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Title: Is allergy immunotherapy with birch sufficient to treat patients allergic to pollen of tree species of the birch homologous group?

Short title:
AIT with birch against tree pollen allergy

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Abbreviations:
AIT, allergy immunotherapy; AR, allergic rhinitis; AR/C, allergic rhinitis/conjunctivitis; ARC, allergic rhinoconjunctivitis; BPS, birch pollen season; DSS, daily symptom score; DMS, daily medication score; EEC, environmental exposure chamber; IgE-BF, IgE blocking factor; NPT, nasal provocation test; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; TCS, total combined score; TPS, tree pollen season.

Abstract (word count: 200)

Pollen from various *Fagales* tree species prolong the season and make tree pollen allergy a major health problem. Despite involving the same causative allergens, allergy immunotherapy (AIT) treatment habits differ significantly across different geographical regions. Diagnosis and treatment with AIT in patients allergic to tree pollen were discussed by a group of German medical experts who give practical recommendations based on the available data.
Regulatory perspective: According to current guidelines on allergen products birch is the representative allergen source of the birch homologous group including several Fagales trees based on sequence and structural similarity of their allergen proteins.
Immunological perspective: A high level of IgE cross-reactivity towards allergens from the birch homologous group has been observed in basic research and clinical trials.
Clinical perspective: Clinical trial data show that the efficacy of birch AIT is not only related to birch pollen allergy but extends to other trees, especially alder, hazel and oak.
In order to optimise diagnosis and treatment of tree pollen allergy the experts recommend to focus diagnosis and respective treatment with AIT primarily to birch as the representative allergen of the Fagales tree homologous group, but further diagnostics may be needed for some patients to determine adequate treatment.

Main text: (word count: 4256)

1. Introduction

Birch pollen and pollen from other birch-related trees are one of the main allergen sources causing allergic rhinitis in northern and central Europe as well as in certain areas of North America [1]. In Central and Northern Europe, the season may start already from mid-December by pollination of hazel followed by alder with a peak for hazel and alder in February/March and followed by birch in April/May depending on the area, climate and weather conditions [2]. Birch pollen counts often reach up to 10-times the counts of alder and hazel thus making birch the main allergen source. Despite involving the same causative allergens, the treatment habits of the physicians differ significantly across different geographical regions [3]. While in Northern Europe, i.e. in the Scandinavian countries, allergy immunotherapy (AIT) is performed predominantly with allergen extracts from birch as birch monotherapy, in Germany, a mixture of allergen extracts of birch, alder and hazel (tree mix) is predominantly applied for AIT. Looking at these different diagnosis and treatment habits we aim to simplify diagnosis and treatment for the majority of patients. Thus, it is the objective of this review to explore and provide a clear recommendation for

diagnosis and treatment of birch-related tree pollen allergy based on regulatory, immunological and clinical considerations.

2. Regulatory perspective: The principle of homologous groups

The principle of homologous groups has been defined in the EMA/CHMP guidelines 2008 on the quality of allergen products for diagnostics and treatment and the clinical development of allergen products [4,5]. In the current guidelines from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) on allergen products [4] and their clinical development [5] the principle of homologous groups has replaced the previous purely botanical classification of allergen sources and this has also been implemented in the Therapy Allergens Ordinance ("Therapieallergene-Verordnung", TAV) from the German authority, the Paul-Ehrlich-Institut [6].

For tree species Lorenz et al. [7], proposed a homologous group for birch including the 5 members of the order Fagales, *Betula* (birch), *Alnus* (alder), *Corylus* (hazel), *Carpinus* (hornbeam), and *Quercus* (oak), with birch as the representative allergen species and this is the definition used in the current manuscript. The order Fagales comprises many additional species e.g. *Ostrya* (hop hornbeam), *Fagus* (beech) and *Castanea* (sweet chestnut), [2]. Thus, chestnut and beech have been suggested to belong to the birch homologous group as well [4].

The birch homologous group of trees is defined on the basis of structural homology of the respective major allergens, leading to considerable IgE cross-reactivity towards homologous allergens from birch related trees according to Lorenz [7]. Subsequently, data for quality, safety and efficacy of allergen products for the representative allergen source of a homologous group can be extrapolated to a limited extend to all members of this group [5].

Historically, allergen sources have been taxonomically classified (e.g. as mono- and dicotyledonous plants). The concept of homologous groups classifies allergen sources according to their structural similarity of allergen molecules. The EMA guideline on the quality of allergen extracts states that homologous groups should be characterised by comparable properties of the source material, cross-reactivity/structural homology of the allergens, identical formulation of the finished product, and identical production process of the allergen extract and of the finished product [4].

Allergen characterizations during the 1980's and 1990's identified the PR-10 like molecule, Bet v 1, as the major allergen in birch [8,9] and the introduction of molecular biology into the field of allergy [10,11] revealed that various birch related trees contained PR-10 like molecules with high sequence identity to Bet v 1 and very similar tertiary structures [12]. Birch, alder, hazel, and hornbeam were included in most investigations [9,10] whereas oak, beech [13], and especially

chestnut [14] has received less attention. The clinical relevance of birch, alder, hazel, and oak is obvious from clinical practice and has been demonstrated in clinical trials [13,15,16], whereas fewer data are available from trials or clinical practice for hornbeam, beech, and chestnut [13, 14]. These findings and the subsequent characterization of several minor allergens also shared between some or all of the birch-related tree pollen species [17] has been the foundation for the formation of the homologous group of birch-related trees [7]. Convincing evidence for the cross-reactivity was reported by Ipsen et al. [9] and Niederberger et al. [18] who also demonstrated that birch is the dominant common denominator based on IgE inhibition/depletion studies. IgE inhibition data for confirmation of cross-reactivity are not available from all geographical regions in either Europe or North America, but from Denmark (IgE, [9]), Austria (IgE, [18]) and Canada (IgE and treatment induced IgG_4, [19]); where this has been investigated in detail the immunological cross-reactivity has been fully confirmed. Thus, birch is the best characterized species in the birch homologous group with seven allergens identified and listed in the official 'International Union of Societies (IUIS)' list of allergens [20], including numerous isoforms and variants of Bet v 1, which is the obvious representative species for use in AIT for this homologous group.

In summary, the characterization of major allergens in the different allergen sources paved the way from the taxonomical classification towards a modern allergology based on similarity of the allergen molecules. The consequence was the updated EMA-guidelines, which became important for development of modern allergen products.

The principle of representative allergens has replaced the taxonomical classification for allergen sources in the guidelines facilitating characterization, standardization and production of allergen products and clinical development of allergen products from related allergen sources.

3. Immunologic perspective: Mechanism of action and cross-reactivity within homologous groups

AIT modulates the basic immunological mechanism of the allergic disease and is the only known treatment option with the potential to provide long-term, post-treatment benefits and alter the natural course of the allergic disease [21-24].

AIT induces immune tolerance to the allergen to which the patient is allergic, and the effects include induction of regulatory T-cells (Tregs) and a shift in the balance of allergen-specific T-helper 1 (Th1) and T-helper 2 (Th2) cytokine expression, as well as a change in the balance of allergen-specific antibody production [25].

From serological trials of AIT, it is known that clinically successful treatment is accompanied by an early but often transient increase in allergen-specific IgE in serum. In addition, an increase in allergen-specific IgG_4 in serum is a consistent finding, and the allergen-specific non-IgE

antibodies have been shown to inhibit binding of IgE to allergen in a competitive manner inhibiting IgE-mediated T-cell activation and basophil activation [26,27]. The inhibitory activity against allergen-specific IgE has been suggested as a clinically relevant measure of treatment induced immunological changes [27].

Trials with grass [23] and ragweed SLIT-tablets [28] have confirmed IgG_4 increases during treatment, similar to the changes seen for birch subcutaneous immunotherapy (SCIT), [29,30]. During the SQ tree sublingual immunotherapy (SLIT)-tablet clinical development program, serum samples were collected to evaluate allergen-specific immunological changes. Birch specific IgE, IgG_4 or IgE blocking factor (IgE-BF) were measured in all 4 clinical trials (TT-01, TT-02, TT-03 and TT-04). The IgE-BF assay measures IgE binding to allergen in competition with other allergen-specific antibody isotypes. The IgE-BF data supplement the data for IgG_4 and IgE titers with a readout that correlates with IgE-mediated T-cell activation and basophil activation and reflects the combined effect of changes in IgE and non-IgE (including IgG_4) during AIT. Furthermore, the TT-03 (phase II), [19] and TT-04 (phase III), [34] trials also included measurement of alder-, hazel- and oak-specific IgE and IgG_4, as well as correlation analyses for IgE (pre-treatment) and IgG_4 (end of treatment), [manuscript in preparation]. The objectives of the immunological analyses were to determine if the SQ tree SLIT-tablet has an effect on the immune response and if birch specific antibodies cross-react with allergens from trees belonging to the birch homologous group.

The results show that increases in allergen-specific IgE, IgG_4 and IgE-BF occur within the first month of treatment with the 12 SQ-Bet SLIT-tablet. Increases in IgG_4 and IgE-BF levels are maintained throughout the treatment period while IgE levels decrease towards the end of the trial. High levels of cross-reactivity of birch specific IgE towards allergens from the birch homologous trees (pearson correlation coefficients between 0.83 (birch/oak) and 0.98 (birch/alder)) were observed in both TT-03 and TT-04 before treatment initiation (confirmed by inhibition studies for alder, hazel, and oak), which strongly suggests that IgE sensitisation to birch will lead to symptoms when exposed to pollen allergens from the homologous trees as well. Moreover, an almost identical development in IgE responses towards birch, alder, hazel and oak during treatment supported that treatment with the SQ tree SLIT-tablet modulated the immune response to birch and the homologous trees to the same extent. This was further supported by similar changes in allergen-specific IgG_4 responses to birch, alder, hazel, and oak during treatment, as well as a strong cross-reactivity (pearson correlation coefficients between 0.72 (birch/oak) and 0.95 (birch/alder)), at the end of the treatment period, of birch specific IgG_4 (also confirmed by inhibition studies for selected species) towards allergens from the birch homologous trees, including beech but not chestnut, [19, 34, manuscript in preparation]. Similar results were

obtained for experiments with the SQ grass and ragweed SLIT-tablets suggesting that in general AIT with the representative species modulates the immune response to multiple related species [19,32].

In summary for these clinical trials, the cross-reactivity of IgE and IgG_4 towards pollen allergens from birch homologous trees observed during the SQ tree SLIT-tablet development program (including patients from several EU countries as well as Canada) fully support the use of birch as a representative allergen for the birch homologous group in line with similar findings for grass and ragweed AIT [32,33]. The maintained IgG_4 and IgE-BF response observed throughout the treatment period verifies that the SQ tree SLIT-tablet results in sustained immunological changes during treatment, similar to results from previous trials with subcutaneous birch AIT and the SQ grass SLIT-tablet [23,30,31].

For the latter, sustained clinical effect has been demonstrated up to 2 years after end of 3 years treatment, and the similarities in the immunological response to treatment between the SQ grass and tree SLIT-tablets may suggest a durable effect of treatment with the SQ tree SLIT-tablet as well [23,24].

IgE sensitization towards birch, alder, and hazel was also investigated in data from serum samples from allergic subjects, which were analysed for specific IgE against respiratory relevant allergens when received in the ALK serum bank during the course of several years. The subjects were from Northern and Central Europe and had previously been assessed by a clinician (allergologist) as suffering from IgE-mediated allergy determined by positive skin prick test (SPT) against one or more allergens and a case history of allergic symptoms. All available subjects analyzed for IgE towards birch and alder and/or hazel were included in the study population. Specific IgE against both birch (*Betula verrucosa)* and alder *(Alnus glutinosa)* were measured in N=991 samples, and against both birch and hazel *(Corylus avellana)* in N=587 samples by the highly specific and sensitive Magic Lite SQ assay [35]. In general, the vast majority of samples were positive for both birch and alder (Fig. 1A), and birch and hazel (Fig. 1B); 4.6% of the samples were either IgE positive for birch, but negative for alder, and positive for birch and negative for hazel. Only 1 sample (0.1%) was IgE-positive for alder, but negative for birch, and 2 samples (0.3%) were IgE-positive for hazel, but negative for birch. The data from these unselected patient populations confirm the high level of IgE cross-reactivity towards birch homologous trees and due to the small proportions of patients not reacting to birch also points to birch as the representative species.

Data supporting the use of birch as the representative tree originates mainly from geographical areas where birch trees are present. However, even in the Mediterranean area of central and southern Italy where birch trees are absent Bet v 1 IgE sensitization was the most frequently

observed among this homologous group of allergens [36] which may be the result of long distance dispersion of birch pollens (thousand kilometers or more) making the pollens present anyway [37]. Similar observations on sensitization were reported by Mari et al stating: “IgE reactivity to Bet v 1 seems to be a fine marker of the Fagales sensitization, even for our cohort of patients lacking direct exposure to birch pollen" when investigating Italian patients from Rome, including an intensively cultivated hazel area, north of Rome [38]. A proportion of 13.5% of patients was identified in this area exclusively responding to hazel. The IgE response of these patients were dominated by IgE reactivity to minor hazel allergens and such patients will need further diagnostic tests and also personalized treatment. Thus, even though clinical data from Fagales pollen allergic patients from "birch-free areas" are lacking, sensitization patterns suggest that birch may be used as the representative species in such areas as well, especially if IgE sensitization to the major allergen Bet v 1 is confirmed. Whether patients with separate (non-cross-reactive) sensitizations to components, present in e.g. hazel in addition to sensitization to Bet v 1 and other cross-reactive components present in birch, are existing among patients allergic to birch homologous trees is an interesting question. Such patients are not found among the Canadian patients included in the TT-03 trial or among the patients from Germany, Poland, Czech Republic, France, Sweden, Finland, Russia and Denmark included in the TT-04 trial because none of the IgE correlation plots indicate that the IgE-response of any of the patients was skewed towards a stronger response to a homologous tree pollen compared to the response to birch. In contrast, the data presented in Fig. 1A and B suggest that patients with a slight bias in their IgE reactivity towards the homologous trees compared to the reactivity towards birch do exist (indicated by xxx in Fig 1A and B). However, the percentage of patients with this IgE reactivity pattern is 11.5% for alder and 10.7% for hazel again suggesting that around 90% of these patients with respiratory symptoms during the spring tree pollen season will be fully diagnosed by testing birch IgE or SPT and will have all their IgE reactivities towards birch homologous trees addressed by birch AIT. Whether the skewing of the IgE response in the remaining 10-12% of these patients will mean that the effect of birch AIT on their tree pollen symptoms in the spring will be sub-optimal is an open question that needs to be addressed experimentally in the future. However, some of these patients may need further mapping of their IgE reactivity patterns by the allergy specialist and should be recommended an immunotherapy strategy that match their sensitization in the best possible way.

4. Clinical perspective: birch allergen immunotherapy is effective also in hazel and alder allergic patients

The idea that AIT with an allergen extract from a single tree species may cover allergic responses to several closely related trees has been debated for more than 30 years. The extensive cross-reactivity found for the different grass species [31, 32] and various ragweed species [33] suggested that AIT with the representative species is equally effective as AIT with mixtures of several species. In a double-blind parallel-group study published in 1988, 54 patients received either SCIT with a mixture of hazel, alder and birch allergen extracts or birch monotherapy over three years. Treatment with the monotherapy and the tree mix were equally effective and no significant differences in symptoms and use of symptomatic medication were observed in the tree pollen seasons over the three-year treatment term [15].

Subsequently, several trials have demonstrated the treatment effect for both, birch alone or for birch, alder, and hazel mixtures for both SCIT and SLIT [16,39-41]. Even trials on AIT with recombinant Bet v 1 have demonstrated clinical efficacy very similar to AIT with birch allergen extract, further supporting that this major allergen is the main driver of disease [42]. However, lack of a higher efficacy than for conventional AIT limits the advantage of developing new AIT products based on recombinant proteins [43].

During the development program of the SQ tree SLIT tablet the phase II trial (TT-03) [19] was performed in an environmental exposure chamber (EEC) in Canada to evaluate the optimal dose of the SQ tree SLIT-tablet by monitoring the effect on symptoms induced by birch as well as white oak pollen. Subjects received treatment for up to 24 weeks, and participated in EEC sessions after approximately 8, 16 and 24 weeks of treatment. Primary efficacy results showed a 25.5% reduction in allergic rhinitis/conjunctivitis (AR/C) symptoms during the week 24 birch EEC visit for the 12 SQ-Bet group compared to placebo (absolute reduction=1.81, p=.0164). Secondary efficacy results showed a 23.7% reduction in AR/C symptoms during the week 24 oak EEC visit (absolute reduction=1.77, p=.0298) for the 12 SQ-Bet dose compared to placebo. The results demonstrate that treatment with the 12 SQ-Bet dose reduced symptoms induced by birch as well as induced cross-protection for symptoms induced by pollen from the birch homologous tree, white oak.

The pivotal phase III field trial (TT-04) [34] was conducted in Europe and Russia with 634 subjects receiving treatment with 12 SQ-Bet or placebo prior to and during the 2017 tree pollen season/birch pollen season (TPS/BPS). Subjects initiated treatment at least 16 weeks prior to the start of the TPS (defined by the start of alder/hazel season) and continued until the end of the TPS (i.e. the end of the BPS), with an average treatment duration of 32 weeks.

The results demonstrated statistically significant improvements for 12 SQ-Bet treatment compared to placebo during the BPS (primary endpoint) and TPS (key secondary endpoint) 2017 for the total combined score (TCS) for AR/C symptoms and medication with relative reductions of

39.6% (BPS, absolute reduction=3.02, p<0.0001) and 36.5% (TPS, absolute reduction=2.27, p<0.0001). These results were further substantiated by the other key secondary endpoints demonstrating statistically significant effects compared to placebo, both during the BPS and TPS. Post-hoc analyses were performed for all 3 endpoints (i.e. TCS, daily symptom score (DSS) and daily medication score (DMS)) during the alder/hazel pollen season, and 12 SQ-Bet treatment induced significant improvements for all endpoints investigated compared to placebo during this period. This further supports that treatment with the 12 SQ-Bet dose induced clinical cross-protection for symptoms induced by pollen from other birch homologous trees (alder and hazel).
Regarding clinical cross-reactivity or cross-protection, allergen extract from a single grass species (*Phleum pratense*) administered sublingually is clinically effective in grass seasons in both Europe and North America covering seasonal exposure to multiple grass species [23,44,45]. Moreover, AIT with a single ragweed species (*Ambrosia artemisiifolia*) is clinical effective in the ragweed season in North America where patients experience seasonal exposure to several related ragweed species [28,46]. In contrast, subcutaneous AIT with ragweed-extract has no clinical effect in the preceding grass season in dual-allergic patients [46] and grass tablet treatment did not influence birch allergen induced symptoms in an environmental exposure chamber [48]. From these observations it appears that within closely related species, known as homologous allergen groups [7], immunological cross-reactivity is an important factor in causing not only allergic symptoms but also in securing clinical cross-protection of AIT.
In summary, the SQ tree SLIT-tablet demonstrated a clinically relevant treatment effect, which exceeded the 20% improvement recommended by the World Allergy Organization [48]. The treatment effect was substantial and significant for both TCS, DSS, and DMS during the BPS and throughout the entire TPS (average duration of the TPS was 50 days in the TT-04 trial).
In conclusion, the concept of clinical cross-protection within the birch homologous group evolved on basis of previous trials on birch AIT. Moreover, data on treatment of tree pollen allergic patients with the SQ tree SLIT-tablet further supports this concept by confirming that the patients benefit from symptom improvement and reduced need for medication when exposed for a relatively long pollen season to birch as well as homologous tree pollens.

5. Practical recommendations: diagnostics and therapy only with birch as representative allergen for birch homologous trees

All summarized regulatory, immunological and clinical data suggest that a diagnosis and treatment with a birch extract is sufficient to diagnose and treat patients allergic to pollen from the birch homologous group trees in geographical areas where birch is present, and even in birch

free regions, if IgE sensitization to the major allergen Bet v 1 is confirmed (see discussion above). This increasing knowledge should be implemented into the treatment guidelines.

1. Diagnosis: First, clear guidance will be obtained from a detailed clinical history. Patients usually report typical allergic rhinitis symptoms in the tree pollen season ranging from mid-December until May across Central and Northern Europe, depending on the geographical area, with variations during the different pollen seasons for the different trees. As a proof of sensitization, a SPT or the detection of allergen specific IgE is recommended by the guidelines. As described above, birch allergen extract is the representative allergen source for allergen products for diagnostics and therapy of allergy to pollen of the birch homologous group (birch, alder, hazel, hornbeam and oak) because it is the best characterized allergen source and due to high degree of IgE-mediated cross-reactivity. Limiting the proof of sensitization only to birch like in the Scandinavian countries not only reduces costs and saves time but also eases in our perspective the communication with the patient. Thus, it should be included in the communication with the patient that the seasons for the birch homologous trees are consecutive and partially overlapping and that due to the cross-reactivity in most cases no other tests than with birch are needed and birch is adequate for treatment of Fagales tree pollen allergy. Due to the high degree of IgE cross-reactivity of the tree species, patients are expected to react only to one single species in extremely rare cases (Figs. 1 A and B). In pollen regions where birch is not the dominant allergen source or birch is not present it is recommended to initiate diagnosis with birch and follow-up with other relevant tree extracts if the birch test is negative, indicating an uncommon IgE sensitization profile. Recombinant testing of a sensitivity to rBet v 1 might give more focussed information. A positive result for specific IgE to rBet v 1 in a similar concentration as birch pollen specific IgE is able to rule out a major sensitization to profilin (Bet v 2) and polcalcin (Bet v 4) as pan allergen that is widely distributed in various plant species, particularly grass pollen [50]. In case of a negative outcome of the SPT and/or specific IgE, but existing symptoms in the tree pollen season, a NPT with birch might support a diagnosis of local IgE production. If negative other differential diagnoses or other allergen sources have to be considered.
2. Treatment: Due to the high IgE cross-reactivity towards the allergens of the birch homologous group and according to the clinical data, showing that a birch extract is also effective in the hazel and alder season as well as upon oak exposure, a monotherapy with a birch extract might be preferred compared to a tree mixture. Treatment with the birch monotherapy has several advantages:
   2.1. The medical procedure is simplified if birch is “first choice” leaving more time to unravel the diagnosis and treatment of the uncommon IgE sensitization cases.

2.2. As only one allergen needs to be produced and standardised, a higher batch-to-batch consistency can be achieved more effectively, potentially leading to improved safety for the patient.
2.3. This facilitated production process makes it easier to fulfil the increasing demands by the regulatory authorities which will increase the likelihood of future availability of these products.

Consistency of testing and therapy with birch is easier to understand for the patient and streamlines appropriate treatment for the physician. Therefore, our practical recommendation is to initiate diagnosis of new patients with allergy symptoms in the spring with birch extracts only and aim for treatment this extract as well. Currently, many patients are being treated with a tree mix. Due to the high cross-reactivity these patients are not required to switch the treatment to a birch-only-product. In case that a patient needs to be switched to a birch-only-product a respective dose reduction to the birch content of the mix product is recommended for some SCIT products. If patients shall be switched to product(s) without required up-dosing, as offered in some new AIT tablets, a direct switch to the birch only product is possible.
A summarizing recommended procedure for diagnostics and treatment of patients with tree pollen allergy is shown in Figure 3.
For treatment of tree allergic patients with AIT, the aspects displayed in text box 1 should be considered with respect to patient characteristics, time of start of AIT and education of the patient.

6. Conclusion

In conclusion, birch has been identified as representative allergen source for the tree species of the birch homologous group that includes hazel, alder, birch, oak, and hornbeam because birch is the best characterized species. It has important major and minor allergens that are similar to the other members of the homologous group and the high level of patient serum specific IgE cross-reactivity suggested by multiple studies around the world has been fully confirmed by IgE inhibition experiments in Danish, Austrian and Canadian patients. Immunological and clinical data from recent clinical trials on SLIT-tablets containing birch allergen extract strongly support the concept of using birch as representative allergen source for diagnostics and treatment of patients with allergy to tree pollen. Thus, birch is recommended for diagnostics and treatment of patients with tree pollen allergy.

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All authors participated in the meeting and made contributions to the manuscript from their clinical experience, and carefully reviewed the draft and final versions of the manuscript and Figures.

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Figure Legends:

Figure 1: (A) *Betulaceae* specific IgE in ALK serum bank (birch vs. alder), (B) *Betulaceae* specific IgE in ALK serum bank (birch vs. hazel).
SU/ml: Standardised Units of specific IgE per millilitre of serum. 1 SU/ml is approximately equal to 0.175 kUA/L.

Figure 2: Daily average Total Combined Score (TCS) over the entire tree pollen season (pollen seasons of hazel, alder and birch) in SQ tree SLIT-tablet trial TT-04.

Figure 3: Recommendation for diagnosis and treatment of patients allergic to tree pollen (birch, alder, hazel).
[a]extension to alder, hazel, ash, if birch is negative; *most economic general SPT panel (acc. to GA²LEN):* grasses, house dust mite (*Dermatophagoides pteronyssinus*), birch, cat, mugwort, *Blatella*, olive/ash.
[b]recombinant testing of a sensitivity to rBet v 1 might give additional information whether the patient is sensitised to major allergen relevant for all species of birch homologous group.
[c]solid data from recent clinical trial available [34]; ongoing SCIT treatment with tree mixture should be continued for a complete 3-year cycle or changed to birch with previous dose reduction; a new AIT should be started with birch.
SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Text box 1: Recommendations for treatment of tree allergic patients with allergy immunotherapy (AIT)*:*

Characteristics of patients suitable for AIT:

- patients with a long history of allergic symptoms
- patients with moderate-to-severe persistent allergic rhinoconjunctivitis (ARC), acc. to Allergic Rhinitis and its Impact on Asthma (ARIA), [20]
- patients with ARC and concomitant allergic asthma (FEV_1>70% of predicted value)
- patients with progression of allergic disease (increasing severity of symptoms, extension of sensitization to further allergens)

Time for start of AIT:

- traditionally in October (due to patients with concomitant allergy to grasses)
- May (directly after the end of the birch pollen season)
- January (possibly within hazel season), depending on the product information of AIT product used

Education of patients before AIT:

- Information about treatment with SCIT or SLIT as alternative treatment options
  Treatment with the most dominant allergen(s) in patients with multiple allergy to various allergen sources (e.g. grass, trees, house dust mites)

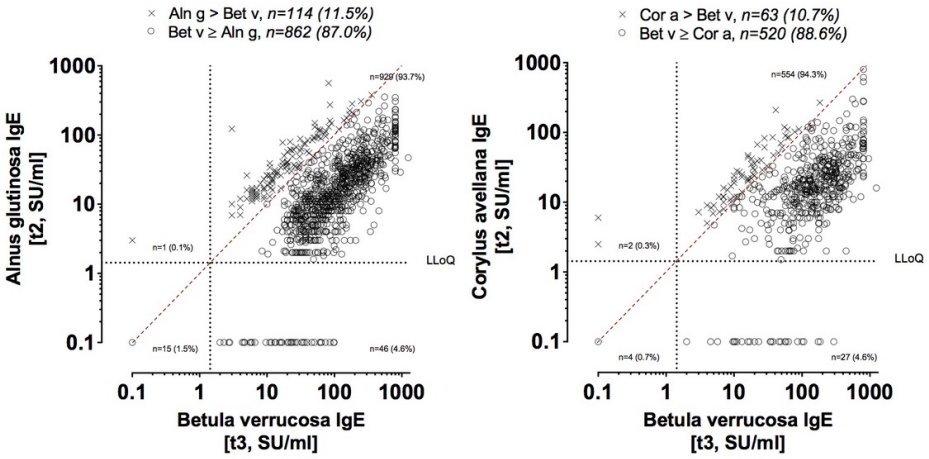

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Fig. 2

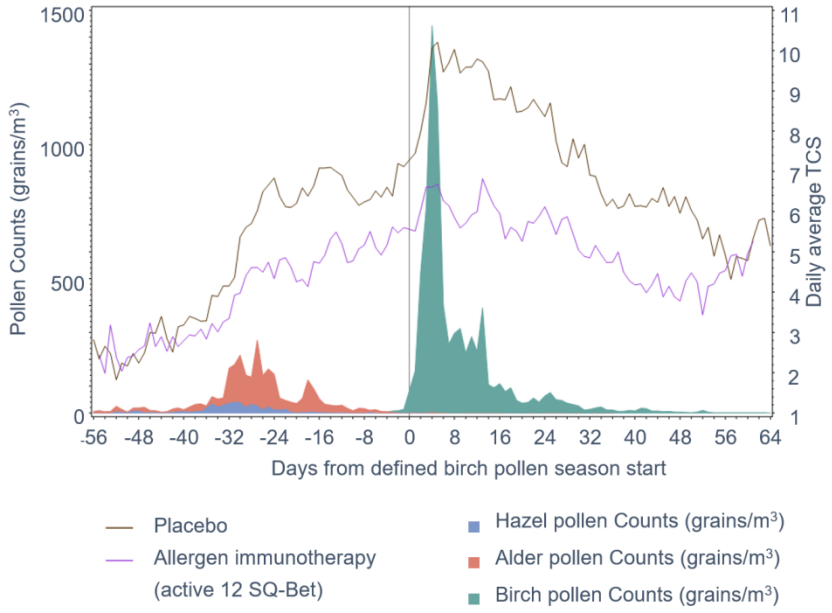

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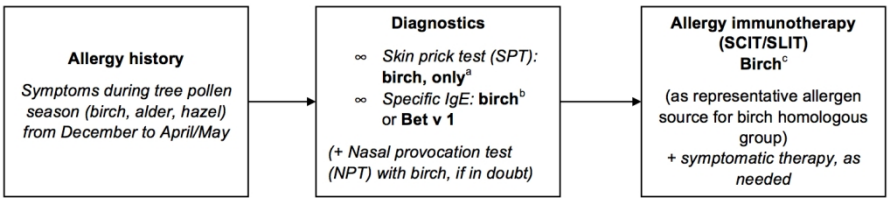
Fig. 3



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