Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ITULAZAX 12 SQ-Bet sublingual lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Standardised allergen extract of pollen from white birch (*Betula verrucosa)* 12 SQ-Bet* per sublingual lyophilisate.

* [SQ-Bet is the dose unit for ITULAZAX. SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract. Bet is an abbreviation for Betula.]

The content of the individual allergen Bet v 1 is determined according to Ph. Eur. to be 194 micrograms on average per sublingual lyophilisate. Clinical efficacy and clinical safety of allergy immunotherapy (AIT) products also depend on other factors e.g. manufacturing process, formulation, product composition and administration.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual lyophilisate

White to off-white freeze-dried debossed sublingual lyophilisate

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ITULAZAX is indicated in adults and children (5 years or older) for the treatment of moderate-to-severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous group
[1].

[1] Birch homologous group: *Betula verrucosa* (birch), *Alnus glutinosa* (alder), *Carpinus betulus* (hornbeam), *Corylus avellana* (hazel), *Quercus alba* (oak) and *Fagus sylvatica* (beech).
. ITULAZAX is indicated in patients with a clinical history of symptoms despite use of symptom-relieving medication and a positive test of sensitisation to a member of the birch homologous group (skin prick test and/or specific IgE).

4.2 Posology and method of administration

Posology
The recommended dose for adults and children (5 years or older) is one sublingual lyophilisate (12 SQ-Bet) daily.

It is recommended that treatment with ITULAZAX should be initiated outside the pollen season and continued during the tree pollen season. Clinical effect during the tree (birch homologous group) pollen season has been demonstrated when treatment is initiated at least 16 weeks prior to the expected start of the tree (birch homologous group) pollen season and continued throughout the season. There are no clinical data available for an in-season treatment start.

International treatment guidelines refer to a treatment period of 3 years for allergy immunotherapy to achieve disease modification. Long-term efficacy has not yet been established. If no improvement is observed during the first year of treatment with ITULAZAX there is no indication for continuing treatment.

Elderly population
Clincial experience in patients ≥65 years of age is limited.

Paediatric population

The posology to be used in children (5-17 years) is the same as in adults. Clinical experience in treatment of allergic rhinitis and/or conjunctivitis with ITULAZAX in children below 5 years of age has not been established. ITULAZAX is not intended for treatment of allergic rhinitis and/or conjunctivitis in children below 5 years of age. Currently available data are described in section 4.8 and 5.1.

Method of administration
ITULAZAX treatment should be initiated by physicians with experience in treatment of allergic diseases. The first sublingual lyophilisate should be taken under medical supervision and the patient should be monitored for at least half an hour to enable discussion and possible treatment of any immediate side effect.

ITULAZAX is a sublingual lyophilisate. The sublingual lyophilisate should be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue, where it will disperse. Swallowing should be avoided for approximately 1 minute. Food and beverages should not be taken for the following 5 minutes.

If treatment with ITULAZAX is interrupted for a period of up to 7 days, treatment can be resumed by the patient. If the treatment is interrupted for more than 7 days it is recommended to contact a physician before resuming the treatment.

4.3 Contraindications

Hypersensitivity to any of the excipients (for a full list of excipients, see section 6.1).

Patients with FEV_1 <70% of predicted value (after adequate pharmacological treatment) at initiation of treatment.

Patients who have experienced a severe asthma exacerbation within the last 3 months prior to initiation.

Patients with uncontrolled asthma within the last 3 months prior to initiation.

Patients with active systemic autoimmune disorders (unresponsive to treatment) and patients with immune defects, immunodeficiencies or immunosuppression (see section 4.4).

Patients with malignant neoplasia with current disease relevance.

Patients with acute severe oral inflammation or oral wounds (see section 4.4).

4.4 Special warnings and precautions for use

Severe systemic allergic reactions
Treatment should be discontinued and a physician should be contacted immediately in case of severe systemic allergic reactions, severe asthma exacerbation, severe pharyngeal oedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat. The onset of systemic symptoms may include flushing, pruritus, sense of heat, general discomfort and agitation/anxiety.

One option for treating severe systemic allergic reactions is adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants, mono amino oxidase inhibitors (MAOIs) and/or COMT inhibitors with possible fatal consequences. The effects of adrenaline may be reduced in patients treated with beta-blockers.

Patients with cardiac disease may be at increased risk in case of severe systemic allergic reactions. Clinical experience in treatment with ITULAZAX of patients with cardiac disease is limited and allergy immunotherapy should be prescribed with caution in patients with severe cardiovascular disease.

Initiation of ITULAZAX in patients who have previously had a systemic allergic reaction to subcutaneous tree pollen allergy immunotherapy should be carefully considered, and measures to treat potential reactions should be available. This is based on post-marketing experience from a corresponding sublingual tablet product for grass pollen immunotherapy which indicates that the risk of a severe allergic reaction may be increased for patients who have previously experienced a systemic allergic reaction to subcutaneous grass pollen immunotherapy.

Asthma
Asthma is a known risk factor for severe systemic allergic reactions.

Severe asthma exacerbation within the last 12 months is a known risk factor for future exacerbations. Limited data is available with ITULAZAX treatment in this situation.

ITULAZAX has not been studied in patients with severe and/or uncontrolled asthma.

Patients with asthma must be informed of the need to seek medical attention immediately if their asthma deteriorates suddenly.

In patients with asthma experiencing an acute respiratory tract infection, initiation of ITULAZAX treatment should be postponed until the infection has resolved.

Oral inflammation
In patients with severe oral inflammation (e.g. oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction, or following tooth loss, initiation of ITULAZAX treatment should be postponed and ongoing treatment should be temporarily interrupted to allow healing of the oral cavity.

Local allergic reactions
When treated with ITULAZAX the patient is exposed to the allergen that causes the allergic symptoms. Therefore, local allergic reactions are to be expected during the treatment period. These reactions are usually mild or moderate; however, more severe reactions may occur. On the first few days of at-home administration adverse reactions, which were not observed on the first day of treatment, may occur. If the patient experiences significant local adverse reactions from the treatment, allergy pharmacotherapy (e.g. antihistamines) should be considered.

Eosinophilic oesophagitis
Cases of eosinophilic oesophagitis have been reported in association with ITULAZAX treatment. In patients with severe or persistent gastro-oesophageal symptoms such as dysphagia or dyspepsia, ITULAZAX should be interrupted and medical evaluation must be sought.

Autoimmune diseases in remission
Limited data is available on treatment with allergy immunotherapy in patients with autoimmune diseases in remission. ITULAZAX should therefore be prescribed with caution in these patients.

Simultaneous vaccination
Clinical experience in relation to simultaneous vaccination and treatment with ITULAZAX is missing. Vaccination may be given without interrupting treatment with ITULAZAX after medical evaluation of the general condition of the patient.

Fish allergy
ITULAZAX may contain trace amounts of fish protein. Available data have not indicated an increased risk of allergic reactions in patients with fish allergy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction trials have been conducted in humans and no potential drug interactions have been identified from any source. Concomitant therapy with symptomatic anti-allergic medications may increase the tolerance level of the patient to immunotherapy. This should be considered at discontinuation of such medications.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no data on the clinical experience for the use of ITULAZAX in pregnant women. Animal studies do not indicate increased risk to the foetus. Treatment with ITULAZAX should not be initiated during pregnancy. If pregnancy occurs during treatment, the treatment may continue after evaluation of the general condition (including lung function) of the patient and reactions to previous administration of ITULAZAX. In patients with pre-existing asthma close supervision during pregnancy is recommended.

Breastfeeding
No clinical data are available for the use of ITULAZAX during lactation. No effects on the breastfed infants are anticipated.

Fertility

There is no clinical data with respect to fertility for the use of ITULAZAX. In a repeat dose toxicity study in naïve mice no effects were observed in the reproductive organs of both genders.

4.7 Effects on ability to drive and use machines

Treatment with ITULAZAX has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile
Patients taking ITULAZAX should primarily expect mild to moderate local allergic reactions to occur within the first few days of treatment and disappear within a few months (in many cases within a week or two). For the majority of events, the reaction should be expected to start within 10 minutes after intake of ITULAZAX on each day of occurrence and abate within an hour. More severe local allergic reactions may occur (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions associated with ITULAZAX obtained from placebo-controlled clinical trials in adult patients and post-marketing surveillance are tabulated below.

Adverse reactions are divided into groups according to the frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Drug Reaction
Immune system disorders	***Common***	Oral allergy syndrome
	Not known	Anaphylactic reaction
Nervous system disorders	***Common***	Dysgeusia
Ear and labyrinth disorders	***Very common***	Ear pruritus
Eye disorders	***Common***	Symptoms of allergic conjunctivitis*
Respiratory, thoracic and mediastinal disorders	***Very common***	Throat irritation
	Common	Cough, dry throat, dysphonia, dyspnoea, oropharyngeal pain, pharyngeal oedema, pharyngeal paraesthesia, rhinitis
	Uncommon	Laryngeal oedema, throat tightness
Gastrointestinal disorders	***Very common***	Oedema mouth, oral pruritus, paraesthesia oral, tongue pruritus
	Common	Abdominal pain, diarrhoea, dyspepsia, dysphagia, gastrooesophageal reflux disease, glossodynia, hypoaesthesia oral, lip oedema, lip pruritus, nausea, oral discomfort, oral mucosal blistering, stomatitis, swollen tongue
	Uncommon	Glossitis, lip blister, mouth ulceration, oesophageal irritation
	Not known	Eosinophilic oesophagitis
Skin and subcutaneous tissue disorders	***Common***	Urticaria
	Uncommon	Angioedema
General disorders and administration site conditions	***Common***	Chest discomfort, sensation of foreign body

* Symptoms of allergic conjunctivitis typically include conjunctival hyperaemia, eye irritation, eye oedema/swelling, eyelid oedema, eye pruritus, lacrimation increased, and ocular hyperaemia.

Description of selected adverse reactions
ITULAZAX allergy immunotherapy involves repeated administration of natural allergen to which the patient is allergic. At initiation of treatment patients should be informed of the adverse reactions they are likely to experience and how to manage these in order to align expectations to treatment and optimise compliance.

Local allergic reactions are manifested in the upper respiratory or gastrointestinal system. Oral pruritus was reported in 38% of the patients, throat irritation in 29% of the patients and tongue pruritus was reported in 13% of the patients.

Systemic allergic reactions, including anaphylactic reactions, are known risks in patients receiving allergy immunotherapy and are considered a class effect.

Symptoms of oral allergy syndrome can occur upon ingestion of certain raw vegetables, fruits or nuts. Treatment with ITULAZAX may worsen the symptoms of existing oral allergy syndrome, and there have been a few new events of oral allergy syndrome reported. Symptoms typically occur at treatment initiation and may resolve with continued treatment.

Paediatric population
The safety profile of ITULAZAX in children (5-17 years) is based on data from double-blind placebo-controlled, multi-regional clinical trials. Overall, the safety profile in children treated with ITULAZAX was similar to that observed in adult patients. The majority of adverse reactions were mild to moderate in severity and seen with a similar frequency category for children compared to adults.

Eczema, headache, mouth swelling, nasal pruritus, oral mucosal erythema, oral pain, oropharyngeal discomfort, pharyngeal swelling, rash, rhinitis allergic, and tongue discomfort were reported with the frequency common (≥1/100 to <1/10).

Anaphylactic reaction, catarrh, oesophageal pain, salivary hypersecretion, and throat tightness were reported with the frequency uncommon (≥1/1,000 to <1/100).

No data on treatment with ITULAZAX in children below 5 years of age exist.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse via HPRA Pharmacovigilance;
Website : www.hpra.ie

4.9 Overdose

In a phase I trial, adult subjects with allergic rhinitis and/or conjunctivitis induced by birch pollen were exposed to doses of up to 24 SQ-Bet. For children, no data are available for exposure above the recommended daily dose of 12 SQ-Bet.

If doses higher than the recommended daily dose are taken, the risk of side effects may increase, including the risk of severe systemic allergic reactions or local allergic reactions. In case of severe systemic allergic reactions, severe asthma exacerbation, severe pharyngeal oedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat, immediate medical evaluation is needed. These reactions should be treated with relevant symptomatic medication.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extracts, tree pollen
ATC code: V01AA05

Mechanism of action
ITULAZAX is an allergen extract for immunotherapy of tree (birch homologous group) pollen-induced allergic rhinitis and/or conjunctivitis. Allergy immunotherapy with allergen products is the repeated administration of allergens to allergic individuals with the purpose of modifying the immunological response to the allergen.

The pharmacodynamic effects of allergy immunotherapy are exerted on the immune system, but the exact mechanism of action underlying clinical efficacy is not fully understood. However, several studies have shown that the immunological response to allergy immunotherapy is characterised by an induction of allergen specific IgG_4. Allergen specific IgG_4 competes with IgE for the binding to allergens, and thereby reduces activation of immune cells. The reduction of IgE binding to birch allergen has been confirmed for subjects treated with ITULAZAX and this was accompanied by induction of a treatment induced systemic IgG_4 response specific for birch. Extensive IgE cross-reactivity was observed towards the birch homologous trees before treatment initiation, thus indicating allergic sensitisation to the trees in this group, and a comparable level of IgG_4

cross-reactivity towards the birch homologous trees was observed after treatment with ITULAZAX. The increase in IgG_4 levels is observed after approximately 1 month of treatment and maintained throughout the treatment period.

Treatment with ITULAZAX also results in a rise in serum levels of apple (Mal d 1) specific IgG_4.

Clinical efficacy and safety

The efficacy and safety of ITULAZAX in the treatment of subjects with birch pollen-induced allergic rhinitis and/or conjunctivitis with or without asthma (controlled/partly controlled) has been demonstrated in 3 double-blind, randomised, placebo-controlled clinical trials (1 phase II and 2 phase III). Overall, ITULAZAX was well tolerated in birch pollen allergic subjects with no major safety concerns detected. ITULAZAX leads to improvements in disease control and quality of life reflected by symptom relief and reduced need for allergy pharmacotherapy/symptom relieving medication. Efficacy results from the 3 trials are described below.

Phase II (TT-03)

The phase II trial was a randomised, double-blind, placebo-controlled trial conducted in an allergen exposure chamber with doses of 2, 7 and 12 SQ-Bet (ITULAZAX) in 219 adults with birch pollen-induced rhinoconjunctivitis. The ITULAZAX group receiving 12 SQ-Bet included 54 subjects and the placebo group included 56 subjects. Subjects were exposed to birch pollen before treatment initiation and after 8, 16 and 24 weeks of treatment, and to oak pollen before treatment initiation and after 24 weeks of treatment. The primary endpoint was the average total symptom score during the week 24 birch challenge session. Total symptom score was calculated as the sum of the total nasal symptom score and the total ocular score.

Treatment with ITULAZAX resulted in a reduction in total symptom score during birch pollen exposure compared to placebo after 16 weeks of treatment, which was sustained until end-of-trial after 24 weeks of treatment (Table 1). Treatment with ITULAZAX also resulted in a reduction in total symptom score during oak pollen exposure after 24 weeks of treatment (Table 1). The results suggest that the clinical efficacy of ITULAZAX is similar during birch and oak pollen exposure.

Table 1 Analyses related to symptom scores during birch and oak sessions (TT-03)

Primary endpoints	**N**	**Adjusted mean**	**Absolute difference (placebo – ITULAZAX) [95% CL]**	**% Relative to placebo [95% CL]**	**p-value***
Average TSS during the week 16 birch session (modified FAS)					
Placebo	56	7.89	---	---	
ITULAZAX	54	6.18	1.70 [0.22 ; 3.18]	22 [3.18 ; 37.28]	0.02
Average TSS during the week 24 birch session (modified FAS)					
Placebo	56	7.10	---	---	
ITULAZAX	54	5.29	1.81 [0.33 ; 3.28]	25 [5.32 ; 42.51]	0.02
Pre-defined secondary endpoint	**N**	**Adjusted mean**	**Absolute difference (placebo – ITULAZAX) [95% CL]**	**% Relative to placebo [95% CL]**	**p-value***
Average TSS during the week 24 oak session (modified FAS)					
Placebo	56	7.47	---	---	
ITULAZAX	54	5.70	1.77 [0.18 ; 3.37]	24 [2.96 ; 41.31]	0.03

N = Number of subjects in analysis set, modified FAS = all subjects with observations, *p-value is for the test of an absolute difference of 0.
The response variable in the analysis was: the square root of the average TSS (results were back-transformed to original scale). The analysis was based on an LME model with treatment, visit (8, 16 and 24 weeks) and their two-factor interaction as fixed class effects, the average TSS at baseline as a fixed regression variable and chamber cohort and subject as random class variables.
TSS= total symptom score. CL = confidence limits.

Phase III (TT-04)

The phase III trial was a randomised, double-blind, placebo-controlled, multinational trial in 634 adults and adolescents (age 12-65) with birch pollen induced allergic rhinitis and/or conjunctivitis.
Subjects received ITULAZAX (12 SQ-Bet) or placebo for approximately 16 weeks prior to start of the tree pollen season and continued throughout the season with an average treatment duration of 32 weeks.

The primary endpoint was the average total combined score (TCS) of rhinoconjunctivitis symptoms and medication use during the birch pollen season (BPS).

The pre-defined key secondary endpoints were the TCS during the tree pollen season (TPS), which was defined by the combined alder, hazel and birch pollen seasons, and the average rhinoconjunctivitis daily symptom score (DSS) during the BPS and TPS. Pre-defined secondary endpoints included the daily medication score (DMS) during the BPS and TPS.

Treatment with ITULAZAX resulted in a statistically significant treatment effect during both the BPS and the TPS. Subjects on ITULAZAX experienced reductions in symptoms and medication scores compared to placebo for an average of 50 days (average duration of the TPS) (Table 2).

Table 2 Analyses related to symptom and medication scores during pollen seasons (TT-04)

Primary endpoint	N	Adjusted mean	Absolute difference (placebo – ITULAZAX) [95% CL]	% Relative to placebo [95% CL]	p-value*
Average TCS during the BPS (FASBPS)					
Placebo	292	7.62	---	---	
ITULAZAX	283	4.61	3.02 [1.99 ; 4.05]	40 [28.24 ; 49.51]	<0.0001
Pre-defined key secondary endpoints	**N**	**Adjusted mean**	**Absolute difference (placebo – ITULAZAX) [95% CL]**	**% Relative to placebo [95% CL]**	**p-value***
Average TCS during the TPS (FASBPS)					
Placebo	292	6.22	---	---	
ITULAZAX	283	3.95	2.27 [1.44 ; 3.11]	37 [24.99 ; 46.62]	<0.0001
Average DSS during the BPS (FASBPS)					
Placebo	292	3.60	---	---	
ITULAZAX	283	2.28	1.32 [0.84 ; 1.81]	37 [25.29 ; 46.70]	<0.0001
Average DSS during the TPS (FASBPS)					
Placebo	292	3.02	---	---	
ITULAZAX	283	2.03	0.99 [0.60 ; 1.38]	33 [21.45 ; 42.56]	<0.0001
Pre-defined secondary endpoints	**N**	**Adjusted mean**	**Absolute difference (placebo – ITULAZAX) [95% CL]**	**% Relative to placebo [95% CL]**	**p-value***
Average DMS during the BPS (FASBPS)					
Placebo	292	3.21	---	---	
ITULAZAX	283	1.63	1.58 [0.94 ; 2.22]	49 [33.38 ; 62.41]	<0.0001
Average DMS during the TPS (FASBPS)					
Placebo	292	2.58	---	---	
ITULAZAX	283	1.37	1.20 [0.69 ; 1.72]	47 [30.47 ; 60.29]	<0.0001
Average TCS during the alder/hazel pollen season (FASBPS)					
Placebo	286	4.07	---	---	
ITULAZAX	278	2.87	1.21 [0.46 ; 1.96]	30 [12.61 ; 43.80]	0.0015

N = number of subjects with observations, CL = confidence limits, TCS = total combined score, BPS = birch pollen season, TPS = tree pollen season, FASBPS = subjects in full analysis set with observations during the BPS, DSS = daily symptom score, DMS = daily medication score, *p-value is for the test of an absolute difference of 0.
DSS was the sum of 4 rhinitis and 2 conjunctivitis symptoms (range 0-18).
DMS was the sum of rescue medication provided by the sponsor (range 0-20).
TPS: Defined as days included in any of the hazel, alder and birch pollen seasons.
BPS: The start date was defined as the first day of 3 consecutive days with birch pollen counts ≥30 grains/m^3 and the stop date was defined as the last day in the last occurrence of 3 consecutive days with birch pollen count ≥30 grains/m^3.
Alder and hazel seasons: The start date was defined as the first day of 3 consecutive days with pollen counts ≥10 grains/m^3 and the stop date was defined as the last day in the last occurrence of 3 consecutive days with pollen count ≥10 grains/m^3.

Additional secondary endpoints supported the overall treatment effect of ITULAZAX. Subjects treated with ITULAZAX reported more days with minimal allergic rhinoconjunctivitis symptoms compared to placebo subjects (mild days) and fewer days with severe rhinoconjunctivitis symptoms during the BPS (Table 3). Rhinitis quality of life as measured by RQLQ(S) was also improved for subjects in the ITULAZAX group compared to placebo during the BPS (Table 4). Similar results were obtained for mild/severe days and RQLQ during the TPS. The results indicated an overall improved well-being for subjects treated with ITULAZAX.

Table 3 Analyses of estimated proportion of mild and severe days during the BPS (FASBPS) (TT-04)

Pre-defined secondary endpoints	N	Estimate	95% CL	p-value
Estimated proportion of mild days during the BPS (%)				
Placebo	292	42.65		
ITULAZAX	283	58.80		
	OR	1.92	[1.79 ; 2.06]	<0.0001
Estimated proportion of severe days during the BPS (%)				
Placebo	292	22.62		
ITULAZAX	283	12.12		
	OR	0.47	[0.43 ; 0.52]	<0.0001

BPS = birch pollen season, FASBPS = subjects in full analysis set with observations during the BPS, N = number of subjects with observations, CL = confidence limits, OR = odds-ratio.
OR: calculated as placebo/active.
Mild day: day without intake of antihistamines or olopatadine eye drops and no individual symptom scores higher than 1 (mild).
Severe day: day with DSS≥6 and at least 2 moderate or 1 severe symptom.

Table 4 Analysis of seasonal overall RQLQ during the BPS (FASBPS) (TT-04)

Pre-defined secondary endpoint	N	Adjusted mean	Absolute reduction (ITULAZAX - placebo) [95% CL]	p-value
Seasonal overall RQLQ during the BPS				
Placebo	292	1.45		
ITULAZAX	283	0.99	-0.45 [-0.63 ; -0.28]	<0.0001

RQLQ = rhinoconjunctivitisquality of life, BPS = birch pollen season, FASBPS = subjects in full analysisset with observations during the BPS, N = number of subjects with observations,CL = confidence limits.
Phase III (TT-06)
The phase III trial was a randomised, double-blind, placebo-controlled, multi-regional trial in 952 children (5-17 years) with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group.
Subjects received ITULAZAX (12 SQ Bet) or placebo for approximately 12 weeks prior to start of the tree pollen season (TPS) and continued throughout the season with an average treatment duration of 36 weeks.

The primary endpoint was the average total combined score (TCS) during the birch pollen season(BPS). The TCS is the sum of the daily rhinoconjunctivitis symptom score (DSS) and the daily medication score (DMS).

The key secondary endpoints were the average TCS during the TPS, the average DSS during the BPS and TPS, and the average DMS during the BPS and TPS. TPS was defined as the combined alder, hazel, birch and oak pollen seasons.

Treatment with ITULAZAX demonstrated statistically significant and clinically relevant improvement in the TCS during both the BPS and TPS compared to placebo treated subjects. The results were substantiated by reductions in both DSS and DMS compared to placebo during the BPS and TPS.

Post-hoc analyses of subgroups showed an absolute treatment difference of 1.81, 95% CI [0.85; 2.77] (relative difference of 26.6%) in TCS during BPS for treatment of subjects 5-11 years of age treated with ITULAZAX compared to placebo (n=597). Treatment of subjects 12-17 years of age with ITULAZAX resulted in an absolute treatment difference of 0.17, 95% CI [-0.91; 1.25] (relative difference of 3.5) in TCS during BPS compared to placebo (n=355).

The treatment effect may vary between patients depending on their asthma status.
Post-hoc analyses of the primary endpoint (TCS during BPS) for subjects 5-17 years of age with and without asthma at baseline compared to placebo showed an absolute treatment difference of 1.85 (95% CI [0.62; 3.08] in subjects with concomitant asthma and an absolute difference of 0.76 (95% CI [-0.11; 1.64] in subjects without asthma at baseline.

Post-hoc analyses of the primary endpoint (TCS during BPS) for subjects 5-11 years of age with and without asthma at baseline compared to placebo showed an absolute treatment difference of 2.64 (95% CI [1.00; 4.28] in subjects with concomitant asthma and an absolute difference of 1.36 (95% CI [0.17; 2.56] in subjects without asthma at baseline.
Post-hoc analyses of the primary endpoint (TCS during BPS) for subjects 12-17 years of age with and without asthma at baseline compared to placebo showed an absolute treatment difference of 0.63 (95% CI [-1.30; 2.56] in subjects with concomitant asthma and an absolute difference of -0.03 (95% CI [-1.34; 1.28] in subjects without asthma at baseline.

A pooled analysis of TCS during BPS across two phase III trials in subjects 5-65 years of age with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group treated with ITULAZAX or placebo (TT-04 and TT-06) showed an absolute difference of 2.35 (95% CI [1.31; 3.39] in subjects with asthma at baseline (n=583) and of 1.21 (95% CI [0.46; 1.96] in subjects without asthma at baseline (n=1003)

Table 5 Analyses related to symptom and medication scores during pollen seasons (FAS) (TT-06)

Primary endpoint	N	Adjusted means (SE)	Absolute difference [95% CI]	Relative difference (%) [95% CI]	p-value
Average TCS during the BPS					
Placebo	479	5.87 (0.34)	1.13 [0.42; 1.84]	19.2 [7.6; 29.5]	0.0019
ITULAZAX	473	4.74 (0.30)			
Key secondary endpoints	**N**	**Adjusted means (SE)**	**Absolute difference [95% CI]**	**Relative difference (%) [95% CI]**	**p-value**
Average TCS during the TPS					
Placebo	479	4.51 (0.26)	0.76 [0.26; 1.26]	16.8 [6.1; 26.4]	0.0031
ITULAZAX	473	3.75 (0.23)			
Average DSS during the BPS					
Placebo	479	2.76 (0.17)	0.28 [-0.06; 0.63]	10.2 [-2.5; 21.4]	0.1115
ITULAZAX	473	2.48 (0.16)			
Average DSS during the TPS					
Placebo	479	2.30 (0.14)	0.20 [-0.07; 0.46]	8.7 [-3.0; 19.1]	0.1421[a]
ITULAZAX	473	2.10 (0.14)			
Average DMS during the BPS					
Placebo	479	2.40 (0.23)	0.80 [0.39; 1.22]	33.5 [18.1; 46.5]	0.0001[a]
ITULAZAX	473	1.59 (0.19)			
Average DMS during the TPS					
Placebo	479	1.71 (0.16)	0.50 [0.22; 0.78]	29.2 [14.1; 42.0]	0.0005[a]
ITULAZAX	473	1.21 (0.13)			

BPS=birch pollen season, CI=confidence interval, DMS=daily rhinoconjunctivitis medication score, DSS=daily rhinoconjunctivitis symptom score, N=number of subjects in full analysis set, p-value=p-value for test of superiority (an absolute difference of 0), SE=standard error, TCS=total combined score, TPS=tree pollen season.
N for placebo consists of 460 observations and 19 imputed observations during the BPS, and 464 observations and 15 imputed observations during the TPS.
N for ITULAZAX consists of 455 observations and 18 imputed observations during the BPS, and 457 observations and 16 imputed observations during the TPS.
Absolute difference: placebo-ITULAZAX, relative difference: (placebo-ITULAZAX)/placebo.
Multiple imputations were used to impute missing data unde the hypothetical strategy. The square root transformed endpoint was analysed in an LME model with treatment, cohort, and age-group as fixed effects, and pollen station within cohort as a random effect with different residual errors specified for each treatment group. Back-transformation was used to estimate the absolute difference.
DSS was the sum of 4 rhinitis and 2 conjunctivitis symptoms (range 0-18).
DMS was the sum of rescue medication provided by the sponsor (range 0-20).
TPS: Defined as days included in any of the alder, birch, hazal and oak pollen seasons.
BPS: The start date was defined as the first day of 3 consecutive days with birch pollen count ≥30 grains/m^3 and the stop date was defined as the last day in the last occurrence of 3 consecutive days with birch pollen count ≥30 grains/m^3.
[a]Observed p-value (not corrected for multiplicity)

On any given day during the BPS the odds of experiencing a severe day was approximately 20% higher in the placebo group compared to the ITULAZAX group, and likewise the odds of experiencing a well day or a symptom-free day was approximately 20-25% lower in the placebo group. The results indicated an overall improved well-being for subjects treated with ITULAZAX.

Table 6 Number of severe days, well days and symptom-free days during the BPS (FAS) (TT-06)

Secondary endpoints	N	Estimate	95% CI	p-value
Estimated proportion of severe days during the BPS (%)				
Placebo	479	0.21	[0.17; 0.26]	
ITULAZAX	473	0.19	[0.15; 0.24]	
	OR	1.14	[1.05; 1.24]	0.0020
Estimated proportion of well days during the BPS (%)				
Placebo	479	0.36	[0.31; 0.42]	
ITULAZAX	473	0.42	[0.36; 0.48]	
	OR	0.78	[0.72; 0.83]	<0.0001
Estimated proportion of symptom-free days during the BPS (%)				
Placebo	479	0.20	[0.15; 0.26]	
ITULAZAX	473	0.23	[0.17; 0.31]	
	OR	0.81	[0.75; 0.87]	<0.0001

BPS = birch pollen season, FAS = full analysis set, N = number of subjects in FAS,
N for placebo consists of 460 observations and 19 imputed observations.
N for ITULAZAX consists of 455 observations and 18 imputed observations.
CL = confidence interval, OR = odds-ratio.
OR: calculated as placebo/active.
Severe day: day with DSS≥6 and at least 2 moderate or 1 severe symptom.
Well day: day with no use of rescue medication (DMS=0 and DSS≤2)
Symptom-free day: day with no symptoms and no use of rescue medication (TCS=0)

Paediatric population

The efficacy of ITULAZAX in adolescents with birch pollen induced allergic rhinitis and/or conjunctivitis was also investigated in the TT-04 trial (n=25 ITULAZAX, n=32 placebo). Treatment with ITULAZAX resulted in a 31% relative reduction (absolute reduction 1.94) in TCS compared to placebo during the birch pollen season for the adolescent subgroup, but data are limited. The safety of ITULAZAX in adolescents with birch pollen induced allergic rhinitis and/or conjunctivitis was investigated in the TT-02 (phase II) and the TT-04 trial. A descriptive comparison of pooled safety data indicated that tolerability for ITULAZAX is similar in adults and adolescents.

The efficacy of ITULAZAX in children (5-17 years) with birch pollen induced allergic rhinitis and/or conjunctivitis was investigated in the TT-06 trial (n=473 ITULAZAX, n=479 placebo). Treatment with ITULAZAX resulted in an absolute difference of 1.13 (relative difference of 19.2%) in TCS compared to placebo during the BPS. The safety profile is similar in children and adults.

The European Medicines Agency has waived the obligation to submit the results of studies with ITULAZAX in children under the age of 5 years in birch pollen-induced allergic rhinitis/rhinoconjunctivitis (treatment of allergic rhinitis/rhino-conjunctivitis)(see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

No clinical studies investigating the pharmacokinetic profile and metabolism of ITULAZAX have been conducted. The effect of allergy immunotherapy is mediated through immunological mechanisms, and there is limited information available on the pharmacokinetic properties.

The active molecules of an allergen extract are composed primarily of proteins. For sublingually administered allergy immunotherapy products, studies have shown that no passive absorption of the allergen through the oral mucosa occurs. Evidence points towards the allergen being actively taken up through the oral mucosa by dendritic cells, in particular Langerhans cells. Allergen which is not absorbed in this manner is expected to be hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract. There is no evidence to suggest that the allergens present in ITULAZAX are absorbed into the vascular system after sublingual administration to any significant extent.

5.3 Preclinical safety data

Conventional studies of general toxicology, genotoxicity and toxicity in relation to reproduction in mice have revealed no special hazards to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatine (fish source)
Mannitol
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original blister in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister cards in outer carton. Each blister card contains 10 sublingual lyophilisates.
Pack sizes: 30 and 90.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

ALK-Abello A/S
Boge Alle 6-8
DK-2970 Horsholm
Denmark

8 MARKETING AUTHORISATION NUMBER

PA1255/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th September 2019
Date of last renewal: 7th June 2024

10 DATE OF REVISION OF THE TEXT

May 2025