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ORIGINAL ARTICLE

Allergen-Specific Immunotherapy and Biologics

Short-course subcutaneous treatment with birch pollen allergoids greatly improves symptom and medication scores in birch allergy

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Abstract

Background: Subcutaneous immunotherapy has emerged as an effective option for treating allergic diseases. Here, we assessed the clinical impact of the mannan-conjugated birch pollen polymerized allergoid T502 in birch pollen-induced allergic rhinoconjunctivitis.

Methods: In this prospective, randomized, double-blind placebo-controlled phase III trial, 298 birch pollen–allergic adult patients were treated across 28 trial sites in Germany. Patients received either placebo or 23,000 mTU T502 subcutaneously over five pre-seasonal visits. Efficacy was assessed by comparing the combined symptom and medication score (CSMS) between placebo and T502 during the peak birch pollen season 2022. Safety, tolerability and immunologic effects were also analyzed.

Results: During the peak birch pollen season, the median CSMS of the T502 group was reduced by 33% ($p = 0.002$) compared to placebo. The median daily symptom score and daily medication score were reduced by 30.4% ($p < 0.001$) and 56.3% ($p = 0.045$), respectively. Health related quality of life improved as reflected by reduction of RQLQ values by 31.5% ($p < 0.0001$). Production of *Bet v 1* sIgG4 and *Bet v 1* sIgG increased up to 6.2-fold and 3-fold respectively in the T502 group ($p < 0.0001$). The sIgE/sIgG4 ratio was strongly reduced in the T502 group at V7 (−62.9%, $p < 0.0001$).

No fatalities nor serious adverse events were reported. In total, 16 systemic allergic reactions occurred (Grade I/II).

Abbreviations: AE(s), adverse event(s); AIT, allergen immunotherapy; ARC, allergic rhinoconjunctivitis; CSMS, combined symptom and medication score; DC(s), dendritic cell(s); dMS, daily medication score; dSS, daily symptom score; EAACI, European Academy of Allergy and Clinical Immunology; GCP, good clinical practice; IMP, investigational medicinal product; ITT, intention to treat; LR, local reaction; mTU, mannan therapeutic units; PP, per protocol; PRO, participant related outcome; QoL, quality of life; RQLQ, rhinoconjunctivitis quality of life questionnaire; S, safety set; SD, standard deviation; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SR, systemic reaction; Tregs, regulatory T cells; V, visit.

For the BetMan study group: The full list can be found in the supplementary material.

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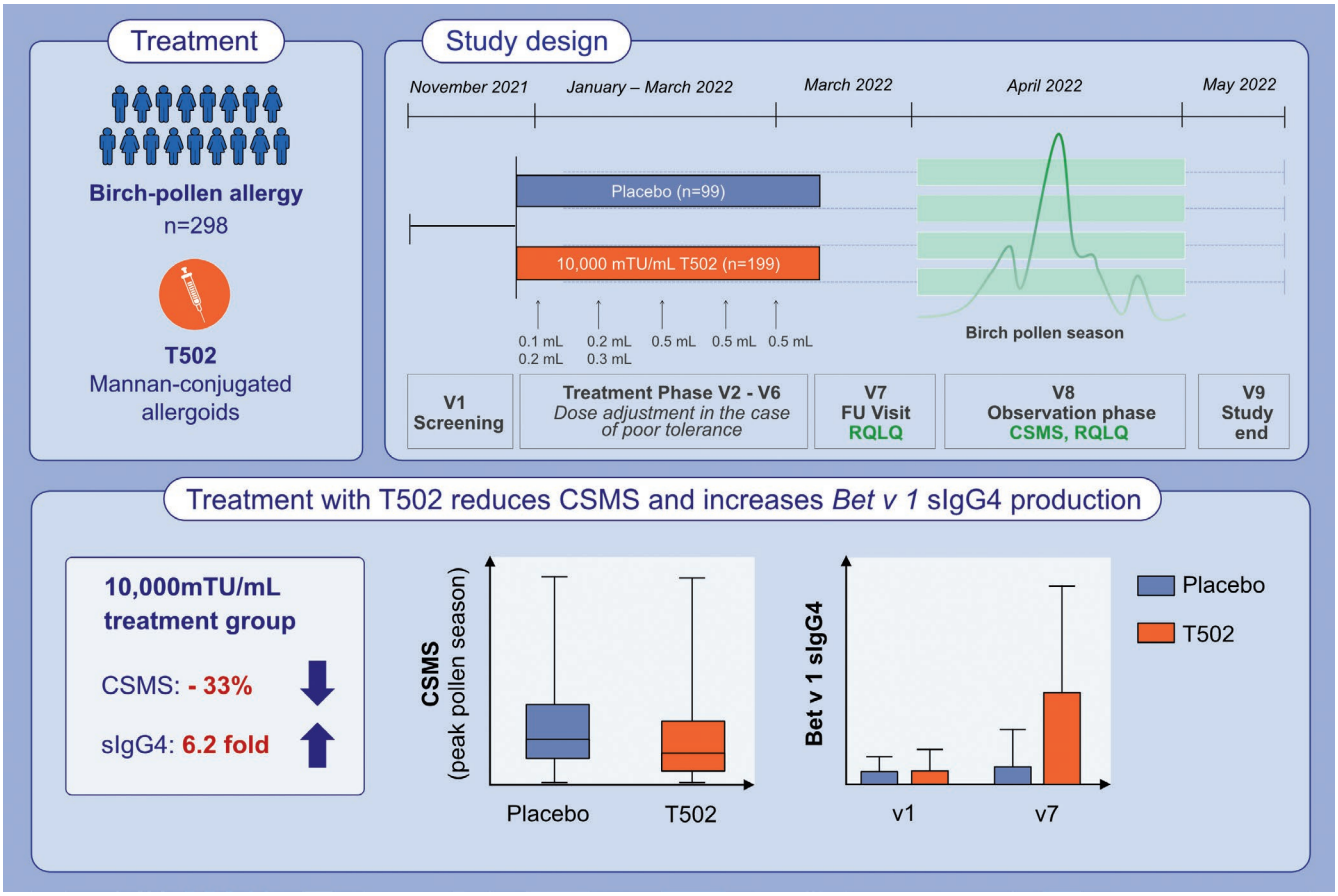
Conclusions: Treatment with T502 significantly reduced symptoms and medication need in rhinoconjunctivitis patients. The treatment is well tolerated and safe.

KEYWORDS
allergic rhinoconjunctivitis, birch pollen, combined symptom and medication score, mannan conjugate, polymerized allergoid



GRAPHICAL ABSTRACT

This pivotal phase III study investigates subcutaneous immunotherapy with T502 in birch-pollen induced allergic rhinoconjunctivitis. Two hundred and ninty-eight birch-pollen allergic adults received short-course treatment of placebo or 10,000 mTU/mL of T502. The treatment with mannan-conjugated birch pollen polymerized allergoid resulted in a reduction of CSMS by 33% (median) and a 6.2-fold increased production of *Bet v1* specific IgG4 compared to placebo.

Abbreviations: CSMS, combined symptom and medication score; Ig, immunoglobulin; mTU/mL, mannan therapeutic units per millilitre; RQLQ, rhinoconjunctivitis quality of life questionnaire; sIg, specific immunoglobulin; T502, mannan-conjugated birch pollen allergoid.

1 | INTRODUCTION

Pollen allergy is currently affecting about 40% of the European population,[1] and its incidence is increasing; tree pollen with birch (Betula), followed by alder (Alnus) and hazel (Corylus) being the most allergenic pollen[2] Depending on the geographic regions, the percentage of subjects with positive skin prick test to birch allergens varies between 5% and 54%.[3]

Treatment of pollen induced allergic rhinoconjunctivitis (ARC) consists generally of symptomatic therapies. However, those therapies cannot sufficiently control allergic symptoms in patients with moderate and severe disease.[4] In addition, symptomatic treatment cannot prevent the development of allergic asthma. Guidelines recommend allergen immunotherapy (AIT) for patients with allergic rhinitis both with and without concomitant asthma.[5-7] AIT is based on repeated administration of allergen, usually in increasing doses, over a period of typically 3–5 years. Unlike symptomatic drugs, AIT controls symptoms by suppressing allergen-induced IgE sensitisation. AIT induces the activation of regulatory T cells (Tregs and Bregs) and production of allergen-specific IgG4 antibodies, which hinder IgE activation and thereby attenuate allergic reactions.[8-10]

In addition to reprogramming the inappropriately reacting immune system, AIT may prevent the development of new allergen sensitizations and it is clinical benefits may remain years after discontinuation of treatment.[11] AIT reduces the risk for the future development of asthma in some patients and is effective in both adults and children.[12]

The classical AIT treatment is subcutaneous immunotherapy (SCIT), which requires slow up-dosing of a native allergen(s) extract and frequent injections during the course of 3–5 years. Generally, SCIT is associated with a higher risk of severe allergic adverse drug reactions (ADRs) compared to the alternative sublingual immunotherapy (SLIT). However, chemical modification of allergens have been shown to improve SCIT safety patterns by reducing allergenicity via disruption of IgE reactive epitopes and maintaining immunogenicity via retention of IgG reactive epitopes,[13] thus achieving a safety profile comparable to SLIT.[14] The danger of life-threatening ADRs is also greatly reduced by careful patient selection and general adoption of precautionary measures such as treatment exclusively in well-equipped specialized units by professionals familiar with anaphylaxis management.

The current trial aimed to investigate effects of T502, a mannan-conjugated birch pollen allergoid. Polymerized allergoids conjugated to mannan have been demonstrated to increase capture/presentation of allergens by dendritic cells (DCs) and to promote the generation of Tregs, which are essential for establishing tolerance against allergens.[15,16] The product investigated in the current trial was glutaraldehyde-polymerized birch pollen allergoids coupled to non-oxidized mannan from *S. cerevisiae*, resulting in high molecular weight glycoconjugates that target DCs through C-type lectin receptors.[16,17]

Based on the results of a previous dose-finding trial,[18] the dose chosen for this trial was 10,000 mTU/mL.

2 | METHODS

2.1 | Trial design

This trial was designed as double-blind, randomized, placebo-controlled multicentre trial in Germany. It encompassed 9 visits (Figure 1): 1 screening visit (V1), 5 treatment visits (V2-V6), 1 treatment follow-up visit (V7), 1 visit at the peak of the birch pollen season 2022 (V8) and 1 end of trial visit after the birch pollen season (V9). It was planned to randomise 360 patients into two groups in a 1:2 ratio (Placebo, 10,000 mTU/mL T502 respectively). A block randomisation with the block size of six was used. Inclusion and non-inclusion criteria are shown in Supplementary Material A.

2.2 | Ethics declaration

Prior to initiation of the trial, relevant trial documentation was submitted to and approved by the responsible Ethics Committee. The trial was approved by the regulatory authority, Paul-Ehrlich-Institute in Germany and registered in the EudraCT database (EudraCT No.: 2021-002252-36). The Declaration of Helsinki (Fortaleza 2013), the guidelines of good clinical practice (GCP-R2) as well as the requirements of national drug and data protection laws and other applicable regulatory requirements were adhered to.

2.3 | Allergen immunotherapy

AIT was carried out with a mannan-allergoid conjugate of *B. pendula* pollen allergens (T502; 10,000 mTU/mL) or placebo. Allergens and mannan were coupled via glutaraldehyde, resulting in a modification of the native allergen proteins, rendering high molecular weight glycoconjugates. Details regarding the manufacturing process are published.[16,19,20] The allergenic potency of T502 is expressed in mannan therapeutic units (mTU).

Patients received five subcutaneous doses of T502 (10,000 mTU/mL) or placebo at five treatment visits with intervals of 12–30 days. At V2 and at V3, the doses were split into two injections into one arm each (0.1 and 0.2 mL at V2; 0.2 and 0.3 mL at V3), whereas one single subcutaneous injection of 0.5 mL was given at V4–V6 (Figure 1).

2.4 | Pollen measurement procedures

Periods of the entire birch pollen season and the peak of the birch pollen season were determined as proposed by the European

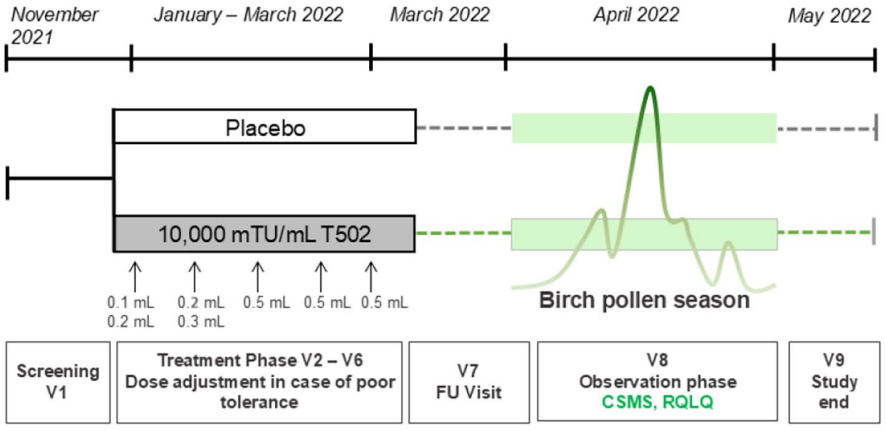


FIGURE 1 Overview of the T502-SIT-045 trial design. Patients received pre-seasonal subcutaneous injections of T502 or placebo (treatment phase). Clinical effects were assessed during the birch pollen season 2022 via assessment of CSMS and RQLQ. mTU/mL, mannan therapeutic units per millilitre; V1-9, visit 1–9; FU, follow-up; CSMS, combined symptom and medication score; RQLQ, rhinoconjunctivitis quality of life questionnaire.

Academy of Allergy and Clinical Immunology (EAACI).[21] Based on daily mean pollen concentration (pollen/m^3) assessed by standardized monitoring stations; entire and peak pollen season were calculated for all 28 participating trial sites.

2.5 | Endpoints and statistical analysis

2.5.1 | Assessment of efficacy–combined symptom and medication score

The combined symptom and medication score (CSMS) was chosen as primary endpoint to assess the clinical impact of T502 treatment in patients with birch pollen-induced ARC. The CSMS evaluates daily symptom score (dSS) and daily medication score (dMS) in an equally weighted manner with scores ranging from 0 to 3 (dSS: no symptoms–severe symptoms; dMS: no medication–maximal allowed medication).[22] The symptom score includes nasal (rhinorrhoea, sneezing, nasal pruritus, nasal congestion) and ocular (ocular pruritus, watery eyes) symptoms. Based on experiences of a previous trial with the same product,[18] scoring of dMS was slightly adapted in the study protocol compared to the scoring method published by Pfaar et al.[22] based on the experience that less than 1% of patients in the previous study received oral glucocorticosteroids: application of the following products was allowed in any order/combination and scored additively as follows: antihistaminic eye drops (score 0.5), antihistaminic tablets (5 mg desloratadine, once daily; score 1.0), nasal corticosteroid (110 µg fluticasone furoate nasal spray per day; score 1.5). Thus, a 7-point scale covering total scores of 0–3 was applied for the determination of the dMS. Both dSS and dMS were documented by patients daily via a mobile application (CSMSplus Diary App).

2.5.2 | Assessment of efficacy–clinical endpoints

Besides the assessment of CSMS, health related quality of life (QoL) was assessed with the rhinoconjunctivitis quality of life questionnaire (RQLQ) before and during the birch pollen season (V7, V8). The disease-specific questionnaire according to Juniper and Guyatt[23] in its validated German form[24,25] was used. The RQLQ was developed to measure problems that adults with rhinoconjunctivitis, both atopic and non-atopic, experience because of their nose and eye symptoms.[23]

To assess the clinical immunogenicity, serum levels of *Bet v 1* specific IgE, IgG, and IgG4 were determined at V1, V7, and V9 or early termination follow-up visit. All clinical laboratory tests were carried out by the central clinical laboratory MLM Medical Labs (Mönchengladbach, Germany).

2.5.3 | Safety and tolerability

Wheals and redness at the injection site were measured by investigators and reported as solicited local adverse events (AEs) 30 min after each injection. In addition, local reactions (LRs) and other AEs (e.g., systemic reactions (SRs)) were documented by patients in the evening of the injection day and during two subsequent days using diary cards. All local symptoms other than wheals or redness and all SRs were reported as unsolicited AEs.

At V2, patients were provided with 10 tablets of Fexofenadine (180 mg) for on demand treatment of side effects induced by the IMP (in accordance with the Summary of Product Characteristics). Intake of rescue medication was recorded by patients in the diary cards. AEs were coded using MedDRA, Version 25.0.

Vital signs and physical examinations were determined at each visit. Blood samples to assess laboratory values (blood count, renal and liver function-related parameters) were taken at V1 and V7.

2.6 | Statistical analysis

The sample size was calculated by SAS for Windows, V.9.4 based on data of a preceding trial, assuming that mean CSMS during the peak birch pollen season upon treatment was 1.36 in the placebo and 0.95 in the T502 treatment group with 1.0 overall standard deviation. Assuming a 5% alpha error and 90% power, it is estimated that, for a 2:1 ratio (Active:Placebo), and assuming approximately 20% loss to follow-up it will be necessary to recruit a total of 360 subjects, 240 for active and 120 for placebo group.

Statistical analysis was performed according to a predefined statistical analysis plan using SPSS Statistics for Windows, Version 29.0.1 (Armonk, NY:IBM Corp.).

The Safety set (S set) comprised all randomized patients with at least one dose of treatment. The intention-to-treat set (ITT set) comprised patients who met key eligibility and evaluability criteria and for whom evaluable CSMSplus Diary data for the peak birch pollen season were available. Immunologic effects were analyzed in the Immunogenicity set, comprising patients with at least two measurements of at least one immunogenicity parameter. Safety and clinical tolerability were analyzed in the S set.

Statistical evaluations for primary and secondary endpoints were performed descriptively and exploratively and comparisons were performed between placebo and active treatment groups.

As data of the primary endpoint did not follow a normal distribution, data were analyzed via nonparametric statistical tests (Mann–Whitney *U*-test and Wilcoxon *W*-test). Average CSMS, dMS and dSS values were calculated for each day per patient over the entire and peak pollen season 2022. Based on those values, descriptive statistical analysis of CSMS, dMS and dSS were performed.

For remaining endpoints, multivariate analysis was carried out using the ANCOVA test.

Immunogenicity parameters were summarized for each time point of determination using descriptive statistics. Serum levels, the ratios IgE/IgG4, IgG/IgG4 and their absolute and relative differences were calculated.

Data was presented in median, and IQ 1–3, and/or means ± standard deviation (SD) of the mean. $p < 0.05$ was considered as

statistically significant. Graphs were prepared with GraphPad Prism version 7 for Windows (GraphPad Software, San Diego, California USA).

3 | RESULTS

3.1 | General trial data and baseline characteristics

The current trial took place between November 2021 (first screening visit) and June 2022 (last end-of-trial-visit) with a mean/median overall trial duration of 149.6/160 days for the placebo group and 143.4/155 days for the T502 group and a mean/median treatment duration of 62.2/63 and 58.9/61 days, respectively. The mean entire birch pollen season across all trial sites was 33 days and the mean peak birch pollen season was 18.4 days.

Of the 405 screened patients, 298 patients were randomized and received either placebo ($N = 99$) or 10,000 mTU/mL T502 ($N = 199$; Figure 2).

Demographics, baseline characteristics and asthma status were comparable between treatment groups (Table 1).

3.2 | Immunological baseline values (safety set)

Baseline immunogenicity parameters were comparable between treatment groups. Baseline birch pollen-specific IgE (common silver birch, t3) serum level was 22.4 kU/L in the placebo and 23.6 kU/L in the T502 group. Mean CAP values for birch pollen were 3.48 (placebo) and 3.53 (T502). For 14 patients, who did not meet the inclusion criterion of CAP class ≥3, inclusion was accepted based on previous analyses confirming results of CAP class ≥3.

3.3 | Comparing the combined symptom and medication score during the peak birch pollen season (intention-to-treat set)

In patients treated with T502, the median CSMS during the peak birch pollen season was reduced by 0.33 points or 33% (median score: 0.67) compared to patients treated with placebo (median score: 1.00; Figure 3). This difference is clinically relevant and statistically significant ($p = 0.002$).

Analysis of the dSS showed that treatment with T502 significantly reduced symptoms by 30.4% (median score: 0.48) compared to placebo (median score: 0.69; $p < 0.001$). The median dMS was reduced by 56.3% (median score: 0.14) compared to placebo (median score: 0.32; $p = 0.045$).

Analysis of data regarding the entire pollen season showed similar results (Figure S1).

3.4 | rhinoconjunctivitis quality of life questionnaire

Improvements upon T502 treatment was also reflected in QoL values: at V7, mean RQLQ results were 1.41 (SD: 1.11) in the placebo group and 1.11 (SD: 0.95) in the T502 group, presenting a statistically

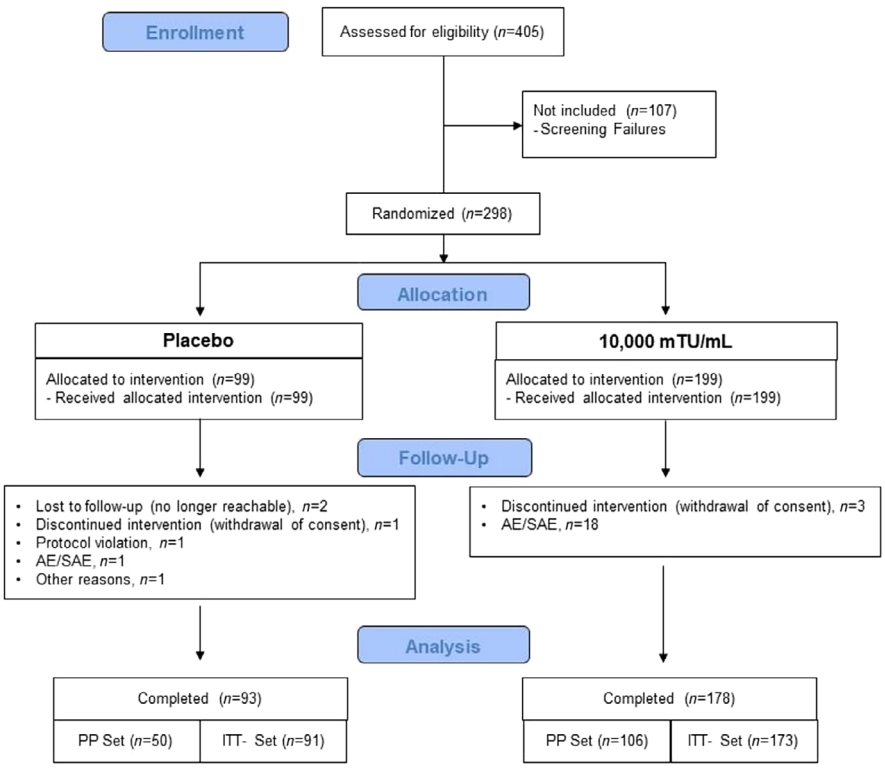


FIGURE 2 CONSORT flow chart of the trial. ITT, intention to treat; PP, per protocol.

TABLE 1 Demographics and baseline characteristics of the safety-set.

Characteristics	Placebo	T502	Total
Patients (*n*)	99	199	298
Patients (%)	33.2	66.8	100
Female (*n*)	50	103	153
Female (%)	50.50	51.80	51.30
Male (*n*)	49	96	145
Male (%)	49.50	48.20	48.70
Age mean ± SD (years)	37 ± 13	39 ± 13	38 ± 13
Height mean ± SD (cm)	175 ± 9	173 ± 10	174 ± 10
Body weight mean ± SD (kg)	78 ± 16	77 ± 16	78 ± 16
Asthma (*n*)	25	60	85
Asthma (%)	25.3	30.2	28.5
Allergic asthma (*n*)	24	58	82
Allergic asthma (%)	24.2	29.1	27.5

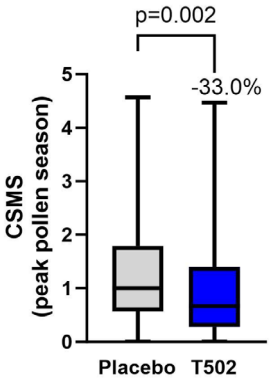


FIGURE 3 Combined symptom and medication score (CSMS) during the peak birch pollen season 2022 in the placebo and T502 treatment group. Data is presented as box plot (minimum, 25th percentile, median, 75th percentile, maximum, and including percentual differences of median values and corresponding *p* value) of the ITT set.

significant difference of 21.3% ($p = 0.031$). At V8, the difference of the mean RQLQ score was more pronounced than at V7 with a score of 1.49 (SD: 1.07) in the placebo group and 1.02 (SD: 0.85) in the T502 group, resulting in a statistically and clinically significant difference of 31.5% ($p < 0.0001$; Figure 4).

3.5 | Development of immunological parameters (Immunogenicity set)

In the immunogenicity set, *Bet v 1* sIgG4 increased 6.2-fold from V1 to V7 (means 0.55 ± 0.79 kU/L–3.40 ± 3.87 kU/L) in the active treatment group ($N = 175$). At V7, sIgG4 values were 5.2-fold higher in the active treatment group ($N = 176$) comparison to placebo ($N = 93$). At V9, sIgG4 values were slightly lower than at V7 in the T502 group

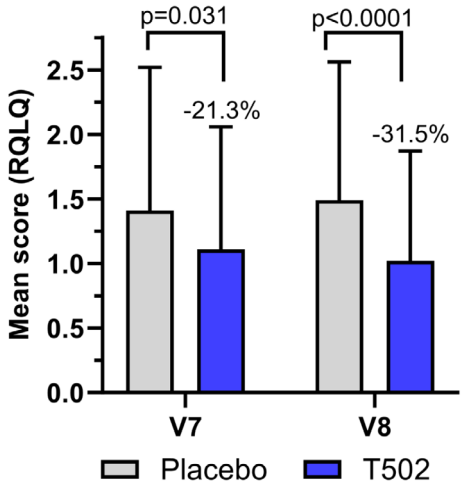


FIGURE 4 Mean RQLQ scores at V7 (before the birch pollen season) and at V8 (at the peak of the birch pollen season) in the placebo and T502 treatment group. Data is presented as mean CSMS+SD of the ITT set. RQLQ, rhinoconjunctivitis quality of life questionnaire.

(mean 2.59 ± 2.70 kU/L, $N = 173$) and 5-fold higher in comparison to placebo (mean 0.51 ± 0.93 kU/L, $N = 90$). These differences were statistically significant ($p < 0.0001$; Figure 5A).

Treatment with T502 increased *Bet v 1* sIgG levels 3-fold from V1 to V7 (from 3.10 ± 1.78 to 9.00 ± 6.23 mg/L) and 2.7-fold in comparison to placebo. At V9, sIgG level was 7.14 ± 4.21 mg/L. Changes from baseline were statistically significant in the T502 treatment group compared to placebo ($p < 0.0001$).

Values of *Bet v 1* sIgE increased from 22.15 ± 23.54 kU/L at V1 to 37.42 ± 32.77 kU/L at V7 in the T502 group and decreased slightly at V9 to 35.11 ± 31.81 kU/L. The differences regarding changes of *Bet v 1* sIgE values from baseline to V7 or V9 were significant between treatment groups ($p < 0.0001$ for delta V1–V7 and $p = 0.003$ for delta V9–V1).

In line with these results, the sIgE/sIgG4 ratio was strongly reduced at the end of the treatment with T502, with a delta of −65% from V1 to V7 ($p < 0.0001$) and a difference of −62.9% at V7 in comparison to placebo, ($p < 0.0001$; Figure 5B).

3.6 | Safety results

Overall, no fatality and no serious AEs that was (possibly) related to the trial medication occurred during the trial. After the reassuring experience of the dose-finding trial no EpiPen was dispensed and epinephrine was not used. In total, 16 systemic allergic reactions (Grade I/II) occurred in the trial.15 SRs occurred in 12 patients (8.1%) treated with T502 and 1 SR occurred in 1 placebo patient (Table S1). None of the concerned patients was asthmatic. Extrapolated to the number of T502-injections ($N = 1313$), SRs occurred in 1.14% of all injections.

Nearly all measured wheal diameters in the T502 treatment group were either 0 cm (26.2%) or of mild intensity (72.8%). No

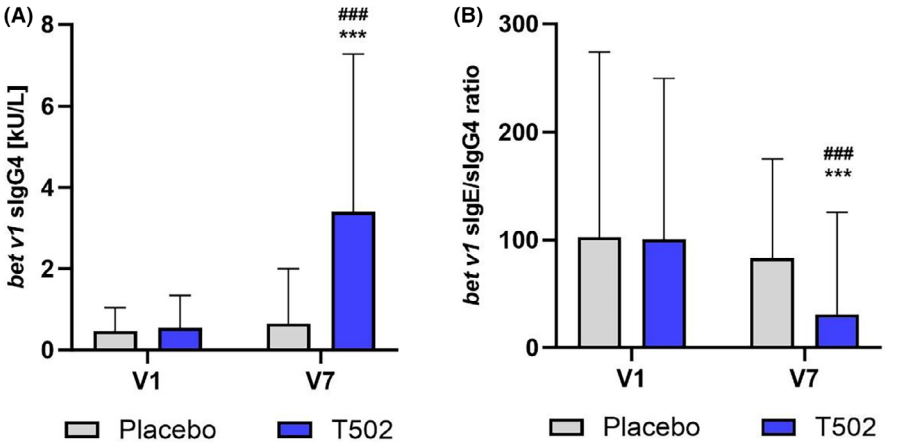


FIGURE 5 (A) *Bet v 1* sIgG4 levels (kU/L) and (B) *Bet v 1* sIgE/sIgG4 ratio at baseline (V1) and after treatment (V7). Data is expressed as mean + SD. ***$p < 0.0001$ in comparison to baseline, ###$p < 0.0001$ in comparison to placebo.

severe LRs occurred following treatment with T502 and 1 severe LR was observed in 1 patient of the placebo group (Table S2). Median wheal diameters were 0 cm over all visits and independent of the treatment group. The largest LR was 10.25 cm in the placebo group and 5.5 cm in the T502 treatment group. In general, wheal diameters increased until V3, but decreased again at the subsequent visits. One patient in the placebo group and 18 out of 199 patients in the T502 group withdrew because of the AEs. Nine of those were systemic reactions of Grade I–II. With regard to late phase LRs, <0.06% ($N = 7$) of all documented wheals were rated as severe (Grade III, wheal size >20 cm) and 137 (1.11%) were rated as moderate (Grade II, 10–20 cm; Table S3). In patients who received the intended treatment schedule (without dose split), mean wheal diameters were <2.0 cm. Regarding unsolicited AEs with a relationship to the treatment, injection site pruritus was the most common (45%), followed by injection site swelling (12%).

4 | DISCUSSION

In this pivotal phase III trial, primary and secondary efficacy endpoints were assessed as participant related outcome (PRO) parameters, documenting the symptoms and medication need during the birch pollen season 2022. The use of PROs is recommended in the EAACI Position Paper by Pfaar et al.[22] Here, we have adapted the medication score proposed in the position paper, based on our experiences from former trials,[18] where analyses of the diary data showed that only a fraction of the participants (less than 1% of participants and less than 0.1% of all data entries) had taken oral corticosteroids. This resulted in a score of only two steps (oral antihistamines + corticosteroid nasal spray) instead of three, leading to reduced sensitivity. Therefore, the score was adapted to meet the medication need of the participants, resulting in a seven-step score which strongly increased the sensitivity of the score. Of note, when the original score[22] was applied to this study, results remained significant.

Treatment with T502 strongly reduced allergic symptoms and medication intake during the peak pollen season as reflected by a significant reduction of median CSMS (−33%, $p = 0.002$), dSS (−30.4%, $p < 0.001$) and dMS (−56.3%, $p = 0.045$) in the active treatment group compared to placebo. In a study published 2018 by Pfaar,[25] CSMS improved by 32% in a patient group treated with sublingual birch solution. At over 1.4 points, the initial level in the placebo group was significantly higher than in our T502 study and the improvement was over 0.4 points. In 2019 Biedermann published a SLIT tablet study.[26] The improvement in symptoms and medication consumption was highly significant and achieved a difference of 40% compared to placebo after 7 months of treatment, with the improvement in the medication score being even more pronounced than that in symptoms. In a 2-year study of patients with ARC due to mixed grass and birch pollen allergy published in 2013 by Pfaar,[27] the mixed symptom medication score was reduced by around 33% in the actively treated group compared to placebo. A 2-year SCIT study using allergoids for 6 months preseasonally published by Worm in 2019[28] described a non-significant reduction of 15% in the combined symptom medication score in the overall population, while this was highly significant at 32.7% in a subpopulation with greater pollen exposure. However, this only relates to results from the second year of treatment. In 2002, Bodtger published a 1-year randomized, double-blind study in which a native birch pollen preparation was used subcutaneously versus placebo.[29] Bodtger describes an approximately 40% reduction in the patients' symptom score and a reduction of almost 50% in the medication score compared to placebo.

In line with those results, significant differences of QoL of 31.5% (0.47 in absolute values; $p < 0.0001$) were shown in patients treated with T502 when compared to placebo. Of note, no baseline assessment of RQLQ was performed upon inclusion in winter. The first assessment at V7 was already influenced by a strong elder pollen exposure in March 2022 and therefore showed differences between the groups. In the study by Pfaar in 2018, RQLQ also improved significantly. The difference of 0.55 compared to placebo was slightly higher than that observed in our treated group, whereas in the Biedermann 2019 study QoL was also significantly improved, with absolute values reaching around 0.46 for the entire birch pollen season.

The production of *Bet v 1* specific IgG4 was strongly increased (more than 5-fold compared to baseline), which is also reflected in a

significant reduction of the sIgE/sIgG4 ratio, supporting a marked clinical efficacy via induction of an immune response in birch pollen allergic patients already after five doses of T502 on five visits within 2 months. Pfaar's patients treated with sublingual drops showed a 3.7-fold increase in the mean values of sIgG4 within the first 12 weeks of treatment, which rose to a value of 6.7 by the end of the therapy. In his subcutaneous study, Pfaar describes a slight increase in the sIgG4 against Betv1, which did not reach the value of 2.0 over 2 years but was statistically significant. Bodger describes a marginal, non-significant increase in sIgE in both treatment groups with native allergens and with placebo.

In this T502 trial, modified allergen extracts with glutaraldehyde (allergoids) were chosen in place of native allergens. This modification results in high molecular weight polymers with low IgE reactivity, thus ensuring an enhanced safety profile while retaining clinical efficacy.[30,31] The results of this trial show at least a non-inferiority regarding tolerability and safety compared to trials using native birch pollen extract such as, Pfaar 2018 (17%, 8% SR Grade I–III, 6% discontinuation due to TAEs),[26] Biedermann 2019 (no info on SR, 8% of discontinuation),[32] Bodger 2002 (no info on AEs, except that more side effects occurred in placebo group),[29] and Worm 2014 (5% of discontinuation due to TAEs).[33]

Regarding solicited AEs, immediate LRs were nearly all of mild intensity, with only 1.11% being moderate. Late phase LRs were also mainly of mild or moderate intensity, with only 0.06% being of severe intensity. As the treatment progressed, LRs decreased in both size and intensity. SRs (Grade I/II) occurred in 8.1% of the patients, well within line with that observed in other highly effective AITs.[26,34]

Conventional AIT treatment schedules tend to be lengthy and consist of a large number of administrations in order to reach clinical benefit. These factors, along with costs, AEs and non-perception of efficacy often lead to low patient adherence. In traditional 3-year treatments, adherence can range between 23% and 55% in SCIT and 7%–82% in SLIT.[35] In contrast, in the Phase III of the Pollinex study, an ultra-short-course SCIT with only four injections, 95.3% of the patients completed the study, with only 2.5% in the active treatment group withdrawing due to AEs.[36] In comparison, 91% of patients ($N = 271$) completed this T502 trial with a treatment duration of approximately 2 months.

Overall, this trial showed that a short-course of subcutaneous treatment (five doses) with 10,000 mTU/mL mannan-conjugated birch pollen polymerized allergoids was well-tolerated and safe and resulted in clinically relevant and statistically significant improvements of rhinoconjunctivitis symptoms, medication need, and QoL in birch pollen allergic patients.

AUTHOR CONTRIBUTIONS

E. R., R. M., S. A., S. P. C., J. L. S. and M. C. have made substantial contributions to conception and design of the clinical trial. E. R. and C. N. was responsible for the project management of clinical trial and prepared the figures. E. X. and L. D. wrote the manuscript. A. R. was involved in the writing, in review and editing. C. A. and H. S. were responsible for acquisition and analysis of data. M. C. was the coordinating investigator, while L. K., O. P., and S. T. were principal investigators and mad contribution to conception and design of the clinical trial. All authors approved the final version of the manuscript before submission.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this trial are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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