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Safety of the SQ Tree Sublingual Immunotherapy Tablet: Pooled safety analysis of clinical trials

Tilo Biedermann[1], Peter Couroux[2], Tina Greve[3], and Mika Makela[4]

[1]Technische Universität München
[2]Inflamax Research Inc
[3]ALK
[4]University of Helsinki, the Skin and Allergy Hospital

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Abstract

Background: The SQ tree SLIT-tablet has recently been approved for treatment of tree pollen allergy. Health care workers should be provided with detailed safety data for clinical use. **Objective**: To assess the tolerability and safety of the SQ tree SLIT-tablet in adults and adolescents. **Methods**: Safety data were pooled from two phase-II and one phase-III double-blinded, randomized, placebo-controlled trials including adults and adolescents with allergic rhinitis and/or conjunctivitis treated before and during one pollen season once-daily with the SQ tree SLIT-tablet (12 SQ-Bet) or placebo. **Results**: The most frequently reported IMP-related AEs with 12 SQ-Bet were oral pruritis (39% of subjects) and throat irritation (29%). IMP-related AEs were mainly mild or moderate in severity, and the majority resolved without treatment and did not lead to treatment interruption/discontinuation. With 12 SQ-Bet, oral pruritus was more frequent among PFS subjects (45%) than in subjects without PFS (29%). A greater proportion of PFS subjects interrupted treatment (19%) than subjects without PFS (7%). The 12 SQ-Bet did not seem to induce an increased risk of asthma: 7 events were reported in 7 subjects with 12 SQ-Bet and 11 in 10 subjects with placebo. No differences were seen in the risk of moderate to severe IMP-related AEs regardless of age, PFS status and asthma medical history. **Conclusions**: The 12 SQ tree SLIT-tablet was well tolerated in tree pollen allergic subjects with no major safety concerns detected. This safety profile supports daily at-home sublingual administration once the first dose is tolerated when administered under medical supervision.

Title

Safety of the SQ Tree Sublingual Immunotherapy Tablet: Pooled safety analysis of clinical trials

[title is 97 characters including spaces (should be less than 100).]

Short running title

Safety of the SQ tree SLIT-tablet

34 characters including spaces (less than 50 characters).

Authors

Tilo Biedermann, MD[a], Peter Couroux, MD[b], Tina Maria Greve, MSc, PhD[c] and Mika Mäkelä, MD, PhD, MSc[e].

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Affiliations

[a]Department of Dermatology and Allergology, Technical University of Munich, Munich, Germany, and Clinical Unit Allergology, Helmholtz Zentrum Munich, German Research Center for Environmental Health GmbH, Neuherberg-Munich, Germany, [b] Inflamax Research Inc., Mississauga, Ontario, Canada, [d]Global Clinical Development, ALK, Hørsholm, Denmark,[e]Inflammatory Diseases, Skin and Allergy Hospital, Helsinki University Central Hospital, Finland.

Author e-mails : tilo.biedermann@tum.de, TinaMaria.Greve@alk.net, pcouroux@cliantha.com and Mika.Makela@hus.fi

Corresponding author:

Tilo Biedermann: tilo.biedermann@tum.de.

Conflict of interest statement

The authors has the following potential conflicts of interest: Tilo Biedermann gave advice to or got an honorarium for talks or received a research grant from the following companies: ALK, Mylan, Novartis, Sanofi-Regeneron, Phadia Thermo-Fisher, Celgene, Lilly Deutschland GmbH, Leo Pharma, Symrise AG; Tina Maria Greve is employed by ALK; Peter Couroux and Mika Mäkelä has nothing to disclose.

Author contributions:

All authors made substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data. All authors gave input to the manuscript and revised the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. Tilo Biedermann, Peter Couroux and Mika Mäkelä were signatory investigators in the trials and Tina Maria Greve was responsible for analsis and reporting of the trial safety data.

Abstract

Background : The SQ tree SLIT-tablet has recently been approved for treatment of tree pollen allergy. Health care workers should be provided with detailed safety data for clinical use.

Objective: To assess the tolerability and safety of the SQ tree SLIT-tablet in adults and adolescents.

Methods : Safety data were pooled from two phase-II and one phase-III double-blinded, randomized, placebo-controlled trials including adults and adolescents with allergic rhinitis and/or conjunctivitis treated before and during one pollen season once-daily with the SQ tree SLIT-tablet (12 SQ-Bet) or placebo.

Results : The most frequently reported IMP-related AEs with 12 SQ-Bet were oral pruritis (39% of subjects) and throat irritation (29%). IMP-related AEs were mainly mild or moderate in severity, and the majority resolved without treatment and did not lead to treatment interruption/discontinuation. With 12 SQ-Bet, oral pruritus was more frequent among PFS subjects (45%) than in subjects without PFS (29%). A greater proportion of PFS subjects interrupted treatment (19%) than subjects without PFS (7%). The 12 SQ-Bet did not seem to induce an increased risk of asthma: 7 events were reported in 7 subjects with 12 SQ-Bet and 11 in 10 subjects with placebo. No differences were seen in the risk of moderate to severe IMP-related AEs regardless of age, PFS status and asthma medical history.

Conclusions: The 12 SQ tree SLIT-tablet was well tolerated in tree pollen allergic subjects with no major safety concerns detected. This safety profile supports daily at-home sublingual administration once the first dose is tolerated when administered under medical supervision.

[250 words]

Keywords *:* up to 5, listed in alphabetical order.

Allergy treatment, pollen, rhinitis, vaccines, food allergy.

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Manuscript main text

[3.288 words] (should be less than 3.500 words)

Introduction

The mean prevalence of sensitisation to birch pollen has been estimated to range from approximately 8% to 16% in general European populations, from 9.4% to 22% across different regions of Canada and from 11% to 20% across US regions[1-3]. Pollen from birch and other members of the birch homologous group including alder, hornbeam, hazel, beech and oak is a major reason for allergic rhinitis and possibly also asthma symptoms[1,4-6]. The members of the birch homologous group are all characterized by containing allergen homologous to the major birch allergen Bet v 1.

Allergen immunotherapy (AIT) is the only available treatment modality with the potential to modify the natural course of the allergic disease by induction of tolerance[7]. Recently, the SQ tree sublingual immunotherapy (SLIT)-tablet received regulatory approval across Europe, Canada and Switzerland for the treatment of tree pollen allergy. Hence, a detailed analysis of existing safety data obtained with this tablet in clinical trials will be of high interest to physicians and other health care providers within the field of allergy immunotherapy. The objective of this pooled safety analysis is therefore to provide detailed safety data for health care workers to be used in their clinical practice.

It has been estimated that SLIT is used in 45 % of patients receiving allergen immunotherapy[7], and the safety profile of SLIT appears to be favourable when compared with subcutaneous immunotherapy (SCIT)[7-10]. Anaphylactic reactions occur with SLIT as well as SCIT products, but they are more frequently observed with SCIT products. This is why SLIT rather than SCIT products are recommended for at-home administration. Local application site reactions occur commonly with both products[7], and the local application site reactions with SLIT tend to be mild in nature, transient and self-resolving and occur most frequently early in the treatment period[9,11].

Around 70 percent of individuals with tree pollen allergy also develop allergic symptoms against certain foods such as nuts and apples containing Bet v 1 homologous allergens, and the symptoms are manifested as a condition called pollen food syndrome (PFS)[1,12]. The safety profile of individuals with PFS will be of special interest in the present safety analysis.

The clinical programme conducted so far with the SQ tree SLIT-tablet comprise one phase-I trial, two phase II trials and one pivotal phase-III trial. All trials were conducted as randomised, parallel-group, double-blind, placebo-controlled clinical trials. This pooled safety analysis includes the two phase-II and the pivotal phase-III trials.

Methods

The SQ tree SLIT-tablet is a fast-dissolving pharmaceutical formulation (oral lyophilisate) for daily at-home self-administration apart from the first tablet, that must be administered at the clinic. It contains standardised allergen extract from white birch pollen (*Betula verrucosa*).

Trial design

Safety data were pooled from two phase-II and one pivotal phase-III double-blinded, randomized placebo-controlled, parallel-group trials including adults and adolescents with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group. The data included subjects who

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received placebo or a daily dose of 12 SQ-Bet. The trials were conducted at 124 sites in total in Canada, Czech Republic, Denmark, France, Germany, Finland, Lithuania, the Netherlands, Norway, Poland, Russia and Sweden.

The subjects were treated before and during one pollen season with once-daily SQ tree SLIT-tablet or placebo administered at home. The first dose was administered under medical supervision for 30 minutes after tablet intake to assess tolerability and allow for possible treatment of any immediate side effects. The design as well as efficacy and safety results of the phase II trials and the pivotal phase-III trial have been described separately elsewhere[13-15].

Population

The study populations in the phase-II and phase-III trials comprised adolescents and adults (12-65 years) with persistent moderate-to-severe allergic rhinitis and/or conjunctivitis induced by birch pollen despite having received symptom-relieving medication during the 2 previous tree pollen seasons. Subjects had to have a positive skin prick test response (wheal diameter, >3mm) 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 rhinitis and/or conjunctivitis during the previous birch pollen season. Subjects with uncontrolled asthma or severe asthma exacerbations were excluded from the trial.

The subjects in the pooled safety analysis data set (hereafter called 'pooled population') comprised

subjects from the mentioned phase-II and phase-III trials who were randomized to a daily dose of 12 SQ-Bet or placebo and received at least one dose of treatment.

Endpoints and assessments

Number of treatment-emergent adverse events (AEs) and AEs assessed by the investigator as possibly related to the investigational medicinal product (IMP-related) were summarised by treatment group and MedDRA System Organ Class (SOC), MedDRA Preferred Term and classified by severity (mild, moderate, severe), seriousness, action taken, time from first intake to AE (onset day), and reoccurrence after IMP administration. AEs were recorded from the point in time when subjects signed the informed consent form and up until the last follow-up. All AEs were coded according to the current MedDRA version at the time of trial conduct. For the pooled population, AEs were re-coded to MedDRA version 19.0.

The severity of an AE was a clinical observation assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

An AE was considered treatment-emergent if the time of onset was after the time of first IMP dose. However, if a subject discontinued, only AEs recorded up until 7 days after the discontinuation date were considered treatment emergent.

Statistical methodology

In addition to the pooled population, two other data pools were used in order to investigate the difference between adults and adolescents: One pool including adults ([?] 18 years) and one pool including adolescents (12- < 18 years). The safety analyses were conducted according to the actual treatment that subjects received regardless of randomization.

Demographic (including age and gender) and baseline characteristics was summarised by treatment group. Onset and duration in days were summarised by treatment group and preferred term for most frequent IMP-related AEs ([?] 1% of subjects in the 12 SQ-Bet treatment group). Onset is the time from randomisation to the start of the AE. AEs were summarised in terms of treatment emergent AEs and by causal relation to

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IMP, severity, seriousness, and AEs leading to discontinuation (treatment emergent AEs and AEs related to IMP respectively).

A graphical overview was presented for the frequencies of the most frequent ([?] 5%) IMP-related AEs for subjects on active treatment in the pooled population by preferred term and worst case severity (i.e. if a subject had more than 1 event, only the highest intensity was used). Likewise, IMP-related AEs in adults and adolescents with and without asthma was presented by treatment group (pooled population) and by-worst case severity (for subjects treated with 12 SQ-Bet only).

To evaluate safety across additional intrinsic factors, an analysis of the differences between treatment groups in risk, calculated as hazard ratio, of experiencing first moderate or severe treatment-related AEs in specific subgroups (age (adolescents/adults), asthma status, IgE level (class 2-3 or class 4-6), sensitisation (mono/poly) and PFS) were performed for the pooled population. The results were presented in a forest plot.

Results

Subjects and baseline characteristics

The pooled population comprised 929 randomised subjects (471 subjects treated with 12 SQ-Bet and 458 subjects treated with placebo) aged 12 to 65 years. Of the population exposed to 12 SQ-Bet, 35 subjects (7%) were adolescents. All randomised subjects received at least 1 dose of IMP. A total of 832 subjects (90%) completed the trials. Overall, the treatment groups appeared to be similar (Table 1).

Of subjects exposed to 12 SQ-Bet, 88% were exposed for 24-41 weeks, and twelve percent for less than 24 weeks. The average treatment duration of the three phase-II/III trials varied between 23 and 32 weeks.

Overall safety

A higher proportion of subjects reported IMP-related AEs with 12 SQ-Bet than with placebo (Table 2). IMP-related AEs were mainly local allergic reactions primarily in the oral cavity and throat and were related to the sublingual administration of IMP. They were mild or moderate in severity: 79% were mild and 17% moderate with 12 SQ-Bet and 65% were mild and 31% moderate with placebo. The majority resolved without treatment (76% of events for 12 SQ Bet and 83% for placebo).

Common IMP-related AEs

The most frequently reported IMP-related AEs with 12 SQ Bet were oral pruritus (39% of subjects) and throat irritation (29%). This was the same for placebo but with a lower frequency: 7% (oral pruritus) and 4% (throat irritation) (Figure 1). Frequent IMP-related AEs outside the oral cavity related to treatment with 12 SQ-Bet were: ear pruritus (13% of subjects), cough (6%), and sensation of foreign body (2%). Severe IMP-related AEs reported by more than 1 subject treated with 12 SQ-Bet were oral hypoaesthesia, oral paraesthesia, tongue pruritus, mouth swelling, cough, oropharyngeal pain and lip swelling.

AEs leading to discontinuation

The majority of AEs leading to discontinuations were IMP-related: 33 subjects (7%) discontinued due to IMP-related AEs after treatment with 12 SQ-Bet and 8 subjects (2%) after receiving placebo. The most frequent IMP-related AEs leading to discontinuation after treatment with 12 SQ-Bet were throat irritation (10 subjects), oral pruritus (8 subjects), mouth swelling (8 subjects), swollen tongue (5 subjects), pharyngeal oedema (5 subjects) and ear pruritus (5 subjects). The majority of discontinuations due to IMP-related AEs occurred within the first few weeks of treatment. A greater proportion of subjects with PFS interrupted their treatment (19%) compared with no PFS (7%).

Onset and duration of common IMP-related AEs

The most frequently reported IMP-related AEs had onset early during treatment. For the majority of IMP-related AEs, the median time of onset was within the first week of treatment (Figure 2). The local allergic

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reactions reported most frequently such as oral pruritus, throat irritation, tongue pruritus, oral paraesthesia and pharyngeal oedema all had median onset on day 1. Very few subjects had onset of new events after two weeks of treatment.

Median duration of the AEs was less than two weeks for most types of AEs, and for oral pruritus and throat irritation – the most common AEs – it was 11 days. In the group treated with 12 SQ-Bet, the longest median durations of most frequent IMP-related AEs was seen with dyspepsia (75 days), dry mouth (25 days), oral pain (21 days) and nasal pruritus (18 days).

Serious AEs

No deaths were reported in the pooled phase-II/III trials. 15 subjects (2%) experienced 15 SAEs, 9 of these were reported with 12 SQ-Bet and 6 with placebo. 2 SAEs were assessed as IMP-related: 1 in each of the two groups, both involving accidental intake of IMP by subject's child. Both cases were asymptomatic as has previously been described[13].

Safety in special groups

No events of anaphylactic reactions or eosinophilic esophagitis (EoE) were reported. A subgroup analysis did not show any major differences in the risk of experiencing first moderate to severe IMP-related AEs across subgroups including age, asthma history, sensitisation, IgE level and PFS status (Figure 4). Across all subgroups, hazard ratios were less than 1, i.e. there was an increased risk of IMP-related AEs in the active treatment group compared with placebo as expected. The subgroup analysis did not show any major differences in the risk of experiencing a moderate or severe IMP-related AE across subgroups, including age (adolescents versus adults, p=0.487), sensitisation status (mono- versus poly-sensitisation, p=0.571), birch IgE class (class 2-3 versus 4-6, p=0.573), asthma status (asthma versus no-asthma, p=0.077) and PFS status (PFS versus no-PFS, p=0.589).

PFS: At baseline, 296 (63%) and 296 (65%) of subjects treated with 12 SQ-Bet and placebo respectively reported to have PFS. After treatment, 9 subjects reported AEs of PFS: 7 subjects treated with 12 SQ-Bet (including 4 AEs of worsening of PFS) and 2 subjects treated with placebo (including 1 AE of worsening of PFS). All AEs were assessed as IMP-related when treated with 12 SQ-Bet and 1 was assessed as IMP-related with placebo. A larger proportion of subjects with PFS reported AEs compared with those without PFS. This was observed for both treatments: 89% of subjects with PFS and 80% without PFS experienced AEs with 12 SQ-Bet and 67% versus 56% experienced AEs with placebo. Likewise, of those treated with 12 SQ-Bet, oral pruritus was reported by 45% of subjects with PFS and by 29% of subject with no PFS. No major differences between subjects with and without PFS were seen for severity of AEs. A greater proportion of subjects had IMP interruptions in the PFS subgroup (19%) compared with subjects without PFS (7%).

Asthma : The 12 SQ-Bet treatment did not seem to induce an increased risk of asthma events. In total, 18 AEs of asthma were reported (7 in 7 subjects treated with 12 SQ-Bet and 11 AEs in 10 subjects treated with placebo). These included 6 AEs of asthma exacerbation: 2 in 2 subjects treated with 12 SQ-Bet and 4 in 3 subjects on placebo. The majority of asthma AEs were mild or moderate in severity and assessed as unlikely related to IMP.

For subjects treated with 12 SQ-Bet, the proportion of subjects with asthma who reported any severe IMP-related AEs was 7% compared with 3% for subjects without asthma (Figure 3B).

Slightly more adolescents with asthma tended to experience AEs than adolescents without asthma (85% versus 79%), and these AEs were mild in severity. However, these data should be interpreted with caution as only 13 adolescent subjects with asthma participated in the clinical phase-II/III trial programme.

Eczema : Only one subject reported eczema. This was worsening of a pre-existing eczema (atopic dermatitis) in a subject treated with 12 SQ Bet.

Urticaria related to the IMP was reported by 6 subjects treated with 12 SQ Bet and 4 treated with placebo. The 6 subjects treated with 12 SQ Bet experienced contact urticaria at the administration site (2 subjects

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reported lip urticaria and 1 subject reported local urticaria), urticaria at the hand (1 subject), urticaria in several places of the body (1 subject reported urticaria on the neck after 3 days and on the chest and upper arm after 212 days) and for 1 subject no details were specified. 6 subjects in the placebo group also reported urticaria. In 4 of the subjects the events (5 events) were assessed as possibly related to the treatment despite the subject never being treated with the tree SLIT-tablet. The events included 4 local reactions and 1 with unspecified location. In the remaining 2 subjects, urticaria was assessed as unlikely related to the tree SLIT-tablet.

This suggests either a systemic urticaria or a local urticaria resulting from touching the SLIT-tablet. None of the urticaria events were severe or lead to discontinuation.

Safety in adolescents

No major differences were observed between adolescents (12-17 years) and adults ([?]18 years) in the proportion of subjects reporting AEs including causality, severity, seriousness, and discontinuation (Table 2). Also, for IMP-related AEs no difference was observed, indicating no difference in the overall safety and tolerability between the two subgroups (Table 2).

Discussion

These results from a pooled safety analysis of clinical trials with 929 adults and adolescents with allergic rhinitis and/or conjunctivitis induced by birch pollen, revealed no major safety concerns in relation to daily at-home use of the SQ tree SLIT-tablet. Thus, the safety profile supports daily at-home sublingual administration once the first dose is tolerated when administered under medical supervision: Most application-site reactions were local reactions of the mouth, throat, and ear and were generally occurring early in treatment and were transient, and self-resolving. Also, no anaphylactic reactions or IMP-related SAEs were reported for the subjects.

The results confirm previous safety findings with other SQ sublingual immunotherapy tablets. A grass SLIT-tablet showed a similar safety profile dominated by local allergic applications-site reactions primarily in the oral cavity and throat of mild or moderate severity with an early onset and transient and self-resolving AEs[16-17]. Also, the safety profile of a house dust mite SLIT-tablet revealed transient, mild local allergic reactions representing the most commonly occurring adverse reactions[18].

Around 70 percent of individuals with birch pollen allergy develop pollen food syndrome (PFS)[1], and in the present study 64% of subjects had PFS. This PFS subpopulation could be expected to be more challenged in relation to their allergic disease, and the safety profile may therefore differ compared with a subpopulation with no PFS[19]. In the present data, subjects with PFS tended to experience more AEs regardless of treatment than subjects without PFS, especially oral pruritus. Of subjects treated with 12 SQ-Bet, oral pruritus was reported by almost half of the subjects with PFS (45%) and was thus far more frequent than in subjects without PFS (29%). This difference was not seen in relation to severity. This high reporting of oral pruritus is in accordance with what is usually seen in relation to PFS[19].

The present data suggest no increased risk of asthma events among all subjects treated with 12 SQ-Bet. In addition, no acute asthma worsening was seen in subjects with a medical history of asthma. This is in line with the general safety profile of sublingual immunotherapy revealing no greater risk for adverse reactions in well controlled asthma[7]. However, in the studied population, subjects with severe and/or uncontrolled asthma were excluded, and the safety profile of 12 SQ-Bet remains to be investigated in this subpopulation.

Patients with birch pollen allergy may show urticaria or worsening of atopic dermatitis when exposed to birch pollen[20-21]. In the present pooled safety analysis, only one event of worsening of atopic dermatitis was reported, however we saw more events of urticaria in the group treated with 12 SQ-Bet compared with placebo. Contact urticaria following direct contact to allergen containing SLIT tablets are to be interpreted like PFS developing in the mouth. Only one subject in the active group developed urticaria at sites distant from the local exposure. This may or may not be related to the systemic administration of 12 SQ-Bet, since similar events were reported in the placebo group.

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EoE is highly associated with PFS and one study has found that around half of EoE patients had symptomatic PFS.[22, 23] In the present study, more than 60% of the subjects had PFS, but the incidence of EoE in populations with PFS has to our knowledge not been investigated. No cases of EoE were found during treatment, however the length of the studies including 6-9.5 months of treatment might not have been sufficient to detect possible EoE cases.

The studies included in the present pooled safety analysis were all short-term studies conducted during one pollen season. No long-term studies have been conducted with the SQ tree SLIT-tablet, however long-term studies with the grass SLIT-tablet has revealed a favourable safety profile and long-term treatment effect[17,24].

Conclusion

In conclusion, the 12 SQ tree SLIT-tablet was well tolerated in tree pollen allergic subjects with no major safety concerns detected. The majority of the most frequently reported IMP-related AEs were local allergic reactions primarily in the oral cavity and throat. They resolved without treatment, and they were mild or moderate in severity with the onset of the most frequently reported local reactions on day 1.

This safety profile supports daily at-home sublingual administration once the first dose is tolerated when administered under medical supervision. Additional studies should investigate the long-term safety and tolerability of the SQ tree SLIT-tablet.

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Table legends

Table 1: Demography and baseline characteristics of the pooled population.

Table 2: *Summary of AEs in the pooled population.*

Figure legends

Figure 1:*Most frequently reported IMP-related AEs (>5%) for subjects treated with 12 SQ-Bet (pooled population) by severity.***Figure 2:** *Median onset and duration of most frequent IMP-related treatment emergent AEs ([?]1%) for subjects treated with 12 SQ-Bet, pooled population.* **Figure 3A*: IMP-related AEs in adults and adolescents with and without asthma (pooled population) by treatment group.* Figure 3B*: IMP-related AEs by severity in adults and adolescents with and without asthma for subjects treated with 12 SQ-Bet.***Figure 4:** *Forest plot of hazard ratios of first moderate or severe IMP-related AE in various subgroups.*

SUPPLEMENTARY APPENDIX:

Table E1: *Most frequent treatment emergent AEs ([?]5% of subjects treated with 12 SQ-Bet) according to PFS status (pooled population).*

Table 1: Demography and baseline characteristics of the pooled population +

	Placebo (N=458)	**Placebo (N=458)**	**12 SQ-Bet (N=471)**
	N	%n	N
Sex	Sex	Sex	Sex
Male	220	(48%)	227
Female	238	(52%)	244
Age	Age	Age	Age
Mean (SD)	36.1 (13.2)	36.1 (13.2)	37.3 (13.4)
Min – Max	12.0 - 65.0	12.0 - 65.0	12.0 - 65.0
SPT	SPT	SPT	SPT
Birch only	8	(2%)	11
Birch homologous group only	88	(19%)	99
Birch homologous group only + others	369	(81%)	372
Bet v 1 specific IgE class	Bet v 1 specific IgE class	Bet v 1 specific IgE class	Bet v 1 specific IgE class
2-3	226	(49%)	226
4-6	232	(51%)	243
Unknown	-	-	2
Birch allergy	Birch allergy	Birch allergy	Birch allergy
Birch AR/C	458	(100%)	471
Years with AR/C, mean (SD)	17.0 (11.8)	17.0 (11.8)	15.8 (10.8)
Asthma (any cause)	Asthma (any cause)	Asthma (any cause)	Asthma (any cause)
Asthma at baseline	168	(37%)	184
Years with asthma, mean (SD)	12.9 (10.7)	12.9 (10.7)	12.0 (10.7)
PFS	PFS	PFS	PFS
PFS at baseline	296	(65%)	296
Years with PFS, mean (SD)	14.9 (11.3)	14.9 (11.3)	14.2 (10.9)

+All randomised and treated subjects; N = Number of subjects in pool; n = number of subjects in subgroup; % = percentage of subjects in subgroup; SD = standard deviation. IgE class 2-3: Bet v1 IgE 0.71-17.5 kU/L;

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IgE class 4-6: >17.5 kU/L.

Table 2: Summary of AEs in the pooled population +

	Placebo	**Placebo**	**Placebo adolescents**	**Placebo adolescents**	**Placebo adults**	**Placebo adults**	**12 SQ-Bet**	**12 SQ-Bet**	**12 SQ-Bet adolescents**	**12 SQ-Bet adolescents**	**12 SQ-Bet adults**	**1 S B a**
	(N=458)	**(N=458)**	**(N=37)**	**(N=37)**	**(N=421)**	**(N=421)**	**(N=471)**	**(N=471)**	**(N=35)**	**(N=35)**	**(N=436)**	**(**
Subjects reporting	N	(%n)	N	(%n)	N	(n%)	N	(n%)	N	(%n)	N	(
Treatment emergent AEs	289	(63%)	22	(59%)	267	(63%)	402	(85%)	29	(83%)	373	(
AEs related to IMP	144	(31%)	10	(27%)	134	(32%)	373	(79%)	28	(80%)	345	(
Severe treatment emergent AEs	12	(3%)	1	(3%)	11	(3%)	39	(8%)	2	(6%)	37	(
Severe AEs related to IMP	2	(<1%)	1	(3%)	1	(<1%)	22	(5%)	1	(3%)	21	(
Serious treatment emergent AEs	6	(1%)	–	–	6	(1%)	9	(2%)	–	–	9	(
Serious AEs related to IMP	1	(<1%)	–	–	1	(<1%)	1	(<1%)	–	–	1	(

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	Placebo	**Placebo**	**Placebo adolescents**	**Placebo adolescents**	**Placebo adults**	**Placebo adults**	**12 SQ-Bet**	**12 SQ-Bet**	**12 SQ-Bet adolescents**	**12 SQ-Bet adolescents**	**12 SQ-Bet adults**	**1 S E a**
Treatment emergent AEs leading to discontinuation	11	(2%)	–	–	11	(3%)	39	(8%)	1	(3%)	38	(
AEs related to IMP leading to discontinuation	8	(2%)	–	–	8	(2%)	33	(7%)	1	(3%)	32	(

+All randomised and treated subjects; N = number of subjects in pool; n = number of subjects with events; %n = percentage of subjects with events.

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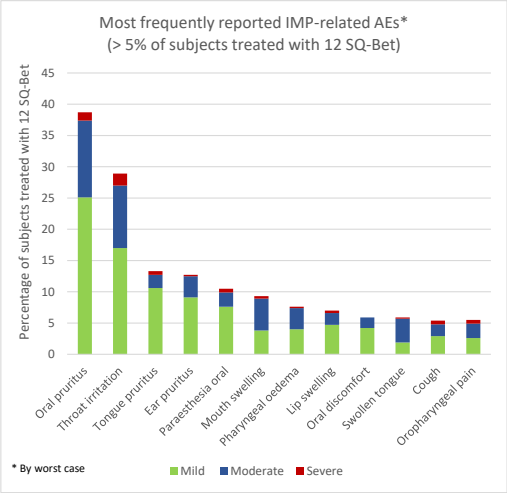

'By worst case': Each subject is counted only once and by worst severity.

Figure1: Most frequently reported IMP-related AEs (>5%) for subjects treated with 12 SQ-Bet (pooled population) by severity.

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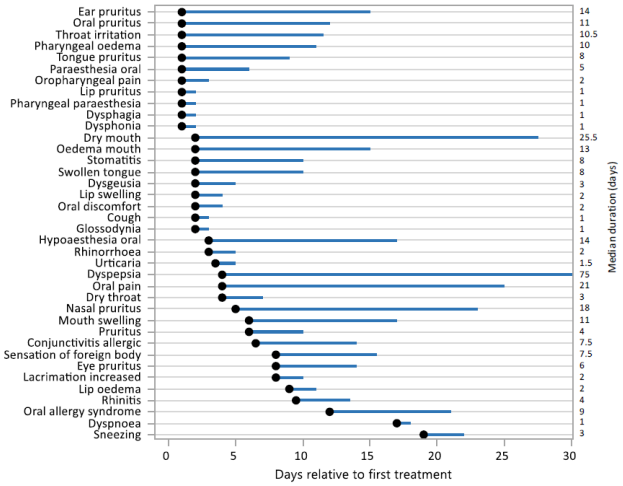

Figure 2: Median onset and duration of most frequent IMP-related treatment emergent AEs (≥1%) for subjects treated with 12 SQ-Bet, pooled population.

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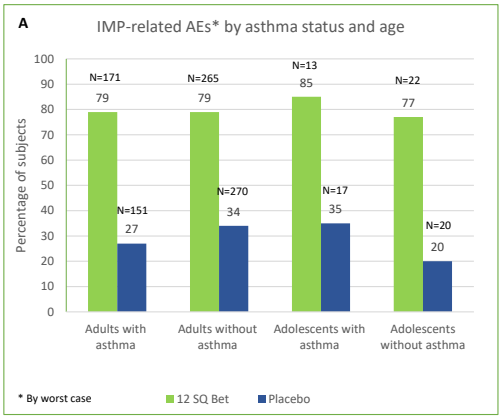

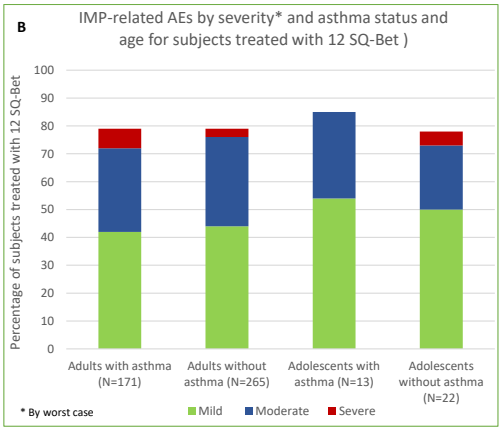

'By worst case': Each subject is counted only once and by worst severity.

Figure 3A: IMP-related AEs in adults and adolescents with and without asthma (pooled population) by treatment group.

Figure 3B: IMP-related AEs by severity in adults and adolescents with and without asthma for subjects treated with 12 SQ-Bet.

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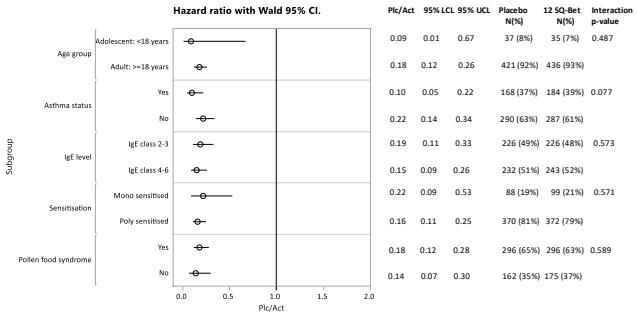

	Plc/Act	95% LCL	95% UCL	Placebo N(%)	12 SQ-Bet N(%)	Interaction p-value
Adolescent: <18 years	0.09	0.01	0.67	37 (8%)	35 (7%)	0.487
Adult: >=18 years	0.18	0.12	0.26	421 (92%)	436 (93%)	
Yes	0.10	0.05	0.22	168 (37%)	184 (39%)	0.077
No	0.22	0.14	0.34	290 (63%)	287 (61%)	
IgE class 2-3	0.19	0.11	0.33	226 (49%)	226 (48%)	0.573
IgE class 4-6	0.15	0.09	0.26	232 (51%)	243 (52%)	
Mono sensitised	0.22	0.09	0.53	88 (19%)	99 (21%)	0.571
Poly sensitised	0.16	0.11	0.25	370 (81%)	372 (79%)	
Yes	0.18	0.12	0.28	296 (65%)	296 (63%)	0.589
No	0.14	0.07	0.30	162 (35%)	175 (37%)	