OR = 0.47, P<0.0001), see Figure 3.3.

Figure 3.3: Proportion of mild and severe days during the BPS



Based on Figure 14 of the CS.[1]

Reference: ITULAZAX CVD data based on TT-04 CSR.[11]

Notes: Mild days, days without intake of antihistamine tablet/eyedrops and no single symptom scoring greater than 1; OR, SQ tree SLIT-tablet/placebo; severe days, days with DSS of 6 or greater and 2 or more moderate or 1 severe symptom.

Data are presented for the FASBPS (all patients with ≥1 observation during the BPS).

[a] A severe day was defined as a day with a DSS ≥6 points and the presence of at least two moderate symptoms or one severe symptom;

[b] a mild day was defined as a day without any intake of antihistamines or olopatadine eye drops and no individual symptom scores >1 point on any of the six individual symptoms – runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, watery eyes.

AR/C = allergic rhinitis with, or without conjunctivitis; BPS = birch pollen season; CS = company submission; CSR = clinical study report; DSS = daily symptom score; FAS = full analysis set; FASBPS = subjects in FAS with observations in the BPS; OR = odds ratio; SLIT = sublingual immunotherapy; TPS = tree pollen season

This endpoint provides a practical measure of treatment benefit from a patient perspective. Reducing the number of severe symptom days may significantly improve patients' ability to perform daily activities and reduce symptom-related disruption. However, since oak and beech pollen were not included in the efficacy analysis, it remains unclear whether patients with sensitisation to these additional pollens would experience the same level of improvement.

3.3.1.3.3 Average rhinoconjunctivitis symptoms VAS during the BPS and TPS

The VAS is a subjective, patient-reported measure of rhinoconjunctivitis symptom severity. During the BPS, the adjusted mean VAS score was significantly lower in the 12 SQ-Bet group, with an absolute difference of 5.77 points (32.37% relative reduction, P<0.0001), see Table 3.13.[11] A similar effect was observed during the TPS, where the absolute difference was 4.25 points (29.63% relative reduction, P<0.0001).

Table 3.13: Analysis of average rhinoconjunctivitis symptoms VAS during the BPS and TPS of the TT-04 trial (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo [95% CI]	P-value
Average rhinoconjunctivitis VAS during the BPS					
Placebo	292	17.83	-	-	<0.0001
12 SQ-Bet	283	12.06	5.77 [3.25, 8.30]	32.37 [19.69, 43.53]	
Average rhinoconjunctivitis VAS during the TPS					
Placebo	292	14.34	-	-	<0.0001
12 SQ-Bet	283	10.09	4.25 [2.20, 6.30]	29.63 [16.56, 41.18]	

Based on Table 21 of the CS.[1]
Reference: TT-04 CSR.[11]
Notes: The response variable in the analysis is: average VAS (0-100 mm). The analysis is based on an LME model with treatment as fixed class effect.
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; FASBPS = subjects in FAS with observations during the BPS; LME = linear mixed effect; TPS = tree pollen season; VAS = visual analogue scale

These reductions suggest that patients perceived a meaningful improvement in symptoms. However, it is unclear whether these reductions are large enough to be clinically meaningful. Additionally, as VAS is a self-reported measure, it could be influenced by patient expectations or functional unblinding due to treatment side effects.

3.3.1.3.4 Global evaluation of efficacy

The global evaluation of efficacy was based on patients' subjective assessment of symptom improvement. Patients were asked, "*Compared to your rhinitis and/or conjunctivitis symptoms in the previous BPS/TPS, how have you felt overall in this BPS/TPS?*" A significantly higher proportion of patients in the 12 SQ-Bet group (91.06%) reported improvement compared to the placebo group (71.71%), see Table 3.14.[11]

Table 3.14: Analysis of global evaluation of efficacy in the TT-04 trial (FASBPS)

	N	Estimate	OR (95% CI)	P-value
Estimated proportion of subjects improved (%)				
Placebo	292	71.71	0.25 (0.15, 0.40)	<0.0001
12 SQ-Bet	283	91.06		

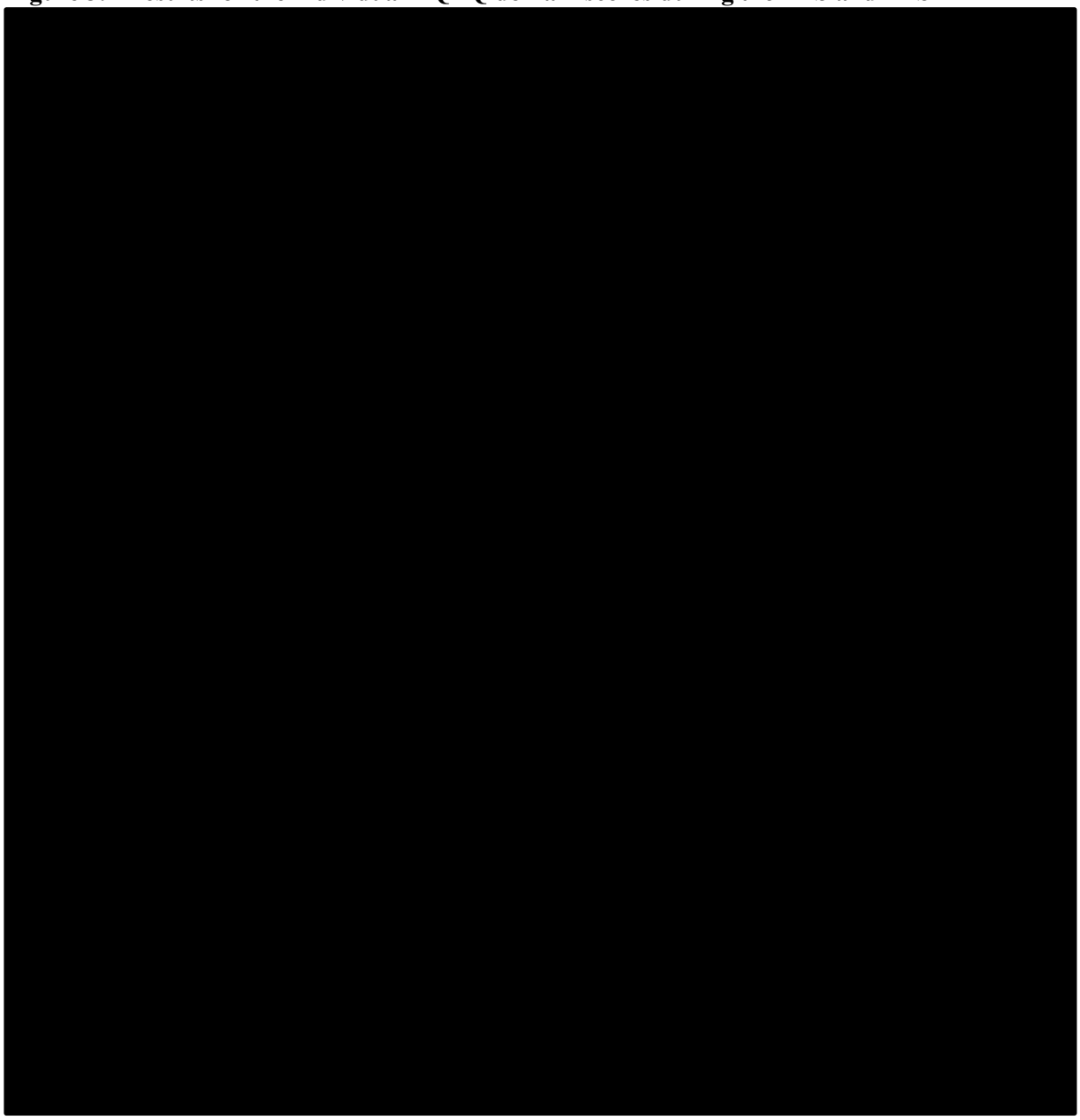
Based on Table 22 of the CS[1]
Notes: The analysis is based on a logistic regression model. ORs are calculated as placebo/active.
FASBPS, subjects in FAS with observations during the BPS.
Reference: TT-04 CSR.[11]
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; FASBPS = subjects in FAS with observations during the BPS; OR = odds ratio

This statistically significant difference (OR = 0.25, P<0.0001) suggests that patients perceived a meaningful benefit from treatment. However, since this measure is entirely subjective in nature, it may be influenced by patient expectations or trial conditions. Additionally, the high placebo response rate (71.71%) suggests that external factors, such as seasonal variation or study participation, may have contributed to symptom relief.

3.3.1.3.5 Overall RQLQ score during the BPS and TPS

The RQLQ is a patient reported QoL assessment used to determine the impact of allergic rhinoconjunctivitis on daily life and well-being. In the TT-04 trial, 12 SQ-Bet significantly reduced the overall RQLQ score by 31% during the BPS (P<0.0001) and by 28% during the TPS (P<0.0001). Further analysis of individual RQLQ domains (activity, sleep, nasal symptoms, eye symptoms, practical problems, emotional function) showed significant improvements with 12 SQ-Bet. The greatest QoL benefits were observed during weeks 2–5 of the BPS and weeks 5–8 of the TPS. the company also stated that [redacted][15] Please see Figure 3.4 for the results of individual RQLQ.

Figure 3.4 Results for the individual RQLQ domain scores during the BPS and TPS



Based on Figure 15 of the CS.[1]
Reference: TT-04 RQLQ analysis tables – data on file.[15]
Notes: ***P<0.0001 versus placebo. Data are presented for the FASBPS (all patients with ≥1 observation during the BPS)
BPS = birch pollen season; CI = confidence interval; CS = company submission; FAS = full analysis set; FASBPS = subjects in FAS with observations in the BPS; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TPS = tree pollen season

A retrospective analysis of the TT-04 study dataset was conducted to determine the minimal clinically important difference for RQLQ. The analysis found that a 0.5-point increase in RQLQ represented a minimally important worsening (MIW), while a 1.0-point increase represented an important worsening of larger magnitude (IWLM), see Table 3.15.

[16]

Table 3.15: The proportion of patients meeting MIW and IWLM in RQLQ total score at BPS week 2

	12 SQ-Bet (n=187)	Placebo (n=193)	P-value
MIW, n(%)			
Worsened by ≥0.5 point	[redacted]	[redacted]	[redacted]
IWLM, n(%)			
Worsened by ≥1.0 point	[redacted]	[redacted]	[redacted]

Based on Table 23 of the CS.[1]
Reference: ALK- Abelló., 2019 – data on file.[16]
BPS = birch pollen season; CS = company submission; IWLM = important worsening of larger magnitude; MIW = minimally important worsening; SQ = standardised quality; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire

The company also reported that *"additional RQLQ data analysis investigated the effect of 12 SQ-Bet when patient QoL was as its worst (i.e, when their RQLQ score was highest).* [redacted] *Therefore, 12 SQ-Bet provides clinically meaningful QoL benefits to significantly more patients than placebo"*.[16]

EAG comment: The FASBPS was used for most of these secondary endpoints, ensuring consistency with the primary analysis. Sensitivity analyses using the FAS, which includes all randomised patients and uses multiple imputation for missing data, confirmed the robustness of findings. However, since FASBPS excludes early dropouts (primarily due to AEs), selection bias remains a concern.

Additionally, while most endpoints demonstrated strong statistical significance, the clinical relevance of some absolute reductions remains uncertain. The CS provides an MCID for RQLQ but does not specify predefined thresholds for DMS, DSS, TCS, or VAS. This limits the ability to assess whether the observed improvements are meaningful in routine clinical practice.

3.3.1.4 Exploratory endpoints: sick days, productivity, asthma-related endpoints, average TCS with EEACI medication score

In addition to primary and secondary endpoints, the TT-04 trial included several exploratory endpoints to assess broader potential benefits of 12 SQ-Bet. These included sick days, productivity, asthma-related endpoints and TCS with the EAACI medication score. These measures provide insights into the impact of treatment on workplace productivity, asthma control, medication use, and cross-reactivity with food allergens. The company were asked to provide objective criteria for troublesome symptoms, sleep disturbance and impairment of school or work.[3] As highlighted in Section 2.1, the company responded by stating that *"patients were included in the TT-04 trial if they stated that they had experienced one or more of these ARIA quality of life items due to allergic rhinitis and/or conjunctivitis during the previous birch pollen season (BPS), consistent with the definition of moderate to severe AR in the ARIA guideline"*.[5]

Across these exploratory endpoints, 12 SQ-Bet demonstrated statistically significant improvements compared to placebo (P<0.05 for all key measures). However, as exploratory outcomes, these results should be interpreted with caution, as they may be less rigorously controlled or predefined than primary or secondary endpoints. Additionally, the clinical significance of some findings is uncertain due to the

lack of predefined minimal clinically important differences or real-world applicability. The following subsections will highlight the exploratory endpoints in more detail.

3.3.1.4.1 The proportion of sick days during the BPS and TPS

AR can significantly impact work and daily activities, leading to absenteeism. In the TT-04 trial, the proportion of sick days taken during the BPS and TPS was recorded. While the overall number of sick days was low across both groups, patients in the placebo group had a significantly higher proportion of sick days compared to those receiving 12 SQ-Bet. During the BPS, the odds of taking a sick day were more than twice as high in the placebo group (OR = 2.07, P<0.0001), see Table 3.16. A similar pattern was observed in the TPS (OR = 1.72, P<0.0001), see Table 3 16.[16, 17]

Table 3.16: Analysis of the proportion of sick days during the BPS and TPS (FASBPS)

	N	Estimate	OR (95% CI)	P-value
Proportion of sick days during the BPS				
Placebo	292	1.78	-	-
12 SQ-Bet	283	0.87	2.07 (1.63, 2.62)	<0.0001
Proportion of sick days during the TPS				
Placebo	292	1.29	-	-
12 SQ-Bet	283	0.75	1.72 (1.42, 2.08)	<0.0001

Based on Table 24 of the CS.[1]
References: TT-04 CSR.[16]
Notes: ORs are calculated as placebo/active. The analysis is based on a logistic regression model with treatment as fixed class effect and pollen region as a random class variable.
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; FASBPS = subjects in FAS with observations during the BPS; OR = odds ratio; TPS = tree pollen season

These findings suggest that 12 SQ-Bet reduced absenteeism, potentially alleviating the socioeconomic burden of AR. However, given the low overall number of sick days recorded in the study, the absolute impact may be minimal. Additionally, it is unclear whether regional variations in workplace policies, seasonal variability, or other external factors influenced these results and therefore they should be viewed with caution.

3.3.1.4.2 Average effect on productivity during the BPS and TPS

Beyond absenteeism, AR can also impact productivity while at work or in daily life. The TT-04 trial assessed the average impact of AR on productivity during the BPS and TPS, measured via a subjective patient-reported scale. Patients in both groups reported that their productivity was not significantly affected overall, but the placebo group reported a greater impact than the 12 SQ-Bet group. During the BPS, 12 SQ-Bet led to a 33.31% improvement in productivity versus placebo (absolute difference: 4.49 points, P=0.0002).[16] A similar effect was observed in the TPS, where productivity improved by 31.67% (absolute difference: 3.39 points, P=0.0004).[16] Table 3.17 presents the analysis of the average effect on productivity during the BPS and TPS.

Table 3.17: Analysis of the average effect on productivity during the BPS and TPS (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo (95% CI)	P-value
Average effect on productivity during the BPS					
Placebo	292	13.47	-	-	0.0002
12 SQ-Bet	283	8.99	4.49 [2.17, 6.80]	33.31 [17.74, 46.78]	
Average effect on productivity during the TPS					
Placebo	292	10.69	-	-	0.0004
12 SQ-Bet	283	7.31	3.39 [1.51, 5.27]	31.67 [15.49, 45.79]	

Based on Table 25 of the CS.[1]
Reference: TT-04 CSR.[16]
Notes: The response variable in the analysis is: the average effect on productivity. The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; FAS = full analysis set; FASBPS = subjects in FAS with observations during the BPS; LME = linear mixed effect; TPS = tree pollen season

These results suggest that 12 SQ-Bet may improve work performance by reducing AR symptoms. However, productivity was assessed subjectively, meaning the results could be influenced by patient perception rather than objective measures. Additionally, it is unclear whether these differences translate into meaningful real-world benefits.

3.3.1.4.3 Asthma-related endpoints

The CS states that *"uncontrolled AR is a risk factor for asthma exacerbations"*.[1] Therefore, the TT-04 trial explored whether 12 SQ-Bet had a beneficial effect on asthma-related symptoms, which assessed: asthma DSS, asthma medication use and asthma control test (ACT) score.

In the FASBPS population, 12 SQ-Bet reduced asthma DSS by 29.3% versus placebo during the BPS (absolute difference: 0.34 points, P=0.0089), see Table 3.18. A similar reduction was observed during the TPS (24.2%, absolute difference: 0.23 points, P=0.0239). These results suggest a small but statistically significant improvement in asthma symptoms.

Table 3.18: Overview of the asthma endpoints of the TT-04 trial (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo (95% CI)	P-value
Average asthma DSS during the BPS (FASBPS)					
Placebo	292	1.15	-	-	0.0089
12 SQ-Bet	283	0.81	0.34 [0.08, 0.59]	29.32 [8.56, 46.21]	
Average asthma DSS during the TPS (FASBPS)					
Placebo	292	0.96	-	-	0.0239
12 SQ-Bet	283	0.73	0.23 [0.03, 0.44]	24.18 [3.71, 41.30]	
Average ACT during the BPS (FASASTHMA)					
Placebo	88	21.80	-	-	0.0365
12 SQ-Bet	96	22.24	-1.22 [-2.36, -0.08]	-5.79 [-11.53, -0.39]	

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo (95% CI)	P-value
Average ACT during the TPS (FASASTHMA)					
Placebo	111	21.80	-	-	0.5282
12 SQ-Bet	110	22.09	-0.30 [-1.22, 0.63]	-1.35 [-5.66, 2.79]	

Based on Table 26 of the CS.[1]
Reference: TT-04 CSR.[16]
ACT = asthma control test; BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; DSS = daily symptom score; FAS = full analysis set; FASASTHMA = subjects in FAS with asthma; FASBPS = subjects in FAS with observations during the BPS; TPS = tree pollen season

In terms of asthma control, ACT scores were generally high, indicating good baseline asthma control across both groups. During the BPS, ACT scores were slightly higher in the 12 SQ-Bet group versus placebo (P=0.0365), but no difference was observed during the TPS (P=0.5282), see Table 3.18 for details.[16]

Despite the statistically significant findings, the absolute improvements in asthma DSS and ACT were small, and no differences were seen in asthma medication use. This suggests that while 12 SQ-Bet may have some benefit for patients with coexisting asthma, the clinical relevance is uncertain, especially for well-controlled asthma populations.[16]

3.3.1.4.4 Average TCS with EAACI medication score during the BPS and TPS

The CS states that *"the EAACI symptom score was calculated by dividing the total symptom score (scale 0-18) by 6, resulting in a scale ranging from 0 to 3, where 0 indicates no symptoms, 1 indicates mild symptoms; 2 indicates moderate symptoms, and 3 indicates severe symptoms. The total combined rhinoconjunctivitis EAACI score was the sum of the EAACI symptom score and the EAACI medication score and assumed values in the range of 0 to 5".* [1, 16]

The average TCS with EAACI medication score was significantly lower in the 12 SQ-Bet group compared to placebo in both seasons (BPS: 37.88% reduction, absolute difference: 0.46, P<0.0001; TPS: 34.94% reduction, absolute difference: 0.35, P<0.0001), see Table 3.19.[16]

Table 3.19: Analysis of average TCS with EAACI medication score during the BPS and TPS (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo [95% CI]	P-value
Average TCS EAACI during the BPS					
Placebo	292	1.22	-	-	<0.0001
12 SQ-Bet	283	0.76	0.46 [0.30, 0.62]	37.88 [26.67, 47.67]	
Average TCS EAACI during the TPS					
Placebo	292	1.0	-	-	<0.0001
12 SQ-Bet	283	0.65	0.35 [0.22, 0.48]	34.94 [23.66, 44.82]	

Based on Table 28 of the CS.[1]
References: TT-04 CSR.[16]
Notes: The response variable in the analysis is: the square root of the average TCS EAACI. The analysis is based on an LME model with treatment as fixed class effect and pollen region as a random class variable.

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo [95% CI]	P-value
BPS, birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; EAACI = European Academy of Allergy & Clinical Immunology; FAS = full analysis set; FASBPS = subjects in FAS with observations during the BPS; LME = linear mixed effect; TCS = total combined score; TPS = tree pollen season					

These findings align with the primary TCS endpoint, reinforcing the treatment benefit of 12 SQ-Bet. However, since this measure adjusts symptom scores based on medication use, it is unclear whether the observed reductions reflect improved symptom control or simply reduced medication reliance.

EAG comment: Most exploratory endpoints were analysed using the FASBPS population, ensuring consistency with primary analyses. However, as exploratory outcomes, these findings should be interpreted with caution, as they were not primary trial objectives and may not have been powered to detect clinically meaningful differences.

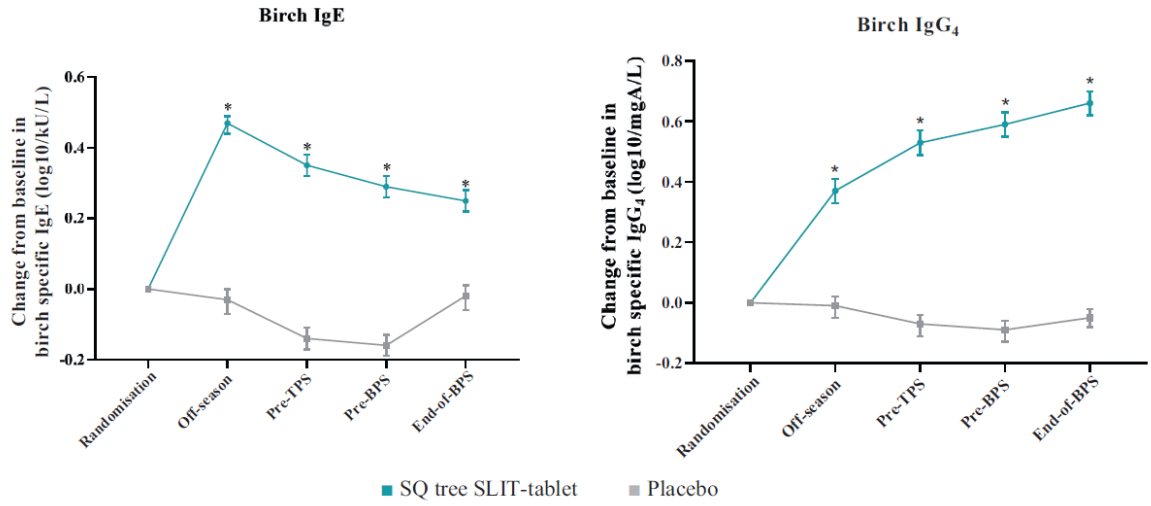
Additionally, while all findings reached statistical significance, the absolute differences in outcomes were often small. The lack of predefined minimal clinically important differences for sick days, productivity or asthma DSS outcomes makes it difficult to determine whether these changes are meaningful in real-world clinical practice and to patients in England and Wales.

3.3.1.5 Pharmacodynamic endpoints

Pharmacodynamic endpoints in the TT-04 trial were assessed to determine the immunological response to 12 SQ-Bet, particularly in terms of allergen-specific immunoglobulin E (IgE) and immunoglobulin G subtype 4 (IgG4) levels. The CS stated that *"as part of the inclusion criteria of TT-04, patients were required to have a positive Bet v 1–specific IgE level (IgE class 2 or greater, >0.7 kU/L). All subjects were sensitised to birch pollen and 57% of participants belonged to the IgE class 4 to 6 (≥17.5 kU/L)"*.[1]

The pharmacodynamic findings from TT-04 confirm that 12 SQ-Bet induces an immune response characteristic of effective allergen immunotherapy. Patients treated with 12 SQ-Bet showed a significant increase in birch-specific IgG4 levels (P<0.0001), while IgE levels initially rose before declining over time (Figure 3.5).

Figure 3.5: Birch IgE and IgG4 results from the TT-04 trial



Based on Figure 16 of the CS.[1]

Reference: Biedermann et al. 2019.[12]
BPS = birch pollen season; CS = company submission; IgE = immunoglobulin E; IgG4 = immunoglobulin G subtype 4; SLIT = sublingual immunotherapy; SQ = standardised quality; TPS = tree pollen season

These immunological changes suggest that 12 SQ-Bet may provide long-term symptom relief beyond the 3-year treatment course. This assumption is supported by long-term data from the standardised quality® (SQ) grass SLIT-tablet, which demonstrated sustained benefits after discontinuation.[18] However, no direct long-term clinical data for 12 SQ-Bet are available, and these conclusions are extrapolated from a different AIT product.

3.3.1.6 Post-hoc analysis of TCS, DSS and DMS by tree pollen seasons

Post-hoc analyses were conducted to further assess the efficacy of 12 SQ-Bet across different pollen seasons, including the AHPS, the TPS, and the oak pollen season (OPS). These analyses aimed to determine whether the treatment effect extended beyond the BPS, particularly in patients sensitised to multiple tree pollens.

The results consistently showed statistically significant reductions in TCS, DSS, and DMS across all pollen seasons (P<0.01 for all comparisons). However, since post-hoc analyses are not pre-specified in the study protocol, their findings should be interpreted with caution, as they are exploratory rather than confirmatory. Nevertheless, the following subsections will explore these results in more detail.

3.3.1.6.1 Alder/hazel pollen season analysis of TCS, DSS and DMS

The TT-04 trial originally analysed efficacy during the full TPS, which included birch, alder, and hazel pollen seasons. A post-hoc analysis was conducted to assess whether 12 SQ-Bet was effective specifically during the AHPS.

The results showed that 12 SQ-Bet significantly reduced TCS by 29.66% (P=0.0015), DSS by 26.04% (P=0.0031), and DMS by 43.81% (P=0.0016) relative to placebo (Table 3.20). However, absolute symptom levels and medication use were lower for both treatment groups during AHPS compared to BPS and TPS.[16] This suggests that overall symptom burden was less severe during AHPS, possibly due to lower allergen exposure.

Table 3.20: Post-hoc analysis of average TCS, DSS, and DMS in the AHPS of TT-04 (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo (95% CI)	P-value
Average TCS in the AHPS					
Placebo	286	4.07	-	-	0.0015
12 SQ-Bet	278	2.87	1.21 [0.46, 1.96]	29.66 [12.61, 43.80]	
Average DSS in the AHPS					
Placebo	286	2.08	-	-	0.0031
12 SQ-Bet	278	1.54	0.54 [0.18, 0.90]	26.04 [9.73, 39.63]	
Average DMS in the AHPS					
Placebo	286	1.45	-	-	0.0016
12 SQ-Bet	278	0.82	0.64 [0.23, 1.04]	43.81 [19.54, 62.45]	
Based on Table 30 of the CS.[1] Reference: TT-04 CSR.[16]					

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo (95% CI)	P-value
AHPS = alder and hazel pollen season; BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; DMS = daily medication score; DSS = daily symptom score; FAS = full analysis set; FASBPS = subjects in FAS with observations during the BPS; TCS = total combined score					

While these results indicate that 12 SQ-Bet was effective during the AHPS, the magnitude of improvement was slightly smaller than during the BPS. The clinical relevance of this difference is uncertain, and further prospective analyses would be required to validate these findings.

3.3.1.6.2 Continuous TPS analysis of TCS, DSS and DMS

The CS presented a post-hoc analysis that had assessed efficacy across the entire TPS, including all days from the start to the end of TPS, regardless of pollen counts.[1] The analysis found that 12 SQ-Bet reduced TCS by 34.97% (P<0.0001), DSS by 31.57% (P<0.0001), and DMS by 45.33% (P<0.0001) compared to placebo (Table 3.21).

Table 3.21: Post-hoc analysis of the average TCS, DSS, and DMS during the continuous TPS of TT-04 (FASBPS)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo [95% CI]	P-value
Average TCS during the continuous TPS					
Placebo	292	5.96	-	-	<0.0001
12 SQ-Bet	283	3.88	2.09 [1.27, 2.90]	34.97 [23.12, 45.30]	
Average DSS during the continuous TPS					
Placebo	292	2.89	---	-	<0.0001
12 SQ-Bet	283	1.98	0.91 [0.53, 1.29]	31.57 [20.02, 41.61]	
Average DMS during the continuous TPS					
Placebo	292	2.48	-	-	<0.0001
12 SQ-Bet	283	1.36	1.13 [0.63, 1.62]	45.33 [28.76, 59.14]	

Based on Table 31 of the CS.[1]
References: TT-04 CSR.[11]; Nolte et al. 2021.[19]
BPS = birch pollen season; CI = confidence interval; CS = company submission; CSR = clinical study report; DMS = daily medication score; DSS = daily symptom score; FAS = full analysis set; FASBPS = subjects in FAS with observations during the BPS; TCS = total combined score; TPS = tree pollen season

These results closely align with the original TPS analysis, reinforcing the overall treatment benefit of 12 SQ-Bet across the extended pollen season. However, since this post-hoc analysis would have included days with lower pollen exposure, it is unclear whether the treatment effect was as strong on days with higher pollen concentrations.

3.3.1.6.3 Oak pollen season analysis of TCS, DSS and DMS

Perhaps the most relevant post-hoc analysis assessed the efficacy of 12 SQ-Bet during the OPS, a period that was not included in the original efficacy analyses. The EAG considers this important because the CS states that *"87%* [of TT-04 trial participants] *were sensitised to oak pollen"*.[1]

The results showed that 12 SQ-Bet significantly reduced TCS by 25% (P<0.001), DSS by 22% (P<0.001), and DMS by 32% (P<0.001) compared to placebo (Table 3.22). These reductions were observed 4 weeks before the start of BPS and persisted through the OPS.[19]

Table 3.22: Post-hoc analysis of the average TCS, DSS, and DMS during the OPS of TT-04 (all randomised subjects)

Trial arm	N	Adjusted mean	Absolute difference (placebo-12 SQ-Bet [95% CI])	% relative to placebo [95% CI]	P-value
Average TCS during the OPS					
Placebo	225	4.80	-	-	<0.001
12 SQ-Bet	211	3.59	1.21 [0.32, 2.11]	25 [8, 41]	
Average DSS during the OPS					
Placebo	225	2.34	-	-	<0.001
12 SQ-Bet	211	1.82	0.52 [0.07, 0.98]	22 [4, 39]	
Average DMS during the OPS					
Placebo	225	1.76	-	-	<0.001
12 SQ-Bet	211	1.19	0.57 [0.06, 1.07]	32 [6, 54]	

Based on Table 32 of the CS.[1]
Reference: Nolte et al. 2021.[19]
Notes: The OPS excludes all days that overlapped with the BPS.
BPS = birch pollen season; CI = confidence interval; CS = company submission; DMS = daily medication score; DSS = daily symptom score; OPS = oak pollen season TCS = total symptom score

The company state that *"oak is a member of the birch homologous group, and the oak allergen is an important Bet v 1 cross-reactive tree pollen allergen. These results further demonstrate the efficacy of 12 SQ-Bet in birch pollen-induced AR over the course of the TPS and extending through the OPS"*.[1] However, since oak pollen was not a pre-specified focus of the trial, these results should be interpreted cautiously.

EAG comment: While post-hoc analyses have potential to provide valuable insights, they come with limitations. Since they were not pre-specified, there is a risk of statistical bias. Additionally, the OPS analysis excluded overlapping days with BPS, which may underestimate the real-world pollen exposure patterns for polysensitised patients.

Furthermore, while the results consistently show treatment benefits across different pollen seasons, absolute symptom reductions were modest. The clinical significance of these reductions remains uncertain, as no predefined minimal clinically important difference was provided for these specific pollen seasons.

The EAG asked the company why the TT-04 trial excluded, oak, beech and chestnut pollen from the efficacy analysis despite their inclusion in the birch homologous group and how this would impact real-word effectiveness of 12 SQ-Bet for UK patients exposed to multiple tree pollens.[3] The company explained in their response that the TT-04 trial selected tree species to ensure coverage of *"both early and late pollinating trees species to ensure the tree pollen season was covered"*.[5] While oak was not part of the main efficacy analysis, a post hoc analysis (Nolte et al. 2021) assessed treatment effects during the OPS and suggested clinical benefit with 12 SQ-Bet.[19] The company also referenced studies (Couroux et al. 2019; Wurtzen et al. 2020)[20, 21] showing *"immunological cross-reactivity between birch and beech pollen"*.[5] Chestnut was excluded from the efficacy analysis due to low levels

of cross-reactivity, with only 14% of patients showing IgE binding to chestnut allergens, and it is not included in the licensed indication for 12 SQ-Bet.

While the company provided a rationale for prioritising certain tree pollen species in the efficacy analysis and referenced immunological cross-reactivity studies, the EAG believe there are important limitations in their response. Firstly, the lack of direct clinical efficacy data for beech and chestnut pollen seasons means that generalisability to UK patients, many of whom are exposed to a broader range of tree pollens, remains uncertain. Secondly, the reliance on post hoc analysis, such as from Nolte et al. 2021 to infer clinical efficacy during the OPS introduces risk of bias and may not be sufficiently robust to support generalisation.[19] These analyses are not pre-specified, and outcomes could be influenced by chance or multiple comparisons. Additionally, although immunological cross-reactivity is demonstrated between birch and other homologous species, immunological cross-reactivity does not necessarily equate to clinical cross-protection, particularly for allergens with different pollen seasons and exposure levels. The evidence provided is biological and inferential i.e., not clinical, which therefore weakens its relevance to real-world effectiveness. Furthermore, the decision to exclude chestnut pollen based on low IgE binding in trial participants may be reasonable given its absence from the licensed indication, but the company's assertion that this exclusion has no impact on real-world effectiveness assumes accurate and consistent diagnostic practices in UK clinical settings, which may not always be the case.

The EAG had asked the company if *"a subgroup analysis conducted to assess whether patients polysensitised to oak and beech pollen experienced a different treatment response compared to those sensitised only to birch, alder, and hazel, and if not, how does this impact the generalisability of the trial results to a UK population"*.[3] The company responded by stating that *"this subgroup analysis was not conducted. The TT-04 trial included a mixture of poly- and mono-sensitised patients, of which a large proportion were polysensitised (76%). More specifically, a large proportion of the TT-04 population also had specific IgE binding to oak (87%) and beech (95%) pollen.[19, 21] Polysensitisation is highly prevalent in the UK patient population; therefore, the trial results and population of the TT-04 trial are generalisable to a UK patient population"*.[5]

The EAG believe that the company's response acknowledges that no subgroup analysis was conducted to assess treatment response in patients polysensitised to oak and beech pollen but claims the trial population is generalisable to the UK based on the high prevalence of polysensitisation (76%). However, IgE binding alone does not confirm whether these patients experienced the same treatment benefit as those primarily affected by birch, alder, and hazel pollen. Without a dedicated analysis, it remains unclear whether patients with significant oak and beech pollen exposure and whose symptoms may extend beyond the BPS, responded similarly to 12 SQ-Bet. This introduces uncertainty about the real-world effectiveness and generalisability of 12 SQ-Bet in the UK, particularly for polysensitised patients.

3.3.2 Adverse Events

An overview of AEs in the TT-04 trial shows that AEs were more common in the 12 SQ-Bet group than in the placebo group. According to the CS, *"a total of 262 (82%) subjects in the 12 SQ-Bet group experienced 1,028 AEs, while 176 (56%) subjects in the placebo group experienced 404 AEs in the 12 SQ-Bet group, 76% of the AEs were IMP-related, while this was the case for 33% of the AEs in the placebo group"*.[1]

Most AEs were mild-to-moderate in both groups, though a slightly higher proportion of severe AEs was reported in the 12 SQ-Bet group (7% versus 2%). Further details can be found below in Table 3.23.

Additionally, discontinuation due to AEs was also more frequent in the 12 SQ-Bet group, where the company reported that *"by the end of the trial 33 subjects (5%) were discontinued from the trial, 25 (8%) subjects in the 12 SQ-Bet group discontinued due to 98 AEs, while 8 (3%) subjects in the placebo group discontinued due to 15 AEs"*.[1]

Table 3.23: Overview of AEs (SAS)

Parameter	Placebo (N=314)				Active 12 SQ-Bet (N=320)			
	n	%n	e	%e	n	%n	e	%e
All AEs	175	56%	404	100%	262	82%	1,028	100%
Causality								
Unlikely	145	46%	271	67%	127	40%	245	24%
Possible	73	23%	133	33%	239	75%	783	(76%)
Severity								
Mild	134	43%	258	64%	218	68%	583	57%
Moderate	82	26%	130	32%	142	44%	394	38%
Severe	5	2%	16	4%	22	7%	51	(5%)
Seriousness								
No	175	(56%)	398	(99%)	262	(82%)	1,024	(>99%)
Yes	6	(2%)	6	(1%)	4	(1%)	4	(<1%)
Changes to IMP								
None	154	(49%)	319	(79%)	240	(75%)	828	(81%)
Temporary interrupted	38	(12%)	70	(17%)	47	(15%)	102	(10%)
IMP discontinued	8	(3%)	15	(4%)	25	(8%)	98	(10%)
Outcome								
Recovered/resolved	168	(54%)	369	(91%)	260	(81%)	983	(96%)
Recovered/resolved with sequelae	3	(<1%)	3	(<1%)	3	(<1%)	3	(<1%)
Not recovered/resolved	20	(6%)	23	(6%)	25	(8%)	35	(3%)
Unknown	8	(3%)	9	(2%)	5	(2%)	5	(<1%)

Based on Table 34 of the CS.[1]
References: TT-04 CSR.[16]
%e = percentage of AEs; %n = percentage of subjects with AEs; AE = adverse event; CI = confidence interval; CS = company submission; CSR = clinical study report; e = number of AEs; IMP = investigational medicinal product; n = number of subjects with AEs; N = number of subjects in SAS; SAS = safety analysis set; SQ = standardised quality

EAG comment: As the discontinuation rate due to AEs was higher in the treatment group, the company has been asked to provide a full breakdown of the nature and severity of these events for both groups.[3] The details of the company response have been provided in Tables 3.24 and 3.25.[5]

Table 3.24: AEs leading to discontinuation in the 12 SQ-Bet treatment group of the TT-04 trial

Subject	AE preferred term	Severity	Outcome	Treatment duration (days)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subject	AE preferred term	Severity	Outcome	Treatment duration (days)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subject	AE preferred term	Severity	Outcome	Treatment duration (days)
	[redacted]	[redacted]	[redacted]	

Based on Table 8 of response to the request for clarification.[5]
AE = adverse event

Table 3.25: AEs leading to discontinuation in the placebo treatment group of the TT-04 trial

Subject	AE preferred term	Severity
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Based on Table 9 of response to the request for clarification.[5]
AE = adverse event; IMP = Investigational Medicinal Product

3.4 Critique of the indirect comparison and/or multiple treatment comparison

No ITC was included in the CS, however, as detailed in Section 2.3, the EAG suggested to perform an ITC to inform a comparison with any form of immunotherapy that is currently used in clinical practice in England and Wales. This has been highlighted as a key issue.

3.5 Conclusions of the clinical effectiveness Section

The CS, Appendix B and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the efficacy and safety of therapies associated with managing birch pollen-induced SAR.[1, 5, 8] Searches were conducted in May to July 2024. Searches were transparent and reproducible, and a good range of bibliographic databases, conference proceedings, trials registers and grey literature resources were searched.

The EAG, however, has some concerns about the literature searches conducted. The structure of the MEDLINE, Embase and Cochrane Library searches meant that these database searches could have been over-restrictive as they limited the results to only those records referring to sublingual therapy. Specifically, studies referring to the clinical efficacy of subcutaneous therapy may have been missed by the database searches.

The differences in relative TCS reductions between FAS (35.69%–36.55%), FASBPS (39.6%), and PP (42.9%) indicate that the real-world effectiveness might be lower than what was reported in the TT-04 trial. Furthermore, when evaluating the potential benefits of 12 SQ-Bet for patients in England and Wales, it's important to factor in adherence levels and the real-world exposure to various tree pollens.

The CS and response to clarification raised concerns regarding the lack of subgroup analyses for patients sensitised specifically to oak and beech pollen tree species which are highly relevant in the UK.[1, 5] This absence creates uncertainty regarding whether treatment efficacy extends to these patients, which has implications for generalisability to a UK setting where such sensitisation is common. There were also concerns with the reliance on immunological markers rather than clinical outcomes to support generalisability. The company's argument rests on sensitisation overlap rather than demonstrated efficacy across relevant subgroups. Furthermore, the response does not address whether treatment effects might vary depending on dominant pollen exposure. While the trial population includes a mix of polysensitised and monosensitised individuals, without direct analysis of outcomes by sensitisation pattern, the claim that *"the trial results... are generalisable to a UK patient population"* is not fully substantiated.[1]

As detailed in Section 3.3.2, there are more AEs in the intervention arm compared to the placebo arm. Some of these AEs led to discontinuation in the 12 SQ-Bet treatment group, [redacted].

4. Cost-effectiveness

4.1 EAG comment on company's review of CE evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to CE presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost-effectiveness Section

The following paragraphs contain summaries and critiques of all searches related to economic evidence, HRQoL and resource use identification presented in the CS.[1] The Canada Drug Agency (formerly the CADTH) evidence-based checklist for PRESS was used to inform this critique.[7] The EAG has presented only the major limitations of each search strategy in the report.

Appendices E and F of the CS provide details of SLRs conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in birch pollen-induced SAR.[9, 22] Searches were conducted in May to July 2024.

EAG comments:

- A single set of searches was undertaken to identify relevant studies on the economic evidence and health care cost/resource use in birch pollen-induced SAR. An additional set of searches was conducted to identify relevant HRQoL data. The CS, Appendices E and F and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[1, 5, 9, 22]
- The following databases were searched for the economic evidence and healthcare resource use SLR on 27 May 2024: Embase, MEDLINE, CDSR, CENTRAL and EconLit. Embase, MEDLINE, CDSR and CENTRAL were searched for the HRQoL SLR searches on 29 May 2024, and an additional search of EconLit was conducted on 5 March 2025 in response to a request for clarification from the EAG.
- For all CE searches six global HTA bodies' websites and the Professional Society of Health Economics and Outcomes Research (ISPOR) presentations database were searched. For the economic evidence/healthcare resource use searches the following were also searched: the Cost-Effectiveness Analysis (CER) Registry, Research Papers in Economics (RePEc) and the International Network of Agencies for HTA. For the HRQoL searches, the University of Sheffield ScHARRHUD utility database and the Health Economics Research Center (HERC) Database of Mapping Studies were searched. All searches were conducted on 29 July 2024.
- Bibliographies of systematic reviews and meta-analyses and other selected studies were reference checked.
- No date or language limits were applied to the CE searches.
- The economic evidence and healthcare resource use searches contained a population facet for SAR. This was then combined with a study design filter containing terms for costs and economic evaluations and facets for comparators/placebo/SLIT. The HRQoL searches contained the same

population facet for SAR. This was then combined with a study design filter containing terms for HRQoL.

- All searches were transparent and reproducible, and contained a good range of search terms, synonyms and subject headings.
- The EAG notes that although validated filters created by Canada's Drug Agency (formerly CADTH)) were used to limit the results to CE studies, this was not appropriate or necessary when used on the EconLit database, which is already a database of economic literature. Given the size of this database, a more sensitive search using the population facet alone would not have greatly increased the screening burden.
- A typographical error for Betula verrucosa was included in the strategies ('Betula verrcose') but given the range of synonyms and indexing terms used, and extensive range of resources covered, this is unlikely to have affected the recall of the literature searches.

4.1.2 Inclusion/exclusion criteria

In- and exclusion- criteria for the review on CE studies, utilities and costs and resource use are presented by the company in Appendices E and F of the CS.[9, 22]

The EAG agrees that the in- and exclusion- criteria are suitable to fulfil the company's objective to identify relevant CE studies in general. Inclusion criteria for population includes children and adolescents, whereas the DP population consists of adults only. This potentially would return less relevant studies. Inclusion criteria for comparator does not include Pollinex trees, which was explicitly mentioned in the final NICE scope, see Section 2.3.[2]

Also, the CE and HRQoL searches were restricted to English language, on non-English with an abstract in English, and the resource use outcomes were limited to European countries. Thus, it is possible that relevant studies may have been missed.

4.1.3 Findings of the cost-effectiveness review

The PRISMA flow diagram for the CE and resource use SLR can be found in Figure 1 of Appendix E of the CS.[9] In total, 14 studies were identified; from these, eight reported results for seven economic evaluations,[23-29] including one HTA submission in Canada.[30] Thirteen of these studies reported costs and/or resource use outcomes from 12 individual studies.[23-36] Three economic evaluations assessed the costs and clinical benefits of SQ tree SLIT-tablets compared to other treatments, for the management and/or treatment of symptoms of tree pollen-induced SAR or allergic rhinitis with, or without conjunctivitis (AR/C).[24, 27, 28]

In addition, the PRISMA diagram for the overall HRQoL/utilities SLR was shown in Figure 1 of Appendix F of the CS.[22] The TT-04 trial (EudraCT-2015-004821-15),[37, 38] by Kozulina et al. 2014 and in Bozek et al. 2020.[39, 40] was identified as the only relevant study investigating the impact of allergen specific immunotherapy on HRQoL for people with birch pollen induced disease. Seventeen studies exploring the impact of SoC treatments on the HRQoL of patients when managing SAR and/or AR/C were identified. No study directly investigated health state utility value (HSUV) for birch pollen-induced SAR and/or AR/C. However, the mapping study from Dick et al. 2020 estimating mean HSUVs for people with birch pollen-induced SAR and/or AR/C, showed differences in mean utilities between 12 SQ-Bet and placebo during the BPS.[41]

4.1.4 Conclusions of the CE review

The CS, Appendices E and F, and the response to the request for clarification[1, 5, 9, 22] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in birch pollen-induced SAR. Searches were conducted in May to July 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, HTA websites and other grey literature resources were searched. Overall, the EAG has no major concerns about the literature searches conducted. Since no economic models to address the current DP were identified by the company, a de novo model was built, which is discussed in the remainder of this Section.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case
Synthesis of evidence on health effects	Based on systematic review	As per the reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	As per the reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	As per the reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	As per the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	As per the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case

CS = company submission; EAG = External Assessment Group; EQ-5D = EuroQoL-5 Dimensions; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

The company developed a de novo economic model in Microsoft Excel® to assess the CE of 12 SQ-Bet compared with ECM.

The model consists of two health states (alive and dead), where transitions are informed by annual mortality rates derived from UK life tables.[42] Individuals enter the model in the alive health state and receive either 12 SQ-Bet or ECM. While individuals are alive, patients incur treatment-specific costs and utilities in each model cycle, which is assumed to be 1 year (consistent with the seasonal nature of the disease, including an entire pollen season). A half-cycle correction was implemented to account for deaths occurring at any time during the cycle. The time horizon was assumed to be lifetime. Annual discount rates of 3.5% were applied to both costs and health benefits, as per the NICE reference case. The input values of the model and their underlying assumptions are further elaborated in the remainder of Section 4 of the EAG report.

The company deemed this modelling approach appropriate given the available data. The company indicated that this approach allows incorporating treatment-specific utility values derived from Dick et al. 2020.[41] The company also mentioned that this approach is consistent with the recent cost-utility analysis of 12 SQ-Bet by Pollock et al. 2023.[27] The company weighed using a more complex modelling approach incorporating multiple health states based on disease severity, but given the available data, the company opted for the simpler approach previously described.

EAG comment: In general, the EAG considers the modelling approach followed by the company appropriate for the DP at hand. However, as discussed in the EAG critique of Section 4.2.6.2, the EAG is concerned that the current approach might be too simplistic to properly incorporate long-term treatment benefit and/or treatment waning in the way the company have intended to do it.

4.2.3 Population

The population in the economic analyses is defined as adult patients (aged 18-65 years) with a confirmed diagnosis of moderate to severe AR and/or conjunctivitis induced by pollen from the birch homologous group despite the use of symptom-relieving medication.[43] This patient population is in line with the NICE final scope[2] and is consistent with the population included in the TT-04 trial.[11] The baseline characteristics used in the economic model are a mean age of 36.01 years, and 47.01% of the cohort were male.

EAG comment: The EAG concerns regarding the definition of the population in this appraisal were discussed in Section 2.1 of this report. These concerns, which have been identified as a key issue, are also relevant for the CE analyses.

4.2.4 Interventions and comparator

The intervention in the economic analyses was 12 SQ-Bet administered sublingually as a tablet daily, which is suitable for at-home administration, following an initial administration under physician supervision.[43] 12 SQ-Bet is proposed to be used in combination with ECM. International treatment guidelines and consensus statements on AIT refer to a treatment period of 3 years to achieve disease modification after its cessation.[43]

The comparator in the economic analyses was ECM without 12 SQ-Bet. Recommendations from the BSACI and the ARIA international guidelines (2016 revision) are incorporated in the NICE Clinical Knowledge Summary on AR for the diagnosis and management of patients with AR.[44-46] For patients

with mild-to-moderate intermittent or mild persistent symptoms, oral or intranasal antihistamines are recommended as first line of therapy. For patients with moderate-to-severe persistent symptoms, or for those for whom the initial treatment is ineffective, intranasal corticosteroids (INCS) are recommended. When symptoms persist despite these initial treatments, combination therapies, including combinations of oral antihistamines and INCS, or combined preparations of INCS and intranasal antihistamines, can be explored.[45, 46]

EAG comment: The EAG concerns regarding the definition of the population in this appraisal were discussed in Section 2.3 of this report and identified as a key issue. In particular, if SCIT is a relevant comparator, it should have been included in the CE analyses and results should have been presented in a full incremental way (considering both ECM and SCIT as comparators).

4.2.5 Perspective, time horizon and discounting

The economic analysis is conducted from the National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 1 year with a lifetime time horizon and a half-cycle correction applied.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness considered in the economic analyses are modelled as both an HRQoL benefit and a reduction in resource use and medications. These are explained in detail in Sections 4.2.7 and 4.2.8. It should be noted though that the treatment benefit is only accrued for a proportion of the cycle length (not the full year), which is dependent on the duration of the selected pollen season. In the company's base-case analysis this is assumed to be 137 days, in line with the full dataset from Dick et al. 2020.[41] In the remaining parts of this Section, assumptions around treatment discontinuation, waning of the treatment effect, and the company's approach to modelling mortality and AEs are discussed.

4.2.6.1 Treatment discontinuation

International treatment guidelines refer to a treatment period of 3 years for AIT to achieve disease modification.[43] However, patients enrolled in the TT-04 trial experienced treatment discontinuation.[11] In the economic model, patients in the 12 SQ-Bet arm are assumed to have a per cycle probability of discontinuing treatment. Treatment discontinuation can be due to AEs or other reasons, and discontinuation rates were sourced from the TT-04 trial. Patients who discontinue treatment with 12 SQ-Bet are assumed to receive ECM, for which no treatment discontinuation was assumed. Details on the two types of discontinuations included in the economic model are provided in the remaining part of this Section.

4.2.6.1.1 Discontinuation due to AEs

AE treatment discontinuation rates were sourced from the TT-04 trial.[11] In the TT-04 trial, 61% of the AEs were reported as mild and 33% as moderate. Furthermore, 99% of patients experiencing an AE had recovered by the end of the trial. Also, the majority of the treatment-related adverse events (TRAEs) included in the analyses reported 1 to 12 minutes median onset after the first Investigational Medicinal Product (IMP) intake, with only few new AEs starting at a later time point. Finally, the median AE resolution time was 6 days, 4.5 days, and 1 day for the three most common AEs.[11] Based on this, the company applied the probability of discontinuation due to AEs in the first model cycle only (i.e., during the first year of treatment). This probability is informed by the proportion of patients who discontinued treatment as a result of IMP-related AEs which was 7.50%.[11]

EAG comment: In CQ C4, the EAG asked the company to provide further justification for the assumption that TRAEs (and their associated discontinuation, costs and QALY loss) occurred only during the first year of treatment (i.e., the duration of the TT-04 trial) and not while patients are on treatment.[3] In the response, the company referred, as in the CS, to the median onset of the most frequent TRAEs in the TT-04 trial (within 1 to 12 minutes after first IMP intake) to infer that most of these AEs are indeed associated with treatment initiation and, therefore, that it is most appropriate to assume that all AEs occur in the first year only, instead of assuming that these should be occur while patients are on treatment.[5]

Likewise, the company considered that applying in the second and third year of treatment the same probability of experiencing AEs based on the frequencies observed in the trial, would likely overestimate of the incidence of AEs in these years since, again, most AEs are associated with treatment initiation. The clinical expert consulted by the EAG indicated that it is perhaps reasonable to assume that these AEs will happen only in the first year of treatment, especially severe mucosal symptoms; however more severe adverse drug reactions after 1 year, especially eosinophilic esophagitis have been observed with SLIT agents. In any case, the company included in the economic model the option to select AEs while patients are on treatment (see "Method for applying AEs" dropdown in model sheet "Adverse Events").[47]

4.2.6.1.2 Discontinuation due to other reasons

Treatment discontinuation rates due to other reasons were also sourced from the TT-04 trial,[11] and are applied in the first three model cycles, reflecting the treatment schedule with 12 SQ-Bet. These probabilities were informed by the proportion of patients who discontinued due to withdrawal or other reasons in the TT-04 trial and was 4.38% for the first model cycle. Since there are no data on treatment discontinuation after 12 months, the same rate was applied in cycles 2 and 3.

EAG comment: In CQ C2, the EAG asked the company to justify the assumption that the discontinuation due to non-AE reasons observed in the trial (4.38%) can be applied in the second and third model cycles, in light of the findings from e.g. Pfaar et al. 2023 and Kiel et al. 2013 regarding treatment persistence.[3, 48, 49]

The company mentioned that UK patients are generally adherent to treatment, and those who do not experience tolerability issues usually complete the full course of treatment.[5] However, no source to support this statement was provided.

The company noted differences in access to AIT between Germany, where Pfaar et al. 2023 was conducted, and the UK.[48] According to the company, AIT use in Germany is far more frequent and heterogeneous, including multiple unlicensed treatments used by patients with milder disease. The company argued that in the UK, SLIT is accessed in secondary care, where referred patients experience a significant disease burden and are highly motivated to continue treatment. The EAG also noticed here no sources to support these statements were provided, and that in addition these statements seem to provide subjective interpretations such as patients being highly motivated to continue treatment. Based on this, the company concluded that persistence estimated by Pfaar et al. 2023 does not reflect the experience of 12 SQ-Bet use in UK clinical practice and reiterated that the discontinuation rates observed in TT-04 likely are the best estimate for UK clinical practice.

The company however did not discuss the findings from Kiel et al. 2013, a study conducted in the Netherlands.[49]

The clinical expert consulted by the EAG indicated that the discontinuation rate due to non-AE reasons (withdrawal or other reasons) observed in the TT-04 trial was somewhat reflective of UK clinical practice, but estimated this rate to be slightly higher, at somewhere between 5-8%. The same expert also considered that discontinuation rates due to non-AE reasons are likely to be higher in the second and third year of treatment, especially if treatment is ineffective. An estimated rate of 10% was provided. Finally, the expert expected issues with treatment compliance like those presented in Pfaar et al. 2023 and Kiel et al. 2013.[48, 49]

Despite the differences in settings, both Pfaar et al. 2023 and Kiel et al. 2013 showed low compliance,[48, 49] which might be expected for 12 SQ-Bet in the UK according to the expert consulted by the EAG. Compliance might be higher in trial settings than in real practice. However, the EAG considers that compliance cannot be properly implemented in the current model. Modelling less compliance would mean less benefit, with lower costs, and fewer AEs. A scenario ignoring the effect of compliance on AEs (there are no data to inform this and the impact on the model results is minimal), and assuming some arbitrary reduction in benefit, while keeping the same costs, could be used as an indication of the effect on compliance on the model results. This scenario was run by the EAG in Section 6.3 of this report.

Finally, it should be noted that Kiel et al. 2013 considered a distinction between persistence and compliance. Compliance would indeed mean not taking the dose as prescribed, but with the same costs, but lack of persistence would have the same impact of costs and effects as discontinuation (basically discontinuing without discussing it with your specialist, just not filling the next prescription). The EAG understands that trial data are available for the first year of treatment only. However, assuming the same discontinuation rate (for reasons other than AEs) for years 2 and 3, as in year 1 in the trial could be an optimistic assumption. The EAG prefers a more conservative approach and assumed that 8% of patients would discontinue treatment for other reasons in year 1, and 10% would discontinue treatment after 2 and 3 years, based on the responses of the expert consulted by the EAG. This could be seen as a way to include the impact of persistence on the model results.

4.2.6.1.3 Treatment effect after discontinuation

Clinical experts consulted by the company during an Advisory Board meeting indicated that patients who discontinue AIT treatment early (i.e., before achieving disease modification) may still benefit from some sustained treatment effect.[50] Two out of three clinicians reported that half of the patients who discontinue may still receive benefits, while one clinician said this would be a small number of patients. In the base-case analysis, the company assumed that 50% of patients who discontinue treatment with 12 SQ-Bet continue to receive the treatment benefit for the rest of the cycle where discontinuation happened. In addition, the company assumed that all patients who discontinue treatment incurred the cost of 6 months' treatment with 12 SQ-Bet, to account for any previous time on treatment.

EAG comment: In response to CQs C1 and C2, the company explained that the full duration of the sustained treatment effect is applied to patients who complete the 3 years of treatment.[5] Patients who discontinue AIT treatment early may still receive treatment benefit, which would be indicative of achieving disease modification.

The company also explained that the assumption that 50% of patients who discontinue treatment with 12 SQ-Bet may continue to receive treatment benefit was informed by clinical opinion and that this was aligned with the accepted assumptions in TA834. Two out of three clinicians consulted by the company indicated that half of patients who discontinue may still receive benefits, while the other clinician believed this would be a small number of patients, but no specific estimate was

provided (Appendix J5).[50] The clinical expert consulted by the EAG was also unable to provide an estimate due to lack of data.

While the impact of using different proportion of patients receiving treatment benefit discontinuation is minor (this was explored in scenario analysis by the company) the EAG prefers using an estimate based on the responses from the three experts and, therefore, 35% (5% assumed for the clinician who said this would be a small number of patients) instead of 50% of patients receiving treatment benefit after discontinuation was assumed in the EAG base-case presented in Section 6 of this report.

4.2.6.2 Long-term treatment effect and waning

The economic model incorporates waning of the treatment effect of 12 SQ-Bet over time. Treatment waning assumptions were adopted from TA834[i], a previous NICE Technology Appraisal (TA) for an AIT for HDMs (12 SQ-HDM).[51] Despite the difference in allergen, this was deemed appropriate by the company given the similar mechanisms of action, and identical manufacturing and standardisation technology. In addition, five UK allergy experts indicated that this waning effect would be applicable to 12 SQ-Bet as well.[52]

During a modified Delphi panel arranged by the company, which included eight secondary care allergy specialists across Ireland, it was agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade, with treatment effectiveness unlikely to completely disappear.[53] In a subsequent Advisory Board conducted with eight clinical experts across the UK, it was also agreed that treatment is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade.[50]

However, the company acknowledged that the long-term effectiveness of 12 SQ-Bet (after 12 months) has not been assessed in a controlled setting, and that key clinical studies have not considered the full guideline recommended 3 years of treatment or collected data after treatment cessation. The company referred to the REACT study, a case-control study where the long-term effectiveness of AIT (for any allergen) for the treatment of AR and asthma in a real-world setting was assessed.[54] The study found that AIT was associated with greater reductions in asthma and AR prescriptions compared to control subjects, which was sustained for 9 years. An improvement in the treatment effect was also reported over the 9-year period. As they did in TA834, the company used the results of the REACT study to justify their base-case assumption that the proportion of 12 SQ-Bet patients receiving treatment benefit increased by 2.5% in each model cycle up to year 10. This assumption was made to reflect the improving treatment effect observed in the REACT study. Furthermore, the company assumed a treatment waning starting at year 15, and by year 20, 80% of patients will have lost treatment benefit.

The company also assumed that a proportion of patients can be retreated with 12 SQ-Bet after 10 years. For retreated patients the same assumptions regarding treatment waning were applied. The company concluded that the approach to modelling 12 SQ-Bet long-term effectiveness was consistent with the one taken in TA834.[51]

[i] The company refers to the appraisal as TA834, however, this TA guidance has been updated and replaced by TA1045

EAG comment: Although the company referred to various expert panels to justify the assumption that there will be a sustained and clinically significant effect of 12 SQ-Bet treatment for at least 10 years with potential waning over the subsequent decade, the company did not present any data to support the assumption that the proportion of patients receiving treatment benefits increases by 2.5% per year for the first 10 years. The clinical experts in the various panels were, as far as the EAG could judge from the provided documents, not asked to comment on this assumption of a 2.5% increase in benefit per year, but instead if they considered it reasonable to assume a sustained and clinically significant effect.

Moreover, the company did not provide a clear definition of 'treatment benefit' in their submission, which makes it difficult to link the various outcomes of the REACT study (e.g. percentage of patients with a prescription for AR treatment, number of AR prescriptions per patient per year, number of outpatient visits, number of inpatient stays) to some percentage increase in benefit per year.

In addition, the EAG identified programming errors in the original model engine, in the calculation of column W (proportion of discontinued population due to other reasons). When the percentage of patients discontinuing per year was set to e.g. 50% (sheet "Effectiveness", cells E12:G12), column W showed values larger than 1, which led to columns referring to the number of patients on treatment (e.g. X, Y) to be negative. The company corrected this error in response to CQ C13, which had a minimal impact on the model results.[3]

4.2.6.3 Mortality

The company assumed that there is no impact of AR on mortality (no deaths were reported in TT-04),[11] and therefore, only age- and gender-adjusted all-cause mortality sourced from UK life tables was included in the economic analyses.[42]

EAG comment: In response to CQ C3,[5] the company explained that the economic model was updated with life tables from the latest version of the National life tables: England and Wales dataset published by the Office for National Statistics (ONS) (release date: 23 October 2024).[42] The updated economic model included the option to select life tables based on 2021-2023 data or 2016-2018 (before coronavirus disease 2019 [COVID-19]) data (see model sheet "Mortality")[47] The latter are used for the EAG base-case defined in Section 6.1 of this report.

4.2.6.4 Adverse events

The company identified AEs based on the most commonly TRAEs reported in in the TT-04 trial.[11] The type and number of events, median duration of event (days), and annual probability of AEs used in the economic model can be seen in Table 4.2. As explained in Section 4.2.6.1.1, the economic analyses assumed that all AEs, and therefore, their associated costs and QALY loss, occurred within the first year only (i.e., in the first model cycle).

Table 4.2: Incidence and annual probability of AEs used in the economic model

Most common TRAEs	Number of events		Annual probability (%)		Median duration (days)
	12 SQ-Bet	Placebo			
	N=314	N=320	12 SQ-Bet	SoC	
Oral pruritis	160	16	50.96	5.00	6.0
Throat irritation	96	8	30.57	2.50	4.5

Most common TRAEs	Number of events		Annual probability (%)		Median duration (days)
	12 SQ-Bet	Placebo			
	N=314	N=320	12 SQ-Bet	SoC	
Oral paraesthesia	42	12	13.38	3.75	1.0
Mouth swelling	38	2	12.10	0.63	15.0
Tongue pruritis	35	6	11.15	1.88	5.0
Oral discomfort	33	1	10.51	0.31	2.0
Pharyngeal oedema	32	1	10.19	0.31	5.0
Oropharyngeal pain	29	3	9.24	0.94	3.5

Based on Table 40 of the CS.[1]
AE = adverse event; CS = company submission; SoC = standard of care; TRAE = treatment-related adverse event

EAG comments: In response to CQ C4, the company explained that AEs "of interest" were pre-defined in the TT-04 trial based on the mode of administration (oral lyophilisate) and mechanism of action (exposing the subject to the allergen) of 12 SQ-Bet.[5] The AEs of interest were the following:

- Local administration site reactions (swelling, itching, pain, redness, blister, etc.) are potential risks when administrating an oral drug such as 12 SQ-Bet, which rapidly disintegrates under the tongue, releasing the allergen extract on the oral mucosa.
- Systemic allergic reactions: since 12 SQ-Bet exposes subjects to the allergen, there is a risk that the immunotherapy itself can trigger a systemic allergic reaction.
- Laryngo-pharyngeal reactions: local allergic reactions such as swellings in the laryngo-pharyngeal area may put the patient as risk by leading to breathing difficulties or suffocation.

As for the criteria for inclusion in the economic model, the company included the eight most frequently reported IMP-related AEs (regardless of severity) from the TT-04 trial. These selection criteria seem arbitrary, but given the impact of including different AEs on the model results is expected to be minimal.

4.2.7 Health-related quality of life data identified in the review

The company performed a SLR in order to find studies assessing the HRQoL and/or utilities on the management and/or treatment of birch pollen-induced AR. Based on that review one relevant study was deemed relevant (Dick et al. 2020) and was used for the utility input parameters of the model.[41]

4.2.7.1 Health state utility values

The 2020 study by Dick et al. was the only identified study from the SLR that published utility values for AR and/or conjunctivitis caused by pollen from the birch homologous group and was used as input for the model.[41] The study by Dick et al. used TT-04 trial data, including RQLQ scores, to generate European Quality of Life-5 Dimensions (EQ-5D) utility values. The TT-04 trial assessed HRQoL of the patients using the RQLQ, which includes 28 questions across seven domains scored on a 0-6 scale. Weekly domain and overall scores were calculated, with higher scores indicating worse HRQoL. The trial found that 12 SQ-Bet significantly improved overall RQLQ scores and individual domain scores compared to placebo during both the BPS and TPS, with the largest improvements in 'activities,' 'eye symptoms,' and 'practical problems'.

Dick et al. 2020 mapped EQ-5D utility values from clinical data, including RQLQ scores, collected in the TT-04 trial. Since TT-04 did not collect preference-based measure (PBM) data like EQ-5D, a

mapping approach was used. A regression model developed from the grass AIT trial data (GT-08), which included both RQLQ and EQ-5D data, was applied to TT-04 to estimate health state utilities.[41] Both trials recorded daily symptoms and medication use, with weekly RQLQ scores, and while TT-04 did not include prednisone, its minimal impact in GT-08 suggested negligible effect on the results.

The mapping model used a two-part approach to address the strong left-skew of EQ-5D data, where 83% of responses indicated perfect health. The data were transformed to a disutility scale to shift the skewness. In the first stage, EQ-5D utilities were modelled as a binary variable (perfect versus imperfect health), while the second stage modelled disutility as a continuous variable for those with imperfect health. Various generalised estimating equation (GEE) models and random effects were tested, with covariates selected based on availability in GT-08 and TT-04 trials and clinical relevance. The final model included statistically significant variables, with a mixed effects logistic model for the first stage and a mixed effects model for the second stage, incorporating subject as a random effect in both stages (see Table 42 in the CS).[1]

Table 4.3 presents the utilities that were used to inform QALY gains. The treatment benefit of 12 SQ-Bet is applied as a disutility to the SoC arm, while the 12 SQ-Bet arm uses general population utilities. In the base-case, the treatment benefit of 12 SQ-Bet is assumed for 137 days, matching the dataset duration from Dick et al. 2020.[41]

Table 4.3: EQ-5D utilities for CEA

Season	Duration (days)	Mean utility difference [SE]	95% CI
BPS	42	0.030 [0.008]	0.015, 0.046
TPS	100	0.019 [0.006]	0.007, 0.030
Full dataset	137	0.018 [0.006]	0.007, 0.030

Based on Table 39 of the CS.[1]
BPS = birch pollen season; CEA = cost-effectiveness analysis; CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; SE = standard error; TPS = tree pollen season

EAG comment: The company modelled treatment benefit of 12 SQ-Bet on HRQoL by applying a disutility to the SoC arm, with the 12 SQ-Bet arm taking on general population utilities. The EAG considered this assumption implausible since Figure 19 in the CS shows a decline in HRQoL also for the intervention group (so lower utilities than in the general populations might be expected).[1] In response to CQ C6, the company acknowledged that assuming general population utilities for 12 SQ-Bet patients implies that the estimated total QALYs may not be reflective of AR/C patients' but the incremental QALYs would remain the same.[5]

In the original economic model, it is mentioned that general population utilities were derived from Ara and Brazier et al. 2010.[55] To align with the NICE reference case, these were replaced by those derived from Hernandez Alava et al. 2022,[56] in response to CQ C7.[5]

4.2.7.2 Disutility values AEs

The AEs included in the economic model were summarised in Table 4.2 and consisted of oral pruritic, throat irritation, oral paraesthesia, mouth swelling, tongue pruritic, oral discomfort, pharyngeal oedema, and oropharyngeal pain. The company did not identify any utility values for AEs in the SLR on HRQoL of patients with birch pollen-induced AR related to SLIT. Therefore, no utility decrements were applied in the model for the AEs. However, given the severity and duration of the reported TRAEs, the company

considered that excluding specific utility decrements was considered unlikely to significantly affect the CE of 12 SQ-Bet.

EAG comments: Based on the values presented in Table 35 of the CS, 75% of patients in the intervention arm experienced on average more than three IMP-related AEs.[1] Looking at the division between severity categories, it can be concluded that some patients experienced multiple AEs of (possibly) different severity. Because in more than 18% of the cases in the intervention arm, an action was taken, the EAG considered that this value large enough to include the effect of AEs in HRQoL (while keeping the effect on costs).

In CQ C4, the EAG asked the company to include this in the economic model and implement it in a multiplicative way to align with the NICE reference case.[3] In response, the company explained that the updated economic model includes this option in the sheet "Adverse Events".[5] This is applied as a weighted QALY loss in the first model cycle only. In the company's base-case, still no AE-related utility decrements were applied since, as mentioned above, the SLR on the HRQoL did not identify any utility values for the AEs associated with SLIT. The company explored a scenario where an arbitrary disutility of -0.02 for each of the most common TRAEs was assumed and the impact on the model results was minimal, even if these were applied while patients are on treatment (and not only during the first year).

Despite the minor impact on the model results, the EAG prefers using AE-related utility decrements in the EAG base-case presented in Section 6 of this report. The arbitrary disutility of -0.02 for each of the AEs was assumed for the EAG base-case.

4.2.8 Resources and costs

The healthcare cost categories included in the model were: costs of treatment acquisition and administration (for 12 SQ-Bet) and costs of ECM; health state costs (i.e., costs associated with the management of patients in primary and secondary care); and costs associated with AEs. Sections 4.2.8.2 to 4.2.8.4 explain how resource use and costs were determined for each cost category.

4.2.8.1 Resource use and costs data identified in the review

The company's SLR identified 14 studies; from these, 13 reported costs and/or resource use outcomes from 12 individual studies.[23-36]

4.2.8.2 Treatment and acquisition costs

4.2.8.2.1 12 SQ-Bet acquisition and administration costs

12 SQ-Bet is provided as an oral lyophilizate, where the recommended dose for adults and adolescents (12-17 years) is once daily. The company indicated that the onset of the clinical effect is expected 8-14 weeks after treatment initiation and if there is no improvement during the first year of treatment, this should not be continued.[43]

The 12 SQ-Bet list price is £80.12 per pack of 30 tablets. This results in an average annual cost of £975.46 per patient. In the economic analyses, treatment costs are applied for the first three model cycles (i.e., 3 years of treatment). Furthermore, it is assumed that all patients discontinuing treatment incurred 1-month costs of 12 SQ-Bet treatment to account for any previous time on treatment. 12 SQ-Bet treatment should be initiated by physicians experienced in treatment of allergic diseases. Treatment administration costs were modelled by assuming the cost of a non-admitted face-to-face attendance with

a respiratory specialist (£264.58, National Schedule of NHS costs, WF01B).[57] In addition, a positive test for birch pollen sensitisation is required prior to treatment initiation. This is modelled assuming the cost of a diagnostic blood test as part of the treatment administration costs (£2.75, National Schedule of NHS costs, DAPS05).[57] In the economic model, administration costs are applied to all patients in the 12 SQ-Bet arm at baseline (cycle 0). After that, patients can self-administer at home and, therefore, no administration costs are incurred.

4.2.8.2.2 Established clinical management (ECM) costs

As explained in Section 4.2.4 of this report, the comparator in the economic analyses was ECM without 12 SQ-Bet. However, since treatment with 12 SQ-Bet is additive, ECM management costs are also applied to the 12 SQ-Bet treatment arm.

ECM costs were estimated from medication use data collected in TT-04. Symptomatic medications permitted in the TT-04 trial, provided at randomisation as pre-defined, open-labelled medication used in addition to the IMP, were the following:

- Oral antihistamine tablets (Desloratadine tablets, 5 mg)
- Nasal corticosteroid spray (Mometasone, 50 µg/dose)
- Antihistamine eye drops (Olopatadine eye drops, 1 mg/ml)

These symptomatic medications were allowed to be used as required in both study arms. Data on the average daily doses for each medication during the BPS and TPS for the 12 SQ-Bet and placebo arms are summarised in Table 4.4, and unit costs for those medications are provided in Table 4.5. The use of these three symptomatic medications in the TT-04 in the trial was considered representative of the SoC medication for patients with AR by nine UK clinical experts in allergy management during an advisory panel conducted in 2024 (Appendix J2).[58] This was confirmed during a Delphi panel comprising three consultant allergists and immunologists, along with two General Practitioners (GPs) with a specialist interest in allergy conducted in 2025 (Appendix J6).[52]

Table 4.4: Symptomatic medication use (mean daily dose) in the TT-04 trial

Medication type	Placebo		12 SQ-Bet	
	BPS	TPS	BPS	TPS
Desloratadine (5 mg), tablets	0.46	0.37	0.32	0.26
Mometasone nasal spray (50 ug/dose), puffs	0.66	0.52	0.39	0.33
Olopatadine eye drop (1 mg/ml), drops	0.58	0.48	0.31	0.27

Based on Table 45 of the CS.[1]
BPS = birch pollen season; CS = company submission; TPS = tree pollen season

Table 4.5: Unit costs for symptomatic medication in the TT-04 trial

Medication type	Pack cost (£)	Pack size	Cost/unit (£)	Source
Desloratadine (5 mg), tablets	0.90	30	0.03	eMIT[59]
Mometasone nasal spray (50 ug/dose), puffs	1.93	140	0.01	
Olopatadine eye drop (1 mg/ml), drops*	3.29	100	0.03	

Based on Table 46 of the CS.[1]
* Assumed 100 drops per 5 ml vial (0.05 ml per drop).
CS = company submission; eMIT = electronic market information tool

Annual ECM treatment costs are calculated by multiplying the mean daily medication dose (Table 4.4) by the cost per unit of the medication (Table 4.5). It is further assumed that ECM costs are only incurred during the pollen season. Thus, the mean daily costs are incurred during 137 days, which is in line with the length of the full dataset from Dick et al. 2020.[41] The annual ECM for both treatment arms are summarised in Table 4.6.

Table 4.6: ECM treatment costs (adjusted for pollen season length) per treatment arm

Treatment arm	BPS (£)	TPS (£)	Full dataset (£)
ECM	1.76	3.41	4.67
12 SQ-Bet	1.06	2.12	2.91

Based on Table 47 of the CS.[1]
* Sourced from Dick et al. 2020.[41]
BPS = birch pollen season; CS = company submission; ECM = established clinical management; TPS = tree pollen season

4.2.8.3 Health state costs

The CE model included costs associated with managing patients in primary and secondary care (also referred to as 'health state costs'). These costs covered 10-minute GP consultations and consultant-led outpatient attendances in the Respiratory Medicine Service.

Since the SLR identified no studies reporting healthcare resource utilisation associated with management of the disease beyond medication use, and since the TT-04 trial did not collect data on healthcare resource utilisation other than medication use, estimates for healthcare resource utilisation (i.e., number of visits to primary and secondary care for patients with birch pollen-induced AR) were derived from a probabilistic Delphi panel.[52] This panel consisted of three consultant allergists and two GPs with a specialist interest in allergy. Their input informed the baseline number of visits modelled in the ECM arm and the relative reduction in visits applied to the 12 SQ-Bet arm, reflecting the improvement in disease control in these patients (Table 4.7).

The panel provided probabilistic judgements on the annual number of GP visits for an average patient with moderate to severe birch pollen-induced AR treated with symptomatic pharmacotherapy (i.e., ECM). The median estimate was 2.61 GP visits per year. The panel then assessed the expected annual number of GP visits for patients receiving 12 SQ-Bet, assuming an average treatment effect. All participants anticipated a reduction in GP visits for patients receiving 12 SQ-Bet compared to those on symptomatic pharmacotherapy alone. For these patients, the median number of GP visits was judged to be 1.00 per year (relative risk [RR] reduction: 61.7%).[52]

Similarly, the Delphi panel provided probabilistic judgements on the annual number of secondary care visits for an average patient with moderate to severe birch pollen-induced AR treated with symptomatic pharmacotherapy. The median estimate for secondary care visits was 1.93 per year. Again, all participants anticipated a reduction in secondary care visits for patients receiving the average treatment effect of 12 SQ-Bet compared to those on symptomatic pharmacotherapy alone. For patients treated with 12 SQ-Bet, the median number of secondary care visits was judged to be 0.75 per year (RR reduction: 61.1%).[52]

These resource use data were combined with unit prices to calculate the costs associated with managing patients in primary and secondary care. The unit cost of a 10-minute GP consultation, which was sourced from the Unit Costs of Health and Social Care 2023 (PSSRU 2023), was £42.00. The cost of a secondary care visit to the Respiratory Medicine Service, derived from the National Schedule of NHS

costs (Year 2022/23), was £199.00. This resulted in annual costs ranging from £41,98 to £384,07 (Table 4.7).[57] In the ECM arm, these costs were applied in each cycle of the model (that is, for all alive patients). In the 12 SQ-Bet arm, the proportion of the cohort receiving treatment benefit incurred the costs associated with the 12 SQ-Bet arm, while those who lost treatment benefit due to discontinuation or treatment waning incurred the costs associated with the ECM arm.

Table 4.7: Resource use and costs associated with the management of patients in primary and secondary care

	ECM	12 SQ-Bet	RR reduction
Annual number of visits			
GP visits	2.61	1.00	61.7%
Secondary care visits	1.93	0.75	61.1%
Annual costs			
GP visits	£109,62	£41,98	N/A
Secondary care visits	£384,07	£149,40	N/A

Based on Table 48 of the CS[1] and on the electronic model after clarification.[47]
CS = company submission; ECM = established clinical management; GP = General Practitioner; N/A = not applicable; RR = relative risk

EAG comment: RRs for the reduction on the number of GP and secondary care visits associated to 12 SQ-Bet compared to ECM were estimated by a panel of experts.[52] The clinical expert consulted by the EAG confirmed the expectation of a reduction in healthcare resource utilisation associated with the management of patients in primary and secondary care for patients treated with 12 SQ-Bet compared to those who are not treated with 12 SQ-Bet for at least 5-6 years following a 3-year course of SLIT, but did not provide an estimate of the expected number of primary and secondary care visits with and without 12 SQ-Bet. Based on this, the EAG considers that a reduction in resource utilisation is expected but how much is uncertain. The impact of changing these parameters on the model results is expected to be large. Therefore, the EAG conducted several scenario analyses which are presented in Section 6 of this report.

4.2.8.4 Adverse event costs

The costs associated with the AEs discussed in Section 4.2.6.4 of this report were included in the economic model. For these events, it was assumed that 18.52% and 15.04% of them required management action in the 12 SQ-Bet and ECM groups, respectively, as observed in the TT-04 trial.[11] Since the majority of AEs in TT-04 were reported as mild or moderate, and because no relevant or appropriate costs for AEs were identified by the company in their SLR, a single GP appointment cost (£42.00; PSSRU 2023), weighted by the proportion of AEs requiring management, was applied as AEs costs in the company's base-case analysis.[60] These resulted in the annual costs per AE shown in Table 4.8. From this, the annual total costs of all AEs, which were used as input in the model, could be calculated at £0.97 for the ECM arm and £11.52 for the 12 SQ-Bet arm. The economic model assumed that these costs associated with AEs occur in the first model cycle only, because the majority of the most frequent AEs were assumed to have a median onset within 1 to 12 minutes after first IMP intake and to have a resolution time of 6 days or less (see Section 2.18.4 of the CS).[1]

Table 4.8: Annual probability and annual costs of AEs

Adverse event	Placebo				12 SQ-Bet			
	Annual probability	AEs requiring action[a]	Management cost per AE	Annual cost	Annual probability	AEs requiring action[b]	Management cost per AE	Annual cost
Oral pruritis	5.00%	0.75%	£42	£0.32	50.96%	9.44%	£42	£3.96
Throat irritation	2.50%	0.38%	£42	£0.16	30.57%	5.66%	£42	£2.38
Oral paraesthesia	3.75%	0.56%	£42	£0.24	13.38%	2.48%	£42	£1.04
Mouth swelling	0.63%	0.09%	£42	£0.04	12.10%	2.24%	£42	£0.94
Tongue pruritis	1.88%	0.28%	£42	£0.12	11.15%	2.06%	£42	£0.87
Oral discomfort	0.31%	0.05%	£42	£0.02	10.51%	1.95%	£42	£0.82
Pharyngeal oedema	0.31%	0.05%	£42	£0.02	10.19%	1.89%	£42	£0.79
Oropharyngeal pain	0.94%	0.14%	£42	£0.06	9.24%	1.71%	£42	£0.72
Total cost (per year)				£0.97				£11.52

Based on Table 40 of the CS[1] and on the electronic model after clarification.[47]

[a] Regarding the placebo group, it was assumed that 15.04% of the AEs required management action, as observed in the TT-04 trial.

[b] Regarding the 12 SQ-Bet group, it was assumed that 18.52% of the AEs required management action, as observed in the TT-04 trial.

AE = adverse event; CS = company submission

4.2.9 Disease severity

The NICE reference case stipulates that the committee will regard all QALYs as being of equal weight. However, the committee may consider the severity of the condition, as determined by the absolute and proportional QALY shortfall (including discounting at the reference case rate), as decision modifier. Severity can be then considered quantitatively in the CEA through QALY weighting, based on the absolute and proportional shortfall, as shown in Table 4.9. Whichever implies the greater severity level will be considered, and if either the proportional or absolute QALY shortfall falls exactly on the cut-off between two severity levels, the higher level will apply.[61]

Table 4.9: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
QALY = quality-adjusted life year		

The results of the QALY shortfall analysis conducted by the company are shown in Table 4.10, where the total lifetime QALYs associated with the disease were obtained from the model results of the base-case analysis, and the estimated total QALYs for the general population reflected the baseline characteristics of the TT-04 trial and the economic analyses (47.01% male and 36.01 years). These results suggest that a QALY weight of 1.0 applies to this appraisal. The results presented by the company were validated by the EAG.

Table 4.10: Summary of company QALY shortfall analysis

Item	Value
Expected total QALYs for the general population	19.61
Expected total QALYs for population with the disease	19.51
Absolute shortfall	0.10
Proportional shortfall	0.51%
Based on Table 49 in CS.[1] CS = company submission; QALY = quality-adjusted life year	

5. Cost-effectiveness results

5.1 Company's CE results

5.1.1 Original company's CE results

In Section B.3.10 of the CS, the company presented their CE results using the list price for 12 SQ-Bet.[1] Table 5.1 shows the company's base-case deterministic CE results for 12 SQ-Bet compared to ECM. All results are discounted. Results indicated that 12 SQ-Bet was less costly and also more effective than ECM (12 SQ-Bet was thus dominant). The incremental net monetary benefit (INMB) at a willingness-to-pay (WTP) threshold of £20,000 per QALY gained was £3,877. Disaggregated discounted costs are shown in Table 5.2.

Table 5.1: Company base-case deterministic CE results (12 SQ-Bet, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
12 SQ-Bet	9,486	22.75	19.34	-1,853	0	0.10	Dominant
ECM	11,339	22.75	19.24				

Based on Table 51 of the CS.[1]
CE = cost-effectiveness; CS = company submission; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 5.2: Disaggregated cost results (12 SQ-Bet, discounted)

	12 SQ-Bet (£)	ECM (£)	Increment (£)
12 SQ-Bet treatment and administration	2,790	0	2,790
Pharmacotherapy	79	106	-27
Primary care	1,459	2,494	-1,035
Secondary care	5,146	8,738	-3,592
Adverse events	12	1	11
Total costs	**9,486**	**11,339**	**-1,853**

Based on Table 52 of the CS.[1]
CS = company submission; ECM = established clinical management

5.1.2 Updated company's CE results

In the original model, the company made an error in columns V and W of the model engine which was corrected by the company in the model version submitted together with the response to the clarification letter. The company presented updated base-case results reflecting two other model changes, namely using life tables based on 2021-2023 data,[42] and general population utilities sourced from Hernández Alava et al. 2022.[56] The updated results after addressing this error and EAG requests in response to the clarification letter are presented in Table 5.3. The results remain similar, with 12 SQ-Bet still being dominant compared to ECM. The company did not provide updated disaggregated results. These results, however, can be found in the updated electronic model and are presented in Table 5.4 below.

Table 5.3: Updated company base-case deterministic CE results (12 SQ-Bet, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
12 SQ-Bet	9,408	22.58	19.31	-1,845	0	0.10	Dominant
ECM	11,253	22.58	19.21				

Based on Table 13 in the response to the request for clarification.[5]
CE = cost-effectiveness; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 5.4: Updated disaggregated cost results (12 SQ-Bet, discounted)

	12 SQ-Bet (£)	ECM (£)	Increment (£)
12 SQ-Bet treatment and administration	2.796	0	2.796
Pharmacotherapy	78	105	-27
Primary care	1.440	2.475	-1.035
Secondary care	5.081	8.672	-3.591
Adverse events	12	1	11
Total costs	**9.408**	**11.253**	**-1.845**

Based on electronic model after clarification.[47]
ECM = established clinical management

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by slightly increasing total QALYs by relieving symptoms during the pollen season.

Overall, based on the company's base-case results, the technology is modelled to affect costs by:

- Reducing the number of visits to primary and secondary care and their associated costs.
- Increasing costs due to treatment acquisition and administration.
- Slightly increasing costs due to experiencing TRAEs and slightly reducing symptomatic pharmacotherapy costs.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 2,000 iterations. The input parameters and the probability distributions used in the PSA can be found in the "Parameters" sheet of the economic model. In the original model the EAG noticed that the same standard errors (SEs) were chosen for all input parameters in the model (Table 50 in CS).[1] In response to CQ C12, the company mentioned that the SE for mean age, primary and secondary care visits/relative reductions, and utility gain in each of the pollen seasons were available.[5] However, for other parameters, a SE of 10% of the input value was assumed due to the lack of source data. The updated average PSA results, including the changes made by the company after clarification, are summarised in Table 5.5 and are overall in line with the deterministic ones shown in Table 5.3.

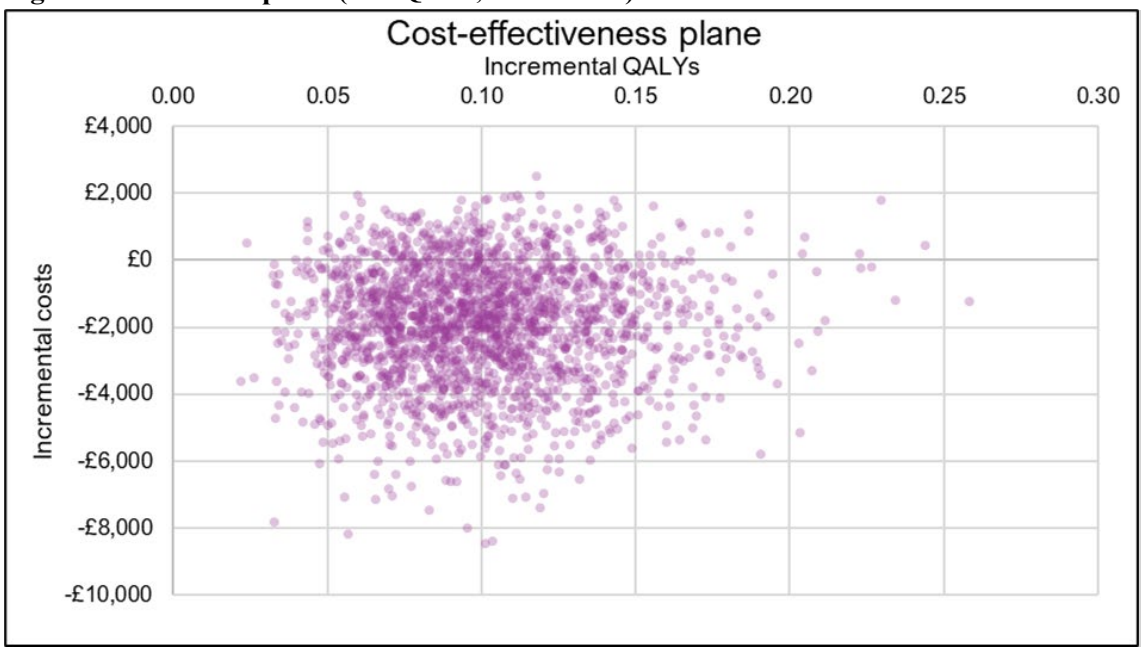
Table 5.5: Company base-case probabilistic CE results (12 SQ-Bet, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
12 SQ-Bet	9,322	22.58	19.32	-1,886	0	0.10	Dominant
ECM	11,209	22.58	19.21				

Based on Table 12 of the response to the request for clarification.[5]
CE = cost-effectiveness; ECM = Established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

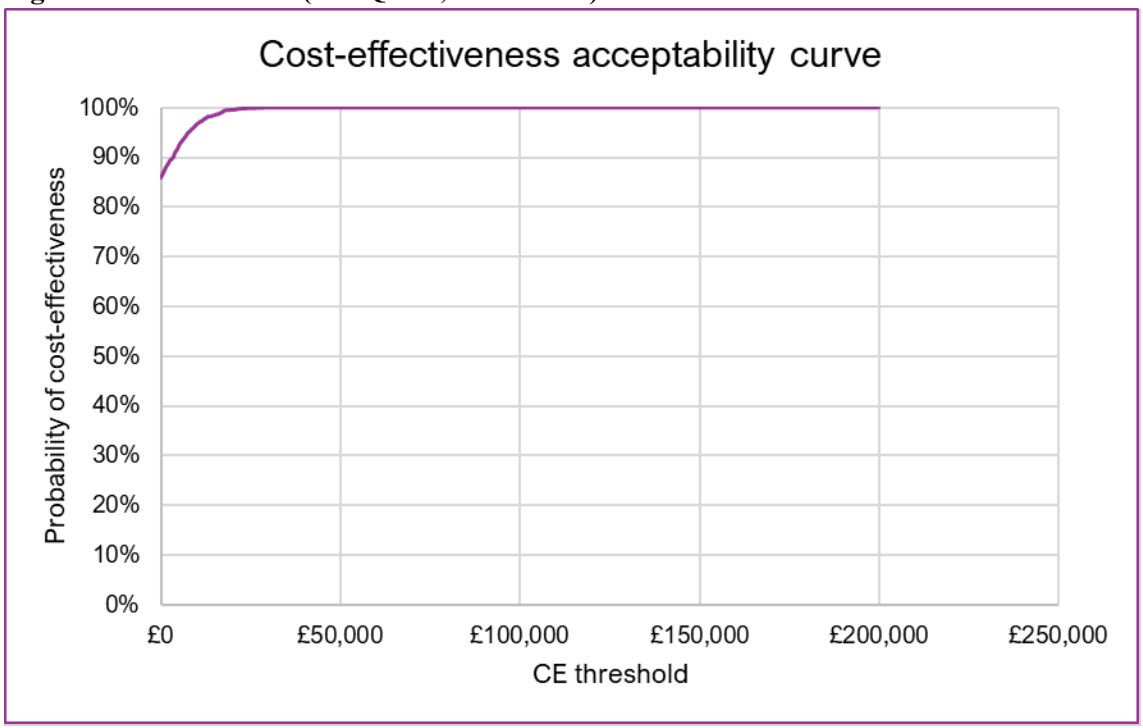
The company also plotted the PSA outcomes on a CE-plane (Figure 5.1). All outcomes reported positive incremental QALYs for 12 SQ-Bet versus ECM. Cost outcomes were spread across North-East and South-East quadrants. A cost-effectiveness acceptability curve (CEAC) was also calculated (Figure 5.2). The CEAC plot indicates that at the common threshold of £20,000 per QALY gained, the estimated probability that 12 SQ-Bet is a cost-effective alternative to ECM was 100%.

Figure 5.1: PSA CE-plane (12 SQ-Bet, discounted)



Based on Figure 4 of the response to the request for clarification.[5]
CE = cost-effectiveness; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: PSA CEAC (12 SQ-Bet, discounted)



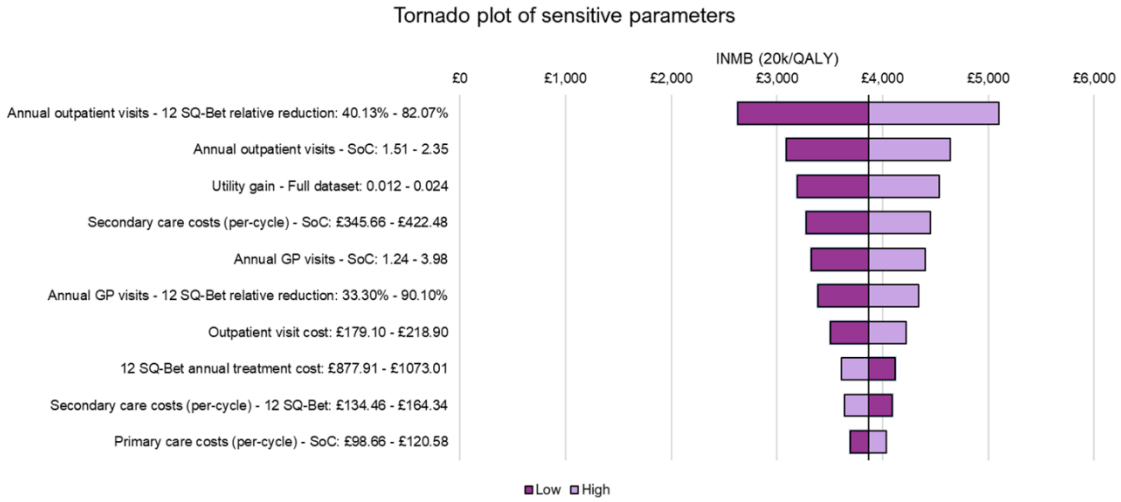
Based on economic model submitted with the response to the request for clarification.[47]
CE = cost-effectiveness; CEAC = cost-effectiveness acceptability curve; PSA = probabilistic sensitivity analysis

EAG comment: The EAG noticed that the same SEs were chosen for all input parameters in the model, which seemed an arbitrary choice that does not conform to best practices (SE for each parameter should be informed separately, ideally based on trial or other source of data). This was especially clear in those parameters informed by the Delphi panel (three participants only) for which the SE would be expected to be much higher than 10%. In response to CQ C12, the company corrected this in the economic model and re-ran the deterministic sensitivity analysis (DSA)and PSA.[5] The results in this and the next Section are based thus on the model with the corrected SE. The company indicated that, in particular, the SE for mean age, primary and secondary care visits/relative reductions, and utility gain in each of the pollen seasons were available; for other parameters, a SE of 10% of the input value is assumed. However, in the updated model after clarification the EAG noticed several input parameters that were estimated as proportions observed in the clinical study for which still a SE of 10% of the mean was used, rather than using the number of 'events' and the sample size to directly obtain the parameters of the required beta distributions. This was corrected by the EAG and included in the model used to produce the EAG PSA.

5.2.2 Deterministic sensitivity analysis

The company also conducted a DSA where all input parameters were varied using a lower and upper bound value of the mean ± SE. A tornado diagram for the INMB is presented in Figure 5.3. This represents updated results after clarification. The INMB was most sensitive to the number and relative reduction of annual outpatient visits, utility gain, secondary care costs and the number and relative reduction of annual GP visits. At a WTP threshold of £20,000/QALY, the INMB was always positive.

Figure 5.3: DSA tornado diagram for INMB



Based on Figure 5 of the response to the request for clarification.[5]
DSA = deterministic sensitivity analysis; GP = General Practitioner; INMB = incremental net monetary benefit; QALY = quality-adjusted life year; SoC = standard of care (note standard of care = established clinical management)

5.2.3 Scenario analysis

The company presented the results of six scenario analyses to assess the robustness of the model against alternative inputs and assumptions. In these scenarios, different assumptions were made regarding the time horizon (scenario 1), treatment waning (scenario 2), 12 SQ-Bet benefits after discontinuation (scenario 3), the reduction in secondary care visits (scenario 4), the duration of treatment benefit for each cycle (scenario 5), and the proportion of patients retreated with 12 SQ-Bet after 10 years (scenario 6). The results of these scenario analyses, in terms of incremental costs, incremental QALYs, the CE ratio of 12 SQ-Bet, and INMB are shown in Table 5.6.

EAG comment: In most scenarios, 12 SQ-Bet remained the dominant strategy compared to ECM, despite a potential reduction of up to 35% of its INMB. In the two scenarios where 12 SQ-Bet was not dominant, the incremental cost-effectiveness ratio (ICER) was well below the WTP threshold of £20,000/QALY.

Table 5.6: Company scenario analysis results (12 SQ-Bet, discounted)

Scenario number	Scenario description	Base-case assumption	Inc. Costs (£)	Inc. QALYs	ICER	INMB (WTP = £20,000)	INMB % change versus base-case
0. Base-case	N/A	N/A	-1,845	0.10	Dominant	3,865	N/A
1. Time horizon	10 years	Lifetime	29	0.06	£469	1,206	-69%
	20 years		-1,382	0.09	Dominant	3,231	-16%
2. Treatment waning	100% loss of treatment benefit after 15 years	Waning starts in year 15. By year 20, 80% of patients in the 12 SQ-Bet arm have lost treatment benefit.	-880	0.08	Dominant	2,512	-35%
	Full treatment benefit for 20 years (100% loss at year 20)		-1,975	0.11	Dominant	4,078	6%
3. Benefit after discontinuation	0% receive 12 SQ-Bet benefit after discontinuation	50% of patients assumed to experience benefits of 12 SQ-Bet after discontinuation.	-1,558	0.09	Dominant	3,452	-11%
	100% receive 12 SQ-Bet benefit after discontinuation		-2,133	0.11	Dominant	4,277	11%
4. Relative reduction in secondary care visits	Source of relative reduction: REACT study: reduction in hospitalisations for patients treated with AIT 9 years after treatment initiation, with an OR of 0.72 (95% CI: 0.54-0.98).	Relative reduction in outpatient visits (61.1%) informed by Delphi panel.	100	0.10	£988	1,919	-50%

Scenario number	Scenario description	Base-case assumption	Inc. Costs (£)	Inc. QALYs	ICER	INMB (WTP = £20,000)	INMB % change versus base-case
5. Proportion of each cycle for which treatment benefit is applied	Treatment benefit accrued for 100 days per cycle (TPS, as defined in Dick et al. 2020) – mean daily utility difference: 0.019; annual QALY gain: 0.0052	Treatment benefit of 12 SQ-Bet lasts for the proportion of the year aligned with the length of the full dataset from Dick et al. 2020 (137 days; mean daily utility difference: 0.018; annual QALY gain: 0.0068), to capture the full treatment benefit of 12 SQ-Bet.	-1,838	0.08	Dominant	3,394	-12%
	Treatment benefit accrued for 42 days per cycle (BPS, as defined in Dick et al. 2020) – mean daily utility difference: 0.030; annual QALY gain: 0.0035		-1,829	0.05	Dominant	2,861	-26%
6. Retreatment	Proportion retreated: 0%	5% of patients are retreated with 12 SQ-Bet after 10 years.	-1,779	0.10	Dominant	3,723	-4%
	Proportion retreated: 20%		-2,045	0.11	Dominant	4,289	11%
	Proportion retreated: 50%		-2,444	0.13	Dominant	5,137	33%

Based on Table 54 of the CS[1] and the economic model submitted in response to the clarification letter.[47]
AIT = allergy immunotherapy; BPS = birch pollen season; CI = confidence interval; CS = company submission; ICER = incremental cost-effectiveness ratio; Inc. = incremental; INMB = incremental net monetary benefit; N/A = not applicable; OR = odds ratio; QALY = quality-adjusted life year; TPS = tree pollen season; WTP = willingness-to-pay

5.3 Model validation and face validity check

In the validation Section of the CS (3.14),[1] the company indicated that technical validation of the model was guided by the TECH-VER checklist,[62] which is included as a sheet in the economic model. The company concluded that, overall, no issues with the structural or computational accuracy of the model were identified. Other validation aspects, such as the validation of some input parameters conducted by experts, were scattered over Document B of the CS and the appendices. In addition, more details about model validation were provided by the company in response to some CQs.[5] In the remainder of this Section, the validation efforts performed on the model, as presented by the company, are categorised according to the types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool.[63]

5.3.1 Validation of the conceptual model

5.3.1.1 Face validity testing (conceptual model)

Throughout the CS, the company indicated where key assumptions were validated by experts through Advisory Board meetings, Delphi panels or surveys.[1] Additional details are provided in Appendices J1 to J6.[50, 52, 53, 58, 64, 65]

5.3.1.2 Cross-validity testing (conceptual model)

The company indicated in response to CQ C16,[5] that the conceptual model was validated by comparing it with the previously published study by Pollock et al. 2023 and with TA834.[27, 51]

The company concluded that the current model structure was aligned to that described in Pollock et al. 2023,[27] and with Dick et al. 2020,[41] and that any differences in the modelling approach could be attributed to the Pollock et al. 2023 study being conducted from a Swedish Societal perspective over a shorter time horizon of 10 years. In addition, the conceptual model was also validated by making sure that that the assumptions around the duration of treatment, impact of early discontinuation on treatment effect, and long-term effectiveness in the model are aligned to those accepted by the Appraisal Committee in TA834.[51]

5.3.2 Input data validation

5.3.2.1 Face validity testing (input data)

The company indicated in response to CQ C16, that all clinical data included in the economic model were sourced from the TT-04 trial where appropriate.[5] The company noted some uncertainty around some model inputs due to lack of available data (e.g., long-term effectiveness), but considered that their base-case assumptions were informed by UK clinical experts and, therefore, were in line with the expectations.

5.3.2.2 Model fit testing

The study by Dick et al. 2020 applied the regression model developed from the GT-08 trial to the TT-04 trial data to predict EQ-5D utilities.[41] The results can be seen in Table 42 of the CS.[1] These are the only input parameters estimated through regression analyses in the company's model. The validity of the regression model in terms of goodness-of-fit was not discussed by the company.

5.3.3 Validation of the computerised model (technical verification)

Validation of the computerised model was performed using the TECH-VER checklist,[62] the results of which are included as a sheet in the economic model.[47]

Even though the company concluded that in the CS, overall, no issues with the structural or computational accuracy of the model were identified, the EAG pointed out what appeared to be programming errors in the model engine leading to negative number of patients on treatment. This was corrected by the company in response to CQ C13.[5] It should be noted that these errors had a relatively minor impact on the model results. In addition, the model was reviewed for links to external files which were subsequently removed. This had no impact on the model results.

5.3.3.1 External review

With the information provided by the company, the EAG cannot determine who conducted the technical verification of the model.

5.3.3.2 Extreme value testing

Extreme value tests are part of the TECH-VER checklist.[62]

5.3.3.3 Testing of traces

Traces can be found in the "Model Engine" sheet of the economic model.[47]

5.3.3.4 Unit testing

This type of validation was not explicitly mentioned in the CS.[1] Therefore, it is unknown whether the Visual Basic for Applications (VBA) code was also included in the verification exercises.

5.3.4 Operational validation (validation of model outcomes)

5.3.4.1 Face validity testing (model outcomes)

Although it is not explicitly mentioned in the CS, the EAG assumed that model results were presented to experts during the Advisory Board and Delphi panel meetings who provided some sort of validation of the model outcomes.

5.3.4.2 Cross validation testing (model outcomes): comparisons with other technology appraisals and other models (not necessarily technology appraisals)

NICE TA834 appraised 12 standard quality house dust mite sublingual lyophilizate (SQ-HDM SLIT) for treating allergic rhinitis and allergic asthma caused by house dust mites.[51] The company used this appraisal to validate modelling aspects such as the conceptual model or several modelling assumptions (for example, long-term effectiveness) but not the model results.

The company also indicated that it is inappropriate to compare the model results to those reported in Pollock et al. 2023, since the latter used a shorter time horizon and was conducted from the Swedish Societal perspective.[5]

5.3.4.3 Validation against outcomes using alternative input data

This type of validation was not explicitly reported by the company unless it was considered part of the scenario analyses.

5.3.4.4 Validation against empirical data

5.3.4.4.1 Comparison with empirical data used to develop the economic model (dependent validation)

This type of validation was not reported by the company.

5.3.4.4.2 Comparison with empirical data not used to develop the economic model (independent validation)

This type of validation was not reported by the company.

6. Evidence Assessment Group's Additional Analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 Explanation of the EAG adjustments

Table 6.1 summarises the CE key issues categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[66]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the DP and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the sources of uncertainty can help determine whether additional clarifications, evidence and/or analyses might help to resolve the key issue. Table 6.1 also includes suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG exploratory analyses, and if additional evidence or analyses might help to resolve the identified key issues.

The changes made by the EAG (to the model received with the response to the clarification letter) can be subdivided into the following categories (according to Kaltenthaler et al. 2016):[67]

- Fixing errors ([FE]; correcting the model where model was unequivocally wrong)
- Fixing violations ([FV]; correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement ([MJ]; amending the model where the EAG considers that reasonable alternative assumptions are preferred).

After the proposed changes were implemented in the company's model, additional scenario analyses were also explored by the EAG in order to assess the impact of alternative assumptions on the CE results.

6.1.2 EAG base-case

The adjustments made by the EAG, to define the EAG base-case (using the base-case after clarification as starting point) are listed below.

6.1.2.1 Fixing errors

1. Errors were found by the EAG in the model provided in response to the clarification letter. These concerned the implementation of the long-term effectiveness as explained in Section 4.2.6.2 of this report. The EAG noticed several input parameters that were estimated as proportions observed in the clinical study for which still a SE of 10% of the mean was used, rather than using the number of 'events' and the sample size to directly obtain the parameters of the required beta distributions. This was also corrected by the EAG.

6.1.2.2 Fixing violations

No violations were identified by the EAG.

6.1.2.3 Matters of judgement

2. The EAG prefers assuming higher discontinuation rates (due to other reasons) than those observed in the TT-04 trial. The EAG also prefers rates that depend on the year on treatment. Thus, the EAG assumed that 8% of patients would discontinue treatment for other reasons in year 1, and 10% would discontinue treatment after 2 and 3 years (Section 4.2.6.1.2).

3. For the proportion of patients receiving benefit after discontinuation, the EAG prefers assuming an estimate based on the responses from the three clinical experts consulted by the company (instead of just two). For the clinician who said this proportion would be a small number of patients, the EAG arbitrarily assumed 5%. In total, the EAG assumed 35% of patients would receive treatment benefit after discontinuation instead of the 50% assumed by the company (Section 4.2.6.1.3).

4. The EAG prefers using life tables (before COVID-19) based on 2016-2018 (Section 4.2.6.3).

5. The EAG prefers using AE-related utility decrements for the first year of treatment. An arbitrary disutility of -0.02 for each of the AEs was assumed for the EAG base-case (Section 4.2.7.2).

6.1.3 EAG exploratory scenario analyses

The EAG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the CE analyses. A description of the scenario analyses conducted by the EAG is provided below.

The EAG explored the impact of changing assumptions regarding treatment discontinuation, both due to AEs and other reasons. The EAG considered very high and low discontinuation rates with the idea to test model validity (in light of the errors identified in the model) rather than scenario plausibility. AEs discontinuation rates (at year 1) were set to 0% and 100%, and discontinuation rates for other reasons were set first at 50% at year 1, and then at 50% at both year 1 and year 2. Given the minor impact of changing the proportion of patients receiving treatment benefit after discontinuation, as shown by the company analyses in Table 5.6, the EAG only explored the scenario where this is 0% to illustrate a worst-case scenario regarding this parameter.

In an attempt to capture the potential impact of compliance, the EAG explored one scenario where 50% reduction in HRQoL benefit was assumed while keeping the same costs (ignore thus the effect of compliance on AEs, which is expected to be negligible).

The EAG anticipated that scenarios considering alternative resource use estimates associated with the management of patients in primary and secondary care might have a large impact on the model results. This is because 1) most of the cost savings associated with 12 SQ Bet are obtained here; and 2) the estimated input parameters are uncertain (sourced from expert elicitation). The EAG approach was to explore scenarios assuming no difference in resource use associated to GP or outpatient visits between 12 SQ Bet and ECM. In addition, the EAG explored a scenario where the costs associated with the management of patients in primary and secondary care were those considered in TA834, as per CQ C11.[5] The differences between the CS and TA834 approaches are the following:

- In TA834 the annual average number of primary care visits for the AR population was 1.7 (informed by clinical expert opinion derived in a Delphi panel). In the CS this was 2.61 (see Table 4.7).

- In TA834 the relative reduction in GP visits associated with 12 SQ-HDM was 4.92% (informed by data collected in the MT-06 trial). In the CS this was 61.7% (see Table 4.7). A large discrepancy can be observed here.
- The annual average number of secondary care visits in TA834 was 2.66 (derived from an assessment of Hospital Episode Statistics data for the average number of episodes per patient between 2016-2021 in each hospital setting for the overall allergy patient cohort at a national level. In the CS this was 1.93 (see Table 4.7).
- In TA834 the relative reduction in secondary care visits for the AR population was 73.53% (informed by an observational, retrospective study conducted in Spain which reported the healthcare resource use for patients treated with SCIT with HDM-induced AA and/or AR). In the CS this was 61.1% (see Table 4.7).

The company indicated however that the study used for the relative reduction in secondary care visits in TA834 was not deemed applicable to this appraisal, since it was conducted in Spain, in a different patient population, and patients were treated with SCIT as opposed to SLIT. The company explained the larger discrepancy in the values for primary care due to the fact that the Delphi panel informing the value used in TA834 included patients with mild disease, who would be expected to visit the GP less frequently compared to those with moderate to severe disease.

Finally, The EAG considered some other scenarios where the impact on the model results was anticipated to be minimal, but again these were explored to test model validity. These scenarios included assuming life tables after COVID-19, allowing the possibility of experiencing AEs while patients are on treatment, not applying AE-related disutility (as per company base-case) and assuming general population utilities per Ara and Brazier et al. 2010 (to test if incremental QALYs remain the same).

6.1.4 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the CE

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Uncertainty in parameters estimated from clinical experts	4.2.6 4.2.8	Imprecision Unavailability	Incorporating additional expert opinion. Exploring new scenario analyses.	+/-	No	Additional data to validate and/or replace estimates provided by the clinical experts.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator
[b] Explored
CE = cost-effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 Results of the EAG preferred base-case scenario

Table 6.2 presents the results of the EAG's base-case (discounted). These results indicate that 12 SQ-Bet was both less costly and more effective than ECM. In other words, 12 SQ-Bet was a dominant strategy compared to ECM. The INMB at a threshold of £20,000 per QALY gained was £3,399. Compared to the company's base-case (i.e., the updated base-case analysis submitted by the company together with the response to the clarification letter, presented in Table 5.3), the incremental costs decreased by £260 (from -£1,845 to -£1,585), while the incremental QALYs decreased by 0.01 (from 0.10 to 0.09). Disaggregated discounted costs are shown in Table 6.3.

Overall, the EAG base-case results were somewhat less favourable for 12 SQ-Bet compared to the company's base-case, although the differences were relatively small. The largest difference was observed in the incremental costs, particularly secondary care costs (incremental costs of -£3,235 in the company's updated base-case versus -£2,838 in the EAG base-case).

Table 6.2: EAG base-case deterministic CE results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
12 SQ-Bet	9,710	22.66	19.38	-1,585	0	0.09	Dominant
ECM	11,294	22.66	19.29				

Based on economic model after clarification.[47]
CE = cost-effectiveness; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 6.3: EAG base-case disaggregated cost results (discounted)

	12 SQ-Bet (£)	ECM (£)	Increment (£)
12 SQ-Bet treatment and administration	2,596	0	2,596
Pharmacotherapy	82	106	-24
Primary care	1,552	2,484	-932
Secondary care	5,469	8,704	-3,235
Adverse events	12	1	11
Total costs	**9,710**	**11,294**	**-1,585**

Based on economic model after clarification.[47]
EAG = External Assessment Group; ECM = established clinical management

6.2.2 Results of the EAG sensitivity analyses

Table 6.4 shows the results of the probabilistic EAG base-case (discounted), which are comparable to the EAG base-case results. The CE-plane presented in Figure 6.1 shows that most of the simulations (85%) fall within the South-East quadrant, with a smaller proportion in the North-East quadrant. This suggests that 12 SQ-Bet is both less costly and more effective than ECM. Based on the CEAC (Figure 6.2), the probability that 12 SQ-Bet is cost-effective at a WTP threshold of £20,000 per

QALY gained is 99%. At a threshold of £30,000 per QALY gained, the estimated probability that 12 SQ-Bet is a cost-effective alternative to ECM increases to 100%.

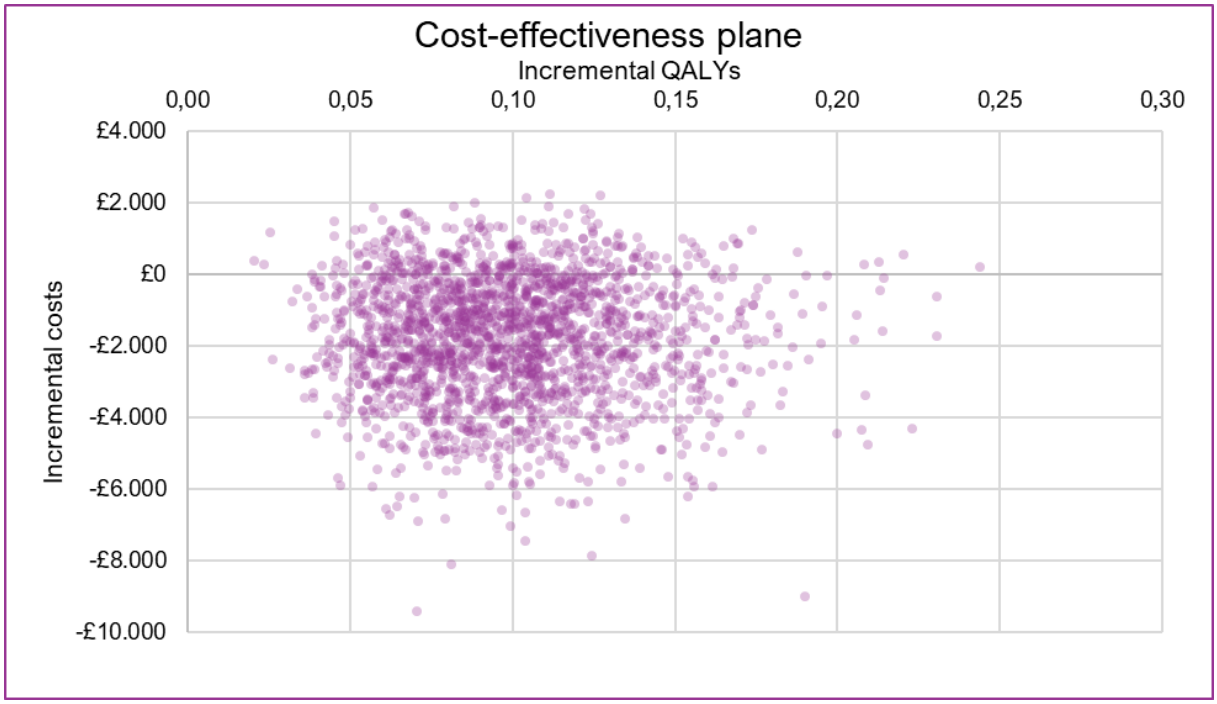
Table 6.4: EAG base-case probabilistic CE results (12 SQ-Bet, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
12 SQ-Bet	9,524	22.66	19.38	-1,796	0	0.10	Dominant
ECM	11,320	22.66	19.28				

Based on economic model after clarification.[47]

CE = cost-effectiveness; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

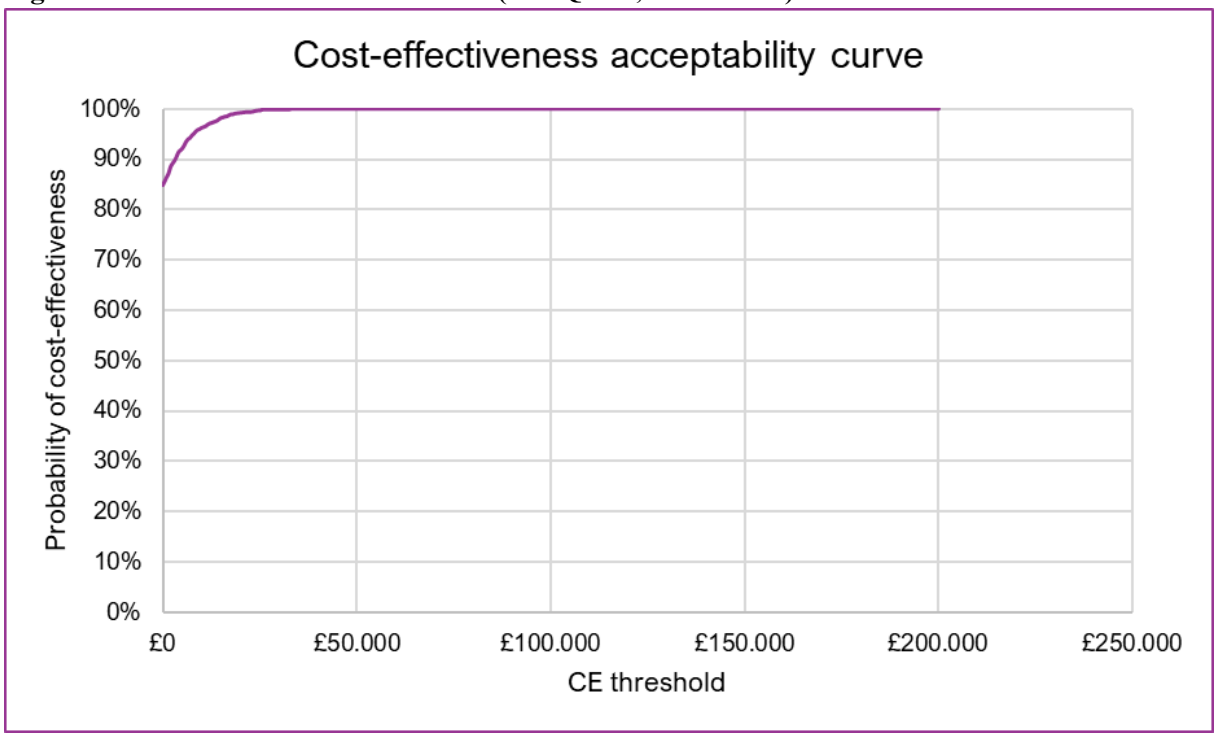
Figure 6.1: EAG base-case PSA CE-plane (12 SQ-Bet, discounted)



Based on economic model after clarification.[47]

CE = cost-effectiveness; EAG = External Assessment Group; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 6.2: EAG base-case PSA CEAC (12 SQ-Bet, discounted)



Based on economic model after clarification[47]
CE = cost-effectiveness; CEAC = cost-effectiveness acceptability curve; EAG = External Assessment Group; PSA = probabilistic sensitivity analysis

6.2.3 Results of the EAG additional exploratory scenario analyses

The results of the EAG scenario analyses are provided in Table 6.5. These results are all conditional on the EAG base-case settings. The scenario analyses conducted by the EAG indicated that in general the results were not sensitive to the changes explored since in most scenarios 12 SQ Bet remained dominant compared to ECM. In all scenarios the incremental QALYs are positive. This is not surprising given that the company have implemented the utility for ECM as a disutility applied to the 12 SQ Bet utility. Since the disutility associated to AEs has been either ignored, or when included in the model the impact was negligible, it can be assumed that there is always a QALY benefit associated to 12 SQ Bet compared to ECM and, therefore, the ICER is expected to be in the Eastern quadrants of the CE-plane. The majority of the costs savings associated with 12 SQ Bet are obtained due to a reduction in both GP and outpatient visits. This reduction is modelled as RRs. When these RRs are large enough (as it happens in all plausible scenarios) the costs savings outweigh the additional acquisition costs due to 12 SQ Bet treatment, and therefore, there is dominance.

The "extreme" scenarios explored by the EAG resulted in no apparent errors observed in the model engine. For a hypothetical 100% discontinuation rate due to AEs at year 1 the ICER was £86,468 per QALY gained, as shown in Table 6.5.

When the discontinuation rates for other reasons were 50% at year 1, or 50% at year 1 and year 2, 12 SQ Bet was still dominant. The EAG observed that even a 100% discontinue at year 1 was assumed, 12 SQ Bet would remain dominant. This is because in the way the model is implemented, there is still a small proportion of patients who discontinue due to AEs at year 1 and half of them still get benefit a treatment benefit.

The scenarios considering “extreme” resource use estimates associated with the management of patients in primary and secondary care can have a large impact on the model results, as expected, but most likely in implausible scenarios. This was more evident for secondary visits, since assuming no difference between 12 SQ Bet and ECM in terms of GP visits, would still result in 12 SQ Bet being dominant, as can be seen in Table 6.5. When no difference in outpatient visits was assumed the ICER was £18,190 per QALY gained, and when no difference was assumed in both types of visits the ICER was £28,466 per QALY gained.

Table 6.5: Results of exploratory scenario analyses by the EAG (discounted)

Scenario	EAG assumption	Scenario assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
EAG base-case			**-1,585**	**0.0907**	**12 SQ-Bet dominant**
Discontinuation rates due to AEs	7.5%	0%	-1,737	0.0978	12 SQ-Bet dominant
		100%	292	0.0034	86,468
Discontinuation rates due to other reasons	8% year 1, 10% years 2 and 3	50%-year 1	-1,319	0.0674	12 SQ-Bet dominant
		50%-year 1 and year 2	-1,101	0.0556	12 SQ-Bet dominant
Treatment effect after discontinuation	35%	0%	-1,176	0.0818	12 SQ-Bet dominant
Waning proportion	2.5% increase per year	0%	-1,070	0.0794	12 SQ-Bet dominant
Compliance	Not considered	Assume 50% reduction in benefit while keeping the same costs	-1,585	0.0452	12 SQ-Bet dominant
Mortality	Life tables before COVID-19	Life tables after COVID-19	-1,577	0.0904	12 SQ-Bet dominant
Adverse events	First year only	While on treatment	-1,570	0.0906	12 SQ-Bet dominant
	AE disutility in year 1	No AE disutility	-1,585	0.0911	12 SQ-Bet dominant
General population utilities	Hernandez-Alava	Ara and Brazier	-1,585	0.0907	12 SQ-Bet dominant
Resource use disease management	GP visits RR = 61.7% Outpatient visits RR = 61.1%	GP RR = 0%	-652	0.0907	12 SQ-Bet dominant
		Outpatient RR = 0%	1,650	0.0907	18,190
		GP RR = 0% Outpatient RR = 0%	2,853	0.0907	28,466
		TA834	-2,831	0.0907	12 SQ-Bet dominant

Based on economic model after clarification.[47]

AE = adverse event; COVID-19 = coronavirus disease 2019; EAG = External Assessment Group; GP = General Practitioner; ICER = incremental cost-effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year; RR = relative risk; TA = Technology Appraisal

6.3 EAG's preferred assumptions

The step-by-step changes made by the EAG to derive its base-case can be seen in Table 6.6. Overall, all changes included in the EAG base-case had a minimal impact on the model results and did not affect the company's general conclusions regarding cost-effectiveness.

Table 6.6: Individual impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
12 SQ-Bet	9,486	19.34	-1,853	0.1012	Dominant
ECM	11,339	19.24			
Company base-case after clarification					
12 SQ-Bet	9,408	19.31	-1,846	0.1010	Dominant
ECM	11,253	19.21			
EAG change 1 – 8% of patients discontinue treatment for other reasons in year 1, and 10% in year 2 and 3					
12 SQ-Bet	9,502	19.31	-1,751	0.0946	Dominant
ECM	11,253	19.22			
EAG change 2 – 35% of patients receive treatment benefit after discontinuation					
12 SQ-Bet	9,494	19.31	-1,759	0.0991	Dominant
ECM	11253	19.22			
EAG change 3 – life tables based on 2016-2018 (before COVID-19)					
12 SQ-Bet	9,440	19.38	-1,885	0.1014	Dominant
ECM	11,294	19.28			
EAG change 4 – AE-related utility decrement (-0.02) for each of the AEs for the first year of treatment					
12 SQ-Bet	9,408	19.32	-1,846	0.1014	Dominant
ECM	11,253	19.21			
EAG's base-case					
12 SQ-Bet	9,710	19.38	-1,585	0.0907	Dominant
ECM	11,294	19.29			

Based on the model submitted following the clarification.[47]
AE = adverse event; COVID-19 = coronavirus disease 2019; CS = company submission; EAG = External Assessment Group; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

6.4 Conclusions of the CE Section

The CS, Appendices E and F, and response to clarification[1, 5, 9, 22] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in birch pollen-induced SAR. Searches were conducted in May to July 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, HTA websites and other grey literature resources were searched. Overall, the EAG has no major concerns about the literature searches conducted. Since no economic models to address

the current DE were identified by the company, a de novo model was built, which complied with the NICE reference case.

The CE-specific key issue highlighted by the EAG throughout this report (and summarised in Table 6.1) was the uncertainty in parameters estimated from clinical experts (some of them might have a major impact on the model results).

There are several minor concerns regarding assumptions on discontinuation rates due to AEs (whether these should be applied during the first year only or not), whether discontinuation rates for other reasons as observed in the trial are representative of clinical practice, whether compliance/persistence should be incorporated in the economic analyses or whether AE disutilities should be applied to the model. However, all these have been shown (through scenario analyses) or are expected to have a minimal impact on the model results.

An overall EAG concern in this submission regarding the definition of the population included in the economic analyses, can obviously have implications for the CE analyses. Likewise, if SCIT is a relevant comparator, it should have been included in the CE analyses and results should have been presented in a full incremental way (considering both ECM and SCIT as comparators).

In the original model the company made an error in column W of the model engine which was amended by the company in the model version submitted together with the response to the clarification letter. The company presented updated base-case results reflecting other model changes as requested by the EAG. These changes included using updated life tables and general population utilities. The company's base-case deterministic CE (discounted) results for 12 SQ-Bet compared to ECM indicated that 12 SQ-Bet was less costly and more effective than ECM; 12 SQ-Bet was thus dominant. Incremental QALYs for 12 SQ-Bet were 0.10 and incremental costs were -£1,845. The average PSA results were in line with the deterministic ones where 12 SQ-Bet was still dominant compared to ECM. The company also plotted the PSA outcomes on a CE-plane and all outcomes reported positive incremental QALYs for 12 SQ-Bet versus ECM. Cost outcomes were spread across North-East and South-East quadrants. From the PSA results, a CEAC was also calculated indicating that at the common threshold of £20,000 per QALY gained, the estimated probability that 12 SQ-Bet is a cost-effective alternative to ECM was 100%. The company's DSA showed that the INMB was most sensitive to the number and relative reduction of annual outpatient visits, utility gain, secondary care costs and the number and relative reduction of annual GP visits. At a WTP threshold of £20,000/QALY, the INMB was always positive. The company's scenario analyses showed that most assumptions explored had a minor impact on the model results, with all scenarios resulting in 12 SQ Bet being dominant, in an ICER well below £20,000 per QALY gained compared to ECM.

The EAG defined a new preferred base-case by:

1. Assuming higher discontinuation rates (due to other reasons) than those observed in the TT-04 trial. In particular, the EAG assumed that 8% of patients would discontinue treatment for other reasons in year 1, and 10% would discontinue treatment after 2 and 3 years.
2. For the proportion of patients receiving benefit after discontinuation, the EAG assumed an estimate based on the responses from the three clinical experts consulted by the company (instead of just two). For the clinician who said this proportion would be a small number of patients, the EAG arbitrarily assumed 5%, resulting in a total of 35% of patients receiving treatment benefit after discontinuation.
3. Selecting life tables (before COVID-19) based on 2016-2018.

4. Using AE-related utility decrements for the first year of treatment. An arbitrary disutility of -0.02 for each of the AEs was assumed for the EAG base-case.

The results of the EAG's base-case analysis indicated that 12 SQ-Bet was still dominant compared to ECM. Compared to the company's base-case (after clarification), costs savings were reduced by £260, and the incremental QALYs decreased by 0.01. The EAG's average PSA results were comparable with the EAG base-case results. The CE-plane, CEAC and tornado diagram derived from the EAG base-case were similar to those presented by the company and the same conclusions can be extracted. The results of the scenario analyses conducted by the EAG indicated that in general the results were not sensitive to the changes explored since in most scenarios 12 SQ Bet remained dominant compared to ECM. In all scenarios the incremental QALYs are positive, which is not surprising given that the company have implemented the utility for ECM as a disutility applied to the 12 SQ Bet utility. Since the disutility associated to AEs is either ignored, or has a negligible impact, it can be assumed that there is always a QALY benefit associated to 12 SQ Bet compared to ECM and, therefore, the ICER is expected to be in the Eastern quadrants of the CE-plane. The majority of the costs savings associated with 12 SQ Bet are obtained due to a reduction in both GP and outpatient visits. This reduction is modelled as RRs. When these RRs are large enough (as it happens in all plausible scenarios) the costs savings outweigh the additional acquisition costs due to 12 SQ Bet treatment, and therefore, there is dominance. Only in "extreme" scenarios regarding discontinuation rates due to AEs (at year 1), discontinuation rates for other reasons or resource use estimates associated with the management of patients in primary and secondary care, 12 SQ Bet was not dominant, or resulted in an ICER above £20,000 per QALY gained compared to ECM.

7. References

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Single Technology Appraisal

Betula verrucosa (Itulazax 12 SQ-Bet) for treating moderate to severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen [ID6462]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **22 April 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 EAG key issue 6 – incorrect interpretation of implementation of long-term effectiveness assumptions as an error

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Key Issue 6, described in full in Section 4.2.6.2 (Page 68), and referenced multiple times throughout the EAG report. The EAG have incorrectly interpreted the implementation of long-term treatment effect assumptions in the model as an error, specifically the improving treatment benefit (increasing by 2.5% in each model cycle up to Year 10) leading to values above 1 in column AB of the model engine (the EAG state these to be invalid intermediate results).	The company propose that the EAG remove this as an issue as well as any description of this implementation being an error or leading to invalid intermediate results. The EAG's base case should also be updated.	Column AB in the model engine allows for changes in the treatment benefit observed within the trial period to change over time. Treatment effect in the model is applied as a disutility (and resultant annual QALY decrement) to the SoC arm, using mean utility differences derived from Dick et al., 2020. These mean utility differences represent the average treatment effect within the TT-04 trial period for the full analysis set (i.e., 100% of the modelled population). The values in column AB represent a transformation factor that is applied to the annual QALY decrement in a multiplicative way. For example, a value of 1 in column AB in a given cycle means that the annual QALY	The EAG agrees with the company. The issue has been removed from the revised EAG report and the EAG base case updated accordingly.

		decrement reported in Dick et al., 2020 is applied in that cycle i.e., the within-trial treatment effect is applied. A value less than 1 in a given cycle means that an annual QALY decrement less than that reported in Dick et al., 2020 is applied in that cycle, representing waning or loss of treatment effect due to discontinuation (relative to the within-trial treatment effect), over time. Oppositely, a value above 1 in a given cycle means that an annual decrement greater than that reported in Dick et al., 2020 is applied in that cycle, representing an increase in the treatment effect (relative to the within-trial treatment effect) over time. Therefore, to most accurately model the long-term effectiveness of 12 SQ-Bet and reflect the improvement in treatment effect over time	

		observed in the REACT study, and implemented in the committee's preferred model base case in TA1045, it is necessary to allow the values in column AB to be greater than 1 such that a treatment effect greater than that observed within the TT-04 trial period can be modelled in any given cycle.	

Issue 2 Impact of treatment compliance on costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.1.2 (Page 66) The EAG state: *"Modelling less compliance would mean less benefit at equal costs, but also less AEs."*	The company suggest amending this statement to "*Modelling less compliance would mean less benefit, with lower costs, and fewer AEs."*	Patients who are less compliant would visit the pharmacy less frequently due to accumulation of drug stock due to missed doses. Therefore, drug acquisition costs incurred over a given period would also be reduced.	The EAG made the requested change.

Issue 3 Details of studies excluded from SLR because of being a non-English language publication with a non-English abstract

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.1.2 (Page 25) The EAG state: *"However, the company did not provide specific details of the excluded studies and therefore it was not possible for the EAG to determine the impact of these omissions on HRQoL and utility estimates. This means that the potential impact of language bias cannot be discounted."*	This statement should be removed from the report.	A full list of studies and their reason for exclusion are provided in Appendix F (SLR report – Appendix C) of the CS, detailing the 3 studies excluded due to being a non-English language publication with a non-English abstract. The omission of these studies was also discussed in response to clarification question B5. The EAG can determine the impact of their omission further by looking at the 3 studies for which references were provided in Appendix F of the CS and in response to clarification question B5.	Details of the three studies excluded for *"being a non-English language publication with a non-English abstract"* were provided in Appendix F as well as in response to the request for clarification. The text *"However, the company did not provide specific details of the excluded studies and therefore it was not possible for the EAG to determine the impact of these omissions on HRQoL and utility estimates. This means that the potential impact of language bias cannot be discounted."* was replaced by *"All three references did provide an*

			English language abstract but did not report outcomes related to the intervention of interest thus the EAG agreed with the exclusion of these studies".

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
No issues identified	NA	NA