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

For public – confidential information redacted [redacted]

Technology appraisal committee B – streamlined meeting [10 June 2025]

Chair: Dr Charles Crawley

Lead team: Vanessa Danielson, Professor David McAllister, Nigel Westwood

External assessment group: Kleijnen Systematic Reviews

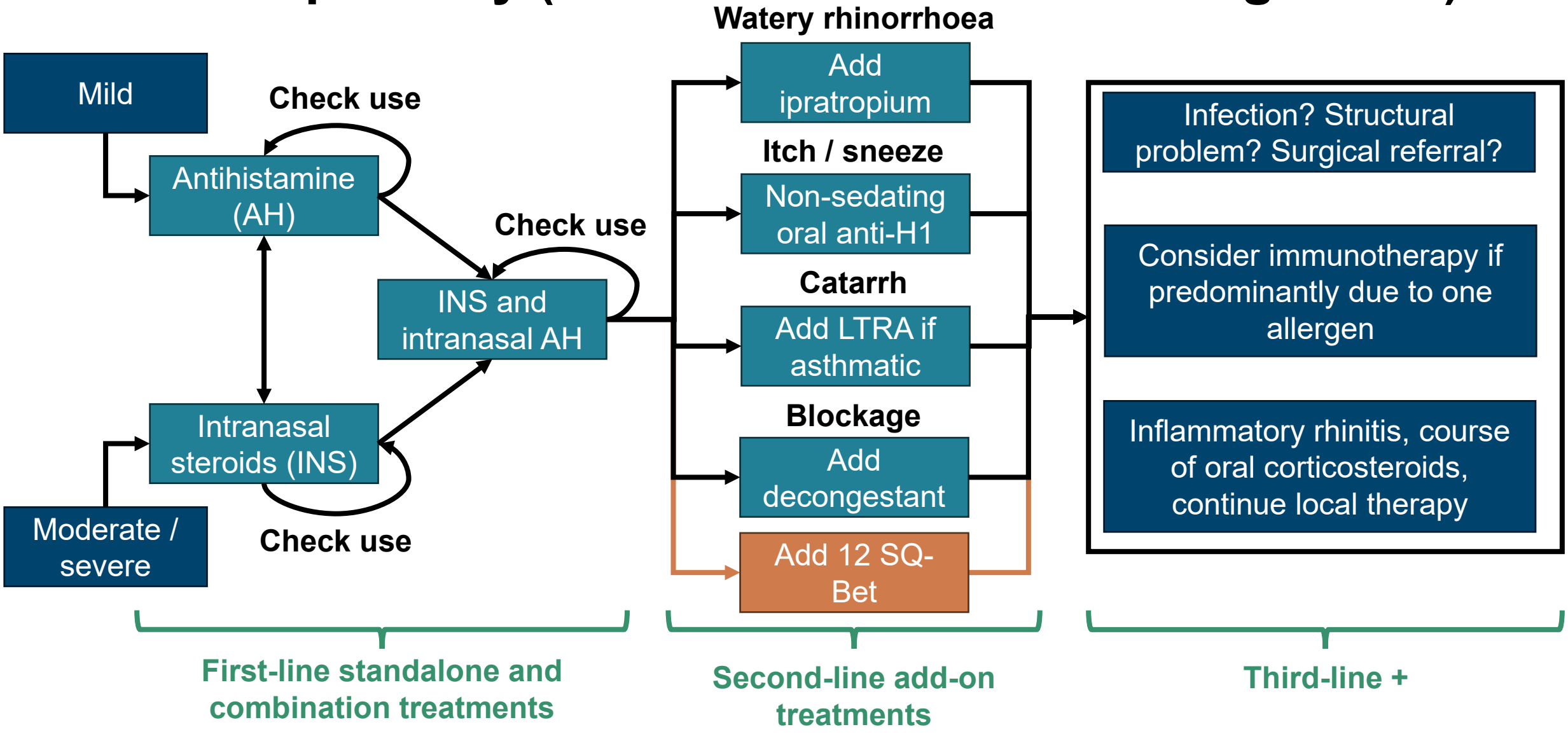
Technical team: Owen Swales, Vicky Kelly, Emily Crowe

Company: Alk-Abelló

Technology (ITULAZAX 12 SQ-Bet, Alk-Abelló)

Marketing authorisation	• Indicated in adult patients for the treatment of moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group • 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) • Birch homologous group: Betula verrucosa (birch), Alnus glutinosa (alder), Carpinus betulus (hornbeam), Corylus avellana (hazel), Quercus alba (oak) and Fagus sylvatica (beech) • UK MHRA marketing authorisation was granted on 9th June 2024
Mechanism of action	• Allergy immunotherapy • Exact mechanism of action not fully understood, but studies show immunological response is characterised by an induction of allergen specific IgG4 which competes with IgE for the binding to allergens, and thereby reduces activation of immune cells
Administration	• One sublingual dose daily, initiated outside the pollen season and continued during the tree pollen season – first dose taken under medical supervision
Price	• List price £80.12 per pack of 30 tablets • Patient access scheme not applicable

Treatment pathway (BSACI rhinitis treatment algorithm)



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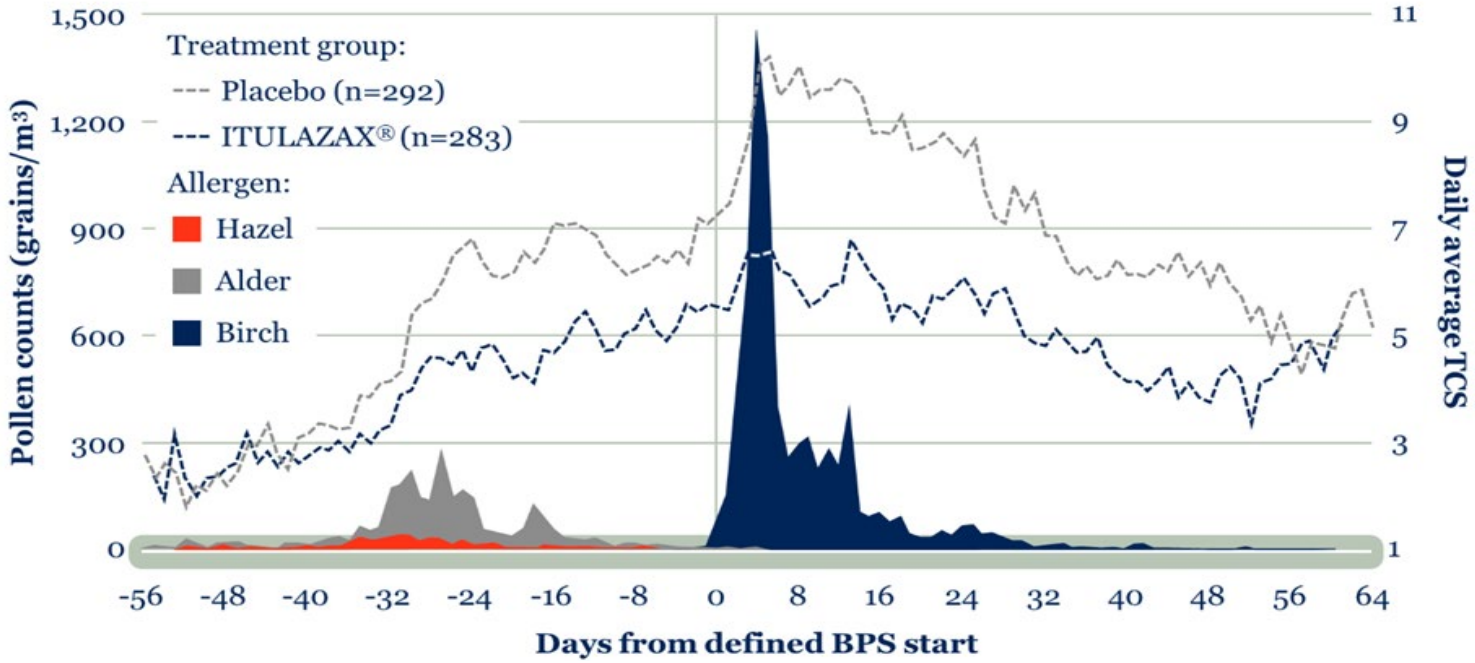
Abbreviations: AH, antihistamine; BSACI, British Society for Allergy & Clinical Immunology; H1; H1 receptor; LTRA, Leukotriene Receptor Antagonists; INS, intranasal steroids

Key clinical trial results – TT-04

12 SQ-Bet reduces TCS vs placebo when added to symptom relieving medication

Average daily pollen counts and average TCS during the birch pollen season



TCS: total combined score
BPS: birch pollen season

TCS = sum of the average **daily symptom score** and average **daily medication score**. Symptom score included 4 rhinitis symptoms and two conjunctivitis symptoms rated daily on a scale of 0 to 3. Medication was assigned a score per dose, depending on the medication used.

TCS during the birch pollen season (BPS) in different analysis sets

Trial arm	N	Adjusted mean	Absolute difference	% change [95% CI]	p-value
TCS during the BPS (full analysis set with observations during BPS)					
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 (per protocol population)					
Placebo	247	7.63	-	-	-
12 SQ-Bet	235	4.35	3.27 [2.17, 4.38]	42.90 [31.11, 53.12]	<0.0001

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Areas of uncertainty

EAG report key issue	Summary of EAG concern	ICER impact
Definition of population of interest is ambiguous	• Clearer definitions of population of interest and line of treatment would decrease ambiguity as well as heterogeneity	Unknown
Omission of immunotherapy as a comparator	• EAG expert notes 30 to 40% of people with moderate-to-severe AR, conjunctivitis, or both, would have immunotherapy	Unknown
Generalisability of trial findings to patients in NHS	• Lack of subgroup analyses for people sensitised specifically to oak and beech pollen (species which are highly relevant in UK) • Reliance on immunological markers rather than clinical outcomes	Unknown
Adverse events	• More AEs in intervention arm than placebo arm, some AEs led to discontinuation, [redacted]	None
Uncertainty in resource use estimated from experts	• EAG expert unable to verify reduction in GP and secondary care visits associated to 12 SQ-Bet compared to ECM	Large

Abbreviations: AE, adverse event; AR, allergic rhinitis; ECM, expected clinical management

Uncertainty: definition of population of interest

EAG concern

- Company defines AR as moderate-to-severe based on criteria in ARIA guideline, but details are limited
- Final scope defines population as adults with AR or allergic conjunctivitis but company refer to allergic rhinoconjunctivitis as a combined condition
- Birch homologous group includes a range of species, not all of which are included in the efficacy analysis
- Line of therapy is unclear, company say used in second line, but later use possible

4 clinical experts (in response to technical team questions)

- Moderate-to-severe allergic rhinitis AND conjunctivitis is essentially one condition (rhinoconjunctivitis)
- Patients simply differ in the extent to which they have more predominant nasal or eye symptoms
- Allergic rhinitis and conjunctivitis very often overlap, either should be eligible for this treatment
- 12 SQ-Bet would be used after pharmacotherapy (antihistamines, nasal sprays, eye drops etc) have been tried and failed (so used in third, fourth, last line)
- But 12 SQ-Bet is not a substitute for pharmacotherapy and should be used in combination with standard treatments; usage of combination treatments maybe reduced over time

Is the modelled line of therapy appropriate? Is the modelled population appropriate?

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Abbreviations: AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma

Uncertainty: immunotherapy as a comparator

Is the modelled comparator appropriate?

EAG concern

- Final scope includes comparator as ECM which includes Pollinex trees but company omits immunotherapy
- EAG expert notes 30 to 40% of people would have immunotherapy

4 clinical experts (in response to technical team questions)

- 2 experts estimate immunotherapy usage at below 5%, 1 expert estimates around 10%, 1 expert estimates immunotherapy usage would be high in specialist care but notes this is a restricted and selective population
- 1 expert notes that pollinex trees are not used in clinical practice due to limited efficacy evidence
- Another notes that service provision is extremely limited and very few patients have immunotherapy
- 1 expert says UK uses immunotherapy about 100-fold less than other countries
- All experts believe 12 SQ-Bet is at least as effective as immunotherapy, likely more effective

NICE technical team

- Even if immunotherapy is a comparator, efficacy estimates show that a conservative assumption would be to assume equal efficacy with 12 SQ-Bet (so a cost comparison)
- 12 SQ-Bet costs £80.15 a month
- Pollinex trees costs £225 a month (£450 for 4 x 2-weekly vials, £128 discounted monthly cost cited here)
- Allegrovit (off-label but usage mentioned by experts) cost is unknown, but price match with Pollinex here
- 12 SQ-Bet drug costs are cheaper than immunotherapy, and admin and monitoring costs will be cheaper
- An ICER less than £20k is likely even if immunotherapy is estimated to have better efficacy than 12 SQ-Bet

Abbreviations: ECM, expected clinical management

Uncertainty: trial generalisability

EAG concern

- Lack of subgroup analyses for people sensitised specifically to oak and beech pollen (species which are highly relevant in UK) and reliance on immunological markers rather than clinical outcomes

4 clinical experts (in response to technical team questions)

- Pollen of oak and beech trees are highly cross-reactive with silver birch pollen, meaning that a patient sensitised to one species is sensitised to the others
- In clinical practice, do not see patients who are exclusively sensitised to oak and/or beech trees
- Decision to offer immunotherapy is not usually based on investigations to that level of tree pollen specificity, due to the cross-reactivity between the tree species
- Would expect 12 SQ-Bet to have an effect against the other tree species, due to cross-reactivity in pollen
- Results of TT-04 are generalisable to people sensitised to oak and beech because these people are also birch sensitised given the very high cross-reactivity, treatment will have protective effects against all

Are the trial results and modelled efficacy generalisable to the NHS?

Uncertainty: adverse events

EAG concern

- More AEs in intervention arm than placebo arm, some AEs led to discontinuation
- [redacted]

4 clinical experts (in response to technical team questions)

- Do not have side effects concerns that would prevent from recommending treatment
- Local oral reactions occur and are expected but of no clinical significance
- Have had a few patients who suspend treatment due to oral itching but side effects are not dangerous
- People who suspended treatment continued with a lower dose until local reactions reduced (off label use)
- Benefit of 12 SQ-Bet over alternatives is the greatly reduced risk of systemic reactions/anaphylaxis - a much more serious concern than the local side effects
- Would naturally stop treatment if significant uncontrollable oral side effects

Does the lead team have any concerns about adverse events?

Abbreviations: AE, adverse event; AR, allergic rhinitis

Uncertainty: resource use

EAG concern

- Company estimated 2.61 annual GP visits for ECM and 1.00 for 12 SQ-Bet (61.7% reduction)
- Company estimated 1.93 annual secondary care visits for ECM and 0.75 for 12 SQ-Bet (61.1% reduction)
- EAG expert unable to verify reduction in resource use visits but agreed there would be a reduction

4 clinical experts (in response to technical team questions)

- Expert 1: 70% reduction in secondary care visits due to no need to attend for injections, 50% reduction in GP visits (a guess)
- Expert 2: 70 to 80% reduction in visits but note that follow up visits are needed to check adherence
- Expert 3: 12 SQ-Bet would need 2 visits plus virtual consults, other treatments need 40 clinic visits
- Expert 4: depends on the context and whether immunotherapy is already offered in the setting, difficult to quantify

What are reasonable assumptions for resource use on GP and secondary care visits?

Abbreviations: ECM, expected clinical management

Proposed recommendation

1.1 **Betula verrucosa (Itulazax 12 SQ-Bet) is recommended, within its marketing authorisation, as an option for treating moderate to severe allergic rhinitis, conjunctivitis, or both, caused by tree pollen in people:**

- **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).**

Cost-effectiveness results

NICE National Institute for Health and Care Excellence

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Treatment discontinuation due to other reasons	4.38% discontinue in model years 1, 2 and 3 based on TT-04 trial data	8% discontinue treatment for other reasons in year 1, and 10% discontinue treatment after 2 and 3 years
Treatment benefit after discontinuation	50% of patients would receive treatment benefit after discontinuation	35% of patients would receive treatment benefit after discontinuation
Life tables	Life tables (after COVID-19) based on 2021-2013	Life tables (before COVID-19) based on 2016-2018
AE utility	No utility decrement for AEs	Arbitrary -0.02 decrement for each AE for first year of treatment

Abbreviations: AE, adverse event

Company base case results

Deterministic incremental base case results (post clarification)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
12 SQ-Bet	9,408	22.58	19.31	-1,846	0	0.10	Dominant
ECM	11,253	22.58	19.21				

Probabilistic incremental base case results (post clarification)

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				

Abbreviations: ECM, expected clinical management; LYG, life years gained; QALYs, quality adjusted life years

Company deterministic scenario analysis

Scenario number	Scenario description	Base-case assumption	Inc. Costs (£)	Inc. QALYs	ICER
Base-case	N/A	N/A	-1,845	0.10	Dominant
Time horizon	10 years	Lifetime	29	0.06	£469
	20 years		-1,382	0.09	Dominant
Treatment waning	100% loss of treatment benefit after 15 years	Waning starts in year 15. By year 20, 80% in the 12 SQ-Bet arm have lost benefit.	-880	0.08	Dominant
	Full treatment benefit for 20 years then 0%		-1,975	0.11	Dominant
12 SQ-Bet benefit after discontinuation	0% receive benefit after discontinuation	50% of patients assumed to experience benefits	-1,558	0.09	Dominant
	100% receive benefit after discontinuation		-2,133	0.11	Dominant
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
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 length of the full dataset from Dick et al. 2020 (137 days; mean daily utility difference: 0.018; annual QALY gain: 0.0068)	-1,838	0.08	Dominant
	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
Retreatment	Proportion retreated: 0%	5% of patients are retreated with 12 SQ-Bet after 10 years.	-1,779	0.10	Dominant
	Proportion retreated: 20%		-2,045	0.11	Dominant
	Proportion retreated: 50%		-2,444	0.13	Dominant

EAG base case results

Deterministic incremental base case results

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				

Probabilistic incremental base case results

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				

Abbreviations: ECM, expected clinical management; LYG, life years gained; QALYs, quality adjusted life years

EAG preferred assumptions

Changes from EAG to company base case

Individual EAG base case changes	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
Company base-case	-1,853	0.1012	Dominant
Company base-case after clarification	-1,846	0.1010	Dominant
8% of patients discontinue in year 1, and 10% in year 2 and 3	-1,751	0.0946	Dominant
35% of patients receive benefit after discontinuation	-1,759	0.0991	Dominant
Life tables based on 2016-2018 (before COVID-19)	-1,885	0.1014	Dominant
AE utility decrement (-0.02) for each AE for first year	-1,846	0.1014	Dominant
EAG base-case	**-1,585**	**0.0907**	Dominant

EAG deterministic scenario analysis

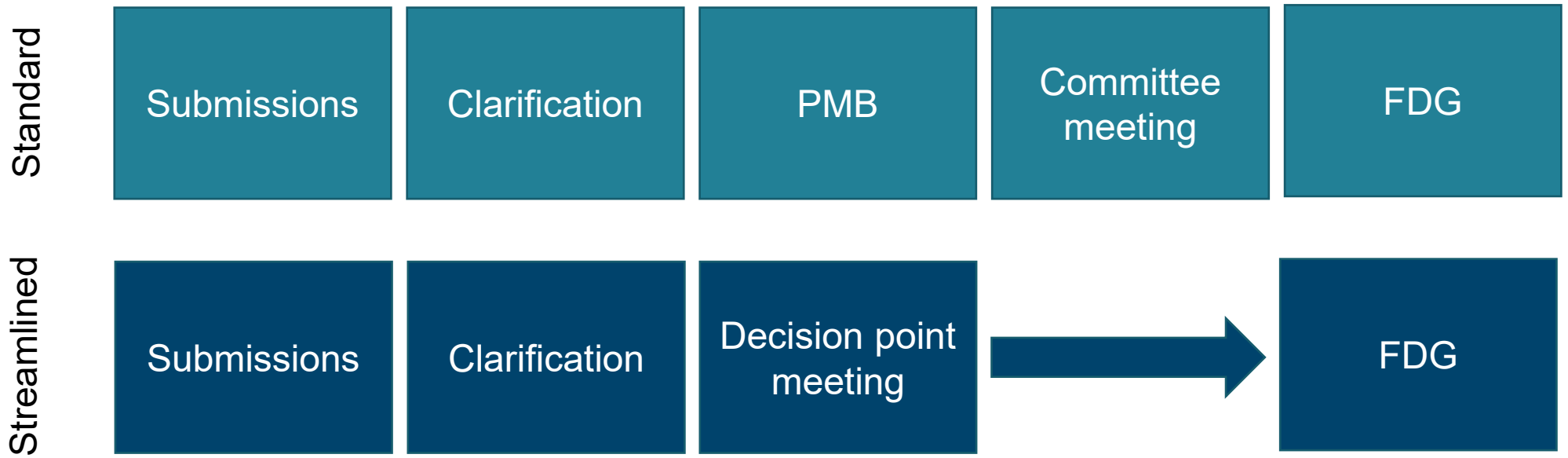
Scenario	EAG assumption	Scenario assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
EAG base-case			-1,585	0.0907	12 SQ-Bet dominant
Discontinuation rates due to AEs	7.5%	0%	-1,737	0.0978	12 SQ-Bet dominant
		100%	292	0.0034	86,468
Discontinuation rates due to other reasons	8% year 1, 10% years 2 and 3	50% in year 1	-1,319	0.0674	12 SQ-Bet dominant
		50% in year 1 and 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 a 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 pop utilities	Hernandez-Alava	Ara and Brazier	-1,585	0.0907	12 SQ-Bet dominant
Resource use disease management	GP visits RR = 61.7%	GP RR = 0%	-652	0.0907	12 SQ-Bet dominant
	Outpatient visits RR = 61.1%	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

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Process: streamlined approach



- Chair/lead team to confirm if they agree with the proposed streamlined process
  - If yes – NICE team to update committee and publish FDG
  - If no – NICE team to schedule full committee meeting
- If more time is needed for scrutinising the evidence before a decision, this is possible

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Abbreviations: FDG, final draft guidance; NICE, National Institute for Health and Care Excellence; PMB, pre-meeting briefing

Key clinical trial

	TT-04
Design	Randomised, double-blind, placebo-controlled, phase 3 trial
Population	634 adults and adolescents (12 to 65) 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.
Intervention	12 SQ-Bet + symptom relieving medication
Comparator	Placebo + symptom relieving medication
Duration	Treatment started at least 16 weeks before the TPS to the end of the TPS, average treatment between 6.5 and 9.5 months
Primary outcome	Average total combined score (TCS) of rhinoconjunctivitis symptoms and medication use during the birch pollen season
Locations	Czech Republic, Denmark, Finland, France, Germany, Poland, Russia, Sweden

Abbreviations: AR, allergic rhinitis; TCS, total combined score; TPS, tree pollen season