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HEALTH TECHNOLOGY BRIEFING
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Betula verrucosa for tree pollen allergy-induced moderate to severe rhinoconjunctivitis

NIHRIO ID	6491	**NICE ID**	9801
Developer/Company	Alk-Abelló Ltd	**UKPS ID**	43045

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Betula verrucosa is in clinical development for the treatment of adults with confirmed tree pollen allergy-induced moderate to severe rhinoconjunctivitis. Allergic rhinoconjunctivitis is an allergic disorder of the nose and resulting in a chronic, mostly eosinophilic, inflammation of the nasal mucosa and conjunctiva. When the conjunctiva is also involved, the term rhinoconjunctivitis is more accurate. This produces typical symptoms of sneezing, nasal itching, discharge (rhinorrhoea), and congestion.

Betula verrucosa is a sublingual allergy immunotherapy (SLIT) tablet indicated for the treatment of tree pollen allergy, because of its high degree of inhibition of the reaction caused by allergen extracts. As an immunotherapy, betula verrucosa offers the advantage of not just being symptomatic, but also inducing tolerance and so alters the natural course of the disease. If licensed, betula verrucosa will offer an

additional treatment option for patients with confirmed tree pollen allergy-induced moderate to severe rhinoconjunctivitis.

PROPOSED INDICATION

Betula verrucosa is indicated in adult patients for the treatment of moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group.[1]

TECHNOLOGY

DESCRIPTION

Betula verrucosa (ALK tree AIT, Itulazax) is a sublingual allergy immunotherapy (SLIT) tablet that contains an allergen extract for immunotherapy of tree (birch homologous group) pollen-induced allergic rhinitis and/or conjunctivitis. Allergy immunotherapy with allergen products is the repeated administration of allergens to allergic individuals with the purpose of modifying the immunological response to the allergen.[1]

The pharmacodynamic effects of allergy immunotherapy is exerted on the immune system, but the exact mechanism of action underlying clinical efficacy is not fully understood. However, several studies have shown that the immunological response to allergy immunotherapy is characterised by an induction of allergen specific IgG_4. Allergen-specific IgG_4 competes with IgE for the binding to allergens, and thereby reduces activation of immune cells. The reduction of IgE binding to birch allergen has been confirmed for subjects treated with Betula verrucosa and this was accompanied by induction of a treatment induced systemic IgG_4 response specific for birch. Extensive IgE cross reactivity was observed towards the birch homologous trees before treatment initiation, thus indicating allergic sensitisation to the trees in this group, and a comparable level of IgG_4 cross-reactivity towards the birch homologous trees was observed after treatment with Betula verrucosa. The increase in IgG_4 levels is observed after approximately 1 month of treatment and maintained throughout the treatment period. Treatment with Betula verrucose also results in a rise in serum levels of apple (Mal d 1) specific IgG_4.[1]

Betula verrucosa is currently in phase III clinical development for patients with confirmed tree pollen allergy-induced moderate to severe rhinoconjunctivitis. In phase III clinical trial (EudraCT 2015-004821-15), subjects were randomised to receive 1 daily tablet of either SQ tree SLIT tablet 12 IU or placebo for at least 16 weeks before the tree pollen season (TPS) and until the end of the TPS. Treatment duration was 6.5 to 9.5 months for subjects completing the trial.[2,3]

INNOVATION AND/OR ADVANTAGES

There are two ways of treating allergic rhinitis, symptomatic treatment and immunotherapy treatment. Both have been shown to provide relief and put an end to discomfort and feeling ill. The main difference between symptomatic and immunotherapy treatment is that immunotherapy induces tolerance and so alters the natural course of the disease.[4]

Betula verrucosa is a type of allergy immunotherapy which treats the underlying cause of allergy and may provide both improvement of symptoms within a few months and long-lasting improvement. This is in contrast to the usual symptomatic medications that are prescribed, such as antihistamines and corticosteroids, which only temporarily relieve the allergy symptoms while the medication is being taken.[4]

The main advantages of allergy immunotherapy are that it reduces symptoms, induces immunological tolerance, reduces use of symptomatic medications, has a persistent effect after end of treatment, prevents development of asthma symptoms, and prevents onset of new allergies.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

It 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).[1]

PATIENT GROUP

DISEASE BACKGROUND

Allergic rhinoconjunctivitis remains the most common immunological disease in man and is still subject to under-recognition and poor management. This matters because allergic rhinoconjunctivitis significantly reduces quality of life (QoL), interferes with both attendance and performance at school and work and results in substantioal societal costs. In addition, as the nose is the gateway to the respiratory tract, rhinitis is associated with symptoms in the eyes, sinuses, middle ear, the nasopharynx and lower airways.[6]

Rhinitis describes inflammation of the nasal mucosa but is clinically defined by symptoms of nasal discharge, itching, sneezing and nasal blockage or congestion. When the conjunctiva are also involved, the term rhinoconjuctivitis is more accurate.[6] Allergies are caused by an overreaction of the body's immune system to substances that in most cases would otherwise be harmless. Common triggers of respiratory allergic disease include pollens, house dust mites, moulds and animal dander.[7]

Allergic rhinitis is a frequent reason for visits in general practice and can decrease quality of life and lead to lower school and work performance. Furthermore, allergic rhinitis is a recognized risk factor for asthma development. Exposure to tree pollen is prominent across Europe and North America and reflected by a high prevalence of sensitization to tree pollen. Tree pollen–induced allergic rhinoconjunctivitis is commonly caused by allergens from the

birch-homologous group, which includes birch, alder, hornbeam, hazel, and oak. Pollens from these trees are characterized by having Betv 1–homologous allergens with high sequence identity, leading to extensive cross-reactivity and ultimately prolonging the season and extending the geographic area in which allergic reactions are triggered.[2]

CLINICAL NEED AND BURDEN OF DISEASE

The UK has some of the highest prevalence rates of allergic conditions in the world, with over 20% of the population affected by one or more allergic disorder. A staggering 44% of British adults now suffer from at least one allergy and the number of sufferers is on the rise, growing by around 2 million between 2008 and 2009 alone. Almost half (48%) of sufferers have more than one allergy.[8]

Allergic rhinitis is very common and affects 10-15% of children and 26% of adults in the UK. It can significantly affect quality of life, work and school performance and attendance, and is a risk factor for the development of asthma.[6]

In England, in 2019-2020, there were 2,974 finished consultant episodes (FCE) and 97 FCE bed days with a primary diagnosis of allergic rhinitis due to pollen (ICD 10: J30.1) leading to 2,961 hospital admissions, of which 2,795 were day cases.[9]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

It is difficult to completely avoid potential allergens, but people can take steps to reduce exposure to a allergen known or suspect is triggering the allergic rhinitis. This will help improve the symptoms.[10]

Treatment for allergic rhinitis depends on how severe the symptoms are and how much they are affecting the everyday activities. In most cases treatment aims to relieve symptoms, such as sneezing and a blocked or runny nose. Regularly cleaning nasal passages with a saltwater solution, known as nasal douching or irrigation, is also recommended to help relieve symptoms. Patients should visit the General Practitioner if the symptoms are more severe and affecting their quality of life, or if self-help measures have not worked.[11]

CURRENT TREATMENT OPTIONS

Among the therapeutic class available to treat the allergic rhinitis are antihistamines (tablet or nasal sprays), corticosteroids (nasal spray or drops, tablet), or immunotherapy (injection or tablet), also known as hyposensitisation or desensitisation, is another type of treatment used for some allergies.[11]

PLACE OF TECHNOLOGY

Betula verrucosa will offer an additional treatment option as third-line therapy for patients aged 18-64 years with confirmed tree pollen allergy-induced moderate to severe rhinoconjunctivitis.

CLINICAL TRIAL INFORMATION

Trial	EudraCT 2015-004821-15; Efficacy and safety of the SQ tree SLIT-tablet in subjects with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch group EudraCT 2015-004821-15 **Phase III, completed** **Location(s):** EU (not including the UK)
Trial design	Randomised, multicentre, double-blind, placebo-controlled study[2]
Population	n=634; adolescents and adults (12-65 years) with persistent moderate-to-severe allergic rhinoconjunctivitis induced by birch pollen, despite having received symptom-relieving medication during the 2 previous tree pollen season. Subjects had to have a positive skin prick test response (wheal diameter, ≥3 mm) to birch, a positive Bet v 1–specific IgE level (IgE class 2 or greater, ≥0.7 kU/L), and affected quality-of-life items (sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; or troublesome symptoms) because of allergic rhinoconjunctivitis during the previous birch pollen season.[2]
Intervention(s)	Participants have received the SQ tree SLIT-tablet, 12 IU once-daily for at least 16 weeks before start the TPS and until the end of the TPS.[2]
Comparator(s)	Placebo
Outcome(s)	Average daily allergic rhinoconjunctivitis total combined score (TCS) during the birch pollen season.[2]
Results (efficacy)	The primary and key secondary end points demonstrated statistically significant and clinically relevant effects of the SQ tree SLIT-tablet compared with placebo. For the birch pollen season, absolute (relative) differences from placebo were 3.02 (40%) for TCS, 1.32 (37%) for daily symptom score (DSS), and 1.58 (49%) for daily medication score (DMS) (all P< .0001). For the TPS, absolute (relative) differences from placebo were 2.27 (37%) for TCS, 0.99 (33%) for DSS, and 1.20 (47%) for DMS (all P< .0001).[2]
Results (safety)	Treatment was well tolerated. The most frequently reported treatment-related adverse events were mild or moderate local reactions related to sublingual administration.[2]

Trial	NCT01675791; A Dose-response Evaluation of ALK Tree AIT **Phase II, completed** **Location(s):** Finland and Netherlands
Trial design	Randomised, parallel assignment

Population	n=637; 12 years to 65 years; a history of moderate to severe birch pollen allergy; use of symptomatic medication for treatment of birch pollen allergy; positive skin prick test to birch extract; positive specific IgE against Bet v 1.
Intervention(s)	Participants were randomised to receive ALK tree AIT, administered sublingually every day in follow dosages: 0.5 DU, 1 DU, 2 DU, 4 DU, 7 DU, 12 DU
Comparator(s)	Placebo
Outcome(s)	Allergy symptom severity scores on a scale from 0-3 [Time frame: During the birch pollen season 2013, an expected average of 3 weeks] Adverse events frequency [Time frame: Throughout the trial, an expected average of 8 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of Betula verrucosa is no yet know.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance was identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance was identified.

OTHER GUIDANCE

- Allergic Rhinitis and its Impact on Asthma (ARIA). ARIA guideline 2019: treatment of allergic rhinitis in the German health system. 2019.[12]
- British Society for Allergy and Clinical Immunology (BSACI). BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). 2017.[6]
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ADDITIONAL INFORMATION

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