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Immunotherapy With the SQ Tree SLIT-tablet in Adults and Adolescents With Allergic Rhinoconjunctivitis

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ABSTRACT

Purpose: The SQ tree sublingual immunotherapy (SLIT)-tablet containing allergen extracts with the major allergen Bet v 1 from birch pollen is currently being developed for the treatment of tree pollen–induced allergic rhinitis/conjunctivitis with or without asthma. The aim of this Phase II trial was to investigate the dose-related efficacy and safety of the SQ tree SLIT-tablet.

Methods: This study was a randomized, parallel-group, double-blind, placebo-controlled, multi-national trial conducted in Europe. A total of 637 participants were randomized equally to receive placebo or treatment with the SQ tree SLIT-tablet in doses of 0.5, 1, 2, 4, 7, or 12 development units (DU). Treatment was initiated ~16 weeks before onset of the 2013 birch pollen season (BPS) and was continued throughout the BPS with a total duration of at least 6 months. During the BPS and tree pollen season (TPS), subjects assessed rhinoconjunctivitis symptoms and medication use on a daily basis in an electronic diary; weekly assessments of rhinoconjunctivitis quality of life were also made.

Findings: Analysis of the average daily symptom score during the BPS and the TPS showed that the difference between active treatment and placebo was statistically significant for the 7 DU group (BPS, $P = 0.02$; TPS, $P = 0.03$), with no clear dose–response relationship. All doses of the SQ tree SLIT-tablet induced changes from baseline in birch-specific IgE and IgG_4 that were statistically significant compared with placebo at all time points assessed ($P < 0.0001$) with a clear dose-response relationship for birch specific IgG_4. In general, the SQ tree SLIT-tablet was well tolerated, with the majority of treatment-related adverse events (≥95%) being mild or moderate in severity. The most frequently reported treatment-related adverse events were generally related to the sublingual administration of the tablet (ie, they occurred in the oral cavity).

Implications: The results from this trial suggest that the SQ tree SLIT-tablet in doses up to 12 DU has a tolerability profile suitable for at-home administration. The immunomodulatory changes indicate a dose–response relationship, but clinical efficacy parameters were inconclusive, probably due to low pollen counts, emphasizing the importance of pollen exposure for the outcome of a pollen allergy immunotherapy trial. EudraCT no: 2012-000031-59. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key Words: allergic rhinoconjunctivitis, birch pollen, clinical efficacy, immunology, sublingual immunotherapy tablet, tolerability.

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INTRODUCTION

Allergic rhinitis has been identified as one of the main reasons for visits to primary care clinics, and although usually not regarded as a severe disease, it may affect quality of life, social life, school learning performance, and work productivity, especially if the patient's symptoms are moderate to severe. Furthermore, allergic rhinitis is regarded as one of the major risk factors for the development of asthma, and >80% of patients with asthma have rhinitis, whereas 10% to 40% of people with rhinitis experience asthma.[1,2]

In Europe and North America, tree pollen–induced allergic rhinitis/rhinoconjunctivitis is commonly caused by allergens from the Fagales order, which includes, among others, birch, alder, hazel, and oak. They all belong to the birch homologous group and are characterized by having Bet v 1 homologous allergens with a high sequence identity, which leads to extensive cross-reactivity. Thus, patients who are sensitized to birch pollen often also experience symptoms in response to pollen from other members of the birch homologous group, which prolongs the season and extends the geographical area that can trigger allergic reactions for these patients.[3–5]

A large number of pollen-allergic individuals also develop allergic symptoms against certain foods such as nuts and apples. The symptoms are manifested as a condition called pollen food syndrome, and its occurrence typically involves presensitization to pollen allergens from the Fagales order. The condition is IgE-mediated and is caused by cross-reactive allergens.[6]

Recommendations for the treatment of allergic diseases are allergen avoidance, symptomatic medications such as antihistamines and corticosteroids, and allergy immunotherapy (AIT).[2] Avoidance of pollen can be difficult to achieve in a normal daily life, and allergy pharmacotherapy is widely used; however, it does not offer causal treatment of the allergic disease, and up to 44% of patients on optimal pharmacotherapy report poor or only partial symptom control.[7]

AIT is the only available treatment modality with the potential to modify the natural course of the allergic disease by induction of tolerance.[2] The use of pollen extract for AIT is well known, both in subcutaneous formulations[8–12] and as sublingual immunotherapy tablets or drops (SLIT-tablets/drops).[13,14] Birch pollen is recommended as a representative allergen source for AIT targeting allergies caused by pollen from the birch homologous group. This recommendation is based on results from in vitro inhibition studies in which birch pollen has shown a high degree of inhibition of human IgE binding to alder, hazel, and oak allergen extracts.[3,15,16]

Although the exact mode of action of SLIT has not been completely established, the downstream effects include induction of IgG_4 at the expense of IgE production. IgG_4 antibodies compete with IgE antibodies for the binding of allergen and thus block the cross-binding of immune cell–associated IgE.[17,18] Decreased allergen-specific IgE, as well as increased IgG_1 and IgG_4, have been shown to be hallmarks of efficacious SLIT.[17,19]

A tree pollen SLIT-tablet containing allergen extracts with the major allergen Bet v 1 from birch pollen is currently being developed by ALK (Hørsholm, Denmark) for the treatment of tree pollen–induced allergic rhinitis and/or conjunctivitis. The aim of the present Phase II trial was to investigate the dose-related efficacy and safety of the SQ tree SLIT-tablet not only during the birch pollen season (BPS) but also during other tree pollen seasons (TPSs) such as hazel and alder.

PATIENTS AND METHODS

Ethics

The trial was designed and conducted in accordance with the principles of the Declaration of Helsinki (1964, and its amendments and subsequent clarifications)[20] and was conducted in compliance with the principles of Good Clinical Practice.[21] The trial was approved by the local independent ethics committes/institutional review board and/or the health authority (as applicable) in each involved country before initiation.

Trial Design

This randomized, parallel-group, double-blind, placebo-controlled, multinational, multisite trial was conducted in Europe. The trial included 65 sites in 7 countries (Denmark, Finland, Lithuania, the Netherlands, Norway, Poland, and Sweden). A total of 637 participants were randomized equally to receive placebo or treatment with the SQ tree SLIT-tablet in doses of 0.5, 1, 2, 4, 7, or 12 development units (DU).