Non-Interventional Post-Authorization Safety Study Report

Study ID: NI-TT-01

Study title
ITULAZAX® Post Authorization Safety (IPAS) Study:
A prospective, non-interventional study assessing the safety and tolerability of ITULAZAX® in adults with tree pollen allergy in real-life practice

Medicinal product:	ITULAZAX®
Active substance:	ATC code V01AA05 12 SQ-Bet *Betula verrucosa* (12 SQ-Bet)
EU PAS register number:	EUPAS31470
Procedure number:	DE/H/4908/001/DC
Development phase:	IV, non-interventional post authorization safety study (PASS)
Countries:	Denmark, Finland, Germany, The Netherlands, Norway, Sweden
Sponsor:	ALK-Abelló Arzneimittel GmbH Medical Department Friesenweg 38 D-22763 Hamburg +49 40 703845-0
Marketing authorization holder(s):	ALK-Abelló A/S Bøge Allé 6-8 DK-2970 Hørsholm
MAH contact person:	Hendrik Wolf, PhD ALK-Abelló Arzneimittel GmbH Hamburg, Germany
Joint PASS:	Yes
Research question and objectives:	Safety and tolerability of ITULAZAX® in the real-life setting
Medical writer/Report originator:	Kathrin Borchert, MPH Xcenda GmbH Lange Laube 31 30159 Hannover
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Synopsis – study NI-TT-01

Title of study ITULAZAX® Post Authorization Safety (IPAS) Study: A prospective, non-interventional study assessing the safety and tolerability of ITULAZAX® in adults with tree pollen allergy in real-life practice
Marketing authorization holder ALK-Abelló A/S Bøge Allé 6-8 DK-2970 Hørsholm
Keywords allergy treatment, tree pollen, safety, tolerability, real-life, SLIT
Investigators For the list of principal investigators (PI), see Appendix I.4.
Study sites 178 planned: 50 in Germany, 80 in the Netherlands, 10-12 in Sweden, 10-12 in Norway, 10-12 in Finland, 10-12 in Denmark 121 included: 42 in Germany, 47 in the Netherlands, 8 in Sweden, 11 in Norway, 2 in Finland, and 11 in Denmark 112 analyzed: 35 in Germany, 46 in the Netherlands, 7 in Sweden, 11 in Norway, 2 in Finland, and 11 in Denmark (excl. sites without verified data)
Publications None.
Study milestones Planned first patient first visit (FPFV) – MAR 2020 Planned last patient last visit (LPLV) – JUN 2022 Planned database lock – NOV 2022 Actual FPFV – 26 MAR 2020 Actual LPLV – 24 JUN 2022 Actual date of database lock – 16 JAN 2023
Rationale and background In the clinical development program, ITULAZAX® was observed to be well-tolerated. However, no safety and tolerability data for the product from the use in a routine care setting were available. This non-interventional observational PASS was conducted to document the safety and tolerability of ITULAZAX® in real-life clinical practice.
Primary objective To investigate the safety and tolerability of ITULAZAX® in adults (18-65 years of age) in the first 4-6 months of treatment in a real-life setting.
Study design Non-interventional, observational, multi-site, open-label, multi-national PASS to investigate the safety and tolerability of ITULAZAX® in adult patients in a real-life setting in Germany, the Netherlands, Denmark, Sweden, Norway, and Finland.
Number of patients planned and analyzed • N=1,000 planned • N=1,111 enrolled (All-Patients-Treated-Set) • N=1,076 completed data verification • N=1 without termination form • N=6 screen failures • N=1,069 analyzed (Final Analysis Set)

Study population
The selection of patients was at the discretion of the investigator, enrollment could be offered to patients who fulfilled the following conditions:

- They were prescribed ITULAZAX® according to the current version of the approved national summary of product characteristics (SmPC)
- They had signed the written patient information and informed consent form before initiation of any study-related activities.

Amendments and updates
Study protocol v1.0-v4.0

Product
ITULAZAX®, 12 Standardized Quality (SQ)-Bet *Betula verrucosa* (12 SQ-Bet), ATC code V01AA05

Duration of treatment
Planned: 4-6 months
Actual: median (min-max) 5.4 (0.03-19.3) months

Assessments
At baseline: demographics, body measurements, previous and concomitant medication, medical history, concomitant diseases and medication, baseline allergy symptoms, baseline symptoms of pollen food syndrome (PFS), immunoglobulins (IgE, $sIgG_4$) and fractionated exhaled nitrogen oxide (FeNO), if routinely measured, first administration of SQ-Bet tree sublingual immunotherapy (SLIT)-tablet, adverse events (AEs) at first administration of ITULAZAX®. All assessments were only performed if they were part of the treating physician's routine practice.

At follow-up visits, since last visit: AEs, allergy symptoms, PFS, symptomatic medication, antibody responder test (ART), if routinely performed in investigator's practice, FeNO, if done; first administration of other SLIT-tablets, if applicable.

Statistical methods
The statistical analysis focused on descriptive statistics. No comparative statistical tests were performed. No sensitivity analyses were anticipated.

For categorical variables, descriptive statistics were calculated in terms of number (N), frequency of patients (n, %), frequency of AEs (e, %).

For continuous variables, the following descriptive statistics were assessed: number (n), mean, standard deviation (SD), minimum (min), 25^{th} percentile (Q1), median, 75^{th} percentile (Q3), maximum (max).

Number of missing values (m), not available (NA), unknown, number of open queries were presented for each variable, if applicable. Proportions and summary measures were rounded to one decimal. Missing data have not been replaced.

AEs as well as breakdown of AEs and treatment-related AEs (possibly related) according to seriousness, severity, and causality were summarized for AEs during administration (V1 to V4).
AEs were categorized by MedDRA System Organ Classes (SOCs) and MedDRA Preferred Terms (PTs) displaying the number of patients, frequency of patients having AEs as well as number of AEs.

All results were stratified in five distinct groups according to the clinical manifestation of the tree pollen allergy and the prevalence of pollen food syndrome: Allergic rhinoconjunctivitis (ARC), allergic rhinoconjunctivitis and allergic asthma (ARC+AA), allergic rhinoconjunctivitis and pollen food syndrome (ARC+PFS), allergic rhinoconjunctivitis and allergic asthma and pollen food syndrome (ARC+AA+PFS), allergic rhinoconjunctivitis and atopic dermatitis with or without allergic asthma and with or without pollen food syndrome (ARC+AD±AA±PFS).

All centers from Germany, the Netherlands, and the 4 Nordic countries (NORDIC) were pooled for the main analyses. In addition, separate analyses for the three regions Germany, Netherlands, and NORDIC were performed.

Patient disposition

- In total, slightly more patients were included in the study in the year 2020 (54.3%) than in 2021 (45.7%).
- Most patients were enrolled in Germany (n=409), followed by 312 patients from the Netherlands, 144 patients from Norway, 113 patients from Sweden, 78 patients from Denmark, and 13 patients from Finland.
- On average, 9.5 patients were included per site (min-max: 1-38).

Demography of study population

- Sex: 46.3% were male and 53.7% were female.
- Mean age was 37.5 years (min-max: 18-65 years).
- Ethnic origin: 65.4% European (Caucasian), 0.9% African, 3.6% Asian, 0.5% Hispanic, 29.6% Other (NA in The Netherlands due to country-specific ethical reasons).
- Mean Body Mass Index (BMI) was 25.6 kg/m^2.

Results

Medical history

- A clinically relevant allergy ('allergy in need of treatment with allergy immunotherapy') was reported in 100.0% of patients for trees (hazel, alder, or birch), 49.9% for grass/rye, 8.0% for house dust mite, 1.8% for animal hair/dander, 1.0% for weed, and 0.7% for other allergies.
- Mean age at first occurrence of allergic reactions to tree pollen was 19.2 years.
- Clinical manifestation of the tree pollen allergy was allergic rhinitis in 99.1% of patients, allergic conjunctivitis in 89.8%, allergic asthma in 38.6%, atopic dermatitis in 14.3%, and other clinical manifestation in 9.5%.
- PFS was present in 52.2% of patients. 40.9% of patients reacted with symptoms to apple, 28.0% to hazelnut, and 14.5% to carrot.
- Almost all patients (99.9%) were positively diagnosed for sensitization to tree pollen (birch, hazel, alder, or tree mix), diagnostic tests were performed in 84.8% of patients with birch allergens, 53.8% with grass, and 24.2% with house dust mite allergens (*Dermatophagoides pteronyssinus* (*D. pter.*)).
- With birch allergens, 84.7% of patients were tested positive by skin prick test and/or specific IgE measurement, 52.9% with grass, and 21.6% with house dust mite allergens (*D. pter.*).
- 99.3% of patients were assessed to have nasal symptoms (47.1% severe), 94.4% eye symptoms (33.4% severe), 51.3% bronchial symptoms (6.7% severe), and 19.7% skin symptoms (2.5% severe) in the last season before initiation of treatment with ITULAZAX®.
- The most common drugs as symptomatic medication used in the last season before ITULAZAX® were oral antihistamines (83.9%), nasal corticosteroids (59.2%), and conjunctival antihistamines (45.6%).
- 13.8% of patients reported previously completed immunotherapy(ies) and 11.5% of patients had concomitant immunotherapy(ies) (10.3% SLIT-tablets, 0.9% SCIT, 0.4% SLIT-drops).
- 1.5% of patients switched from an AIT with allergens of the birch homologous group to ITULAZAX®.
- Relevant previous and concomitant disease(s) were documented in 20.7% of patients and in 19.7% the disease was still ongoing.
- For concomitant diseases, relevant previous and concomitant medication was reported in 27.7% of patients and in 26.8% the medication was still ongoing.
- Birch specific IgG_4 was measured in 2.7% of patients. The mean $sIgG_4$ level was 22.9 mgA/L.
- 31.1% of study sites stated that they routinely measure FeNO and the FeNO breath test was performed at study start in 12.4% of total patients. The mean FeNO value was 24.7 ppb.

Safety results

Primary endpoint

- During the entire course of treatment with ITULAZAX®, e=1,685 local ADRs were reported in 53.3% of total patients (e=2,528 AEs in 61.7% of total patients).

Secondary safety endpoints

- Overall, e=2,038 local, non-local, and systemic AEs, related to treatment (ADRs) were reported in 57.7% of total patients during the entire course of treatment with ITULAZAX®.
- During the entire course of treatment with ITULAZAX®, e=8 systemic ADRs were reported (0.7% of total patients) and e=353 non-local ADRs (19.8% of total patients).
- In total, e=25 SAEs occurred (1.9% of total patients) during the entire course of treatment with ITULAZAX®, and e=7 in 7 (0.7%) patients were assessed as related to treatment with ITULAZAX® and, thus, as serious ADRs (SADRs).
- Within the first 4-6 months of treatment in patients with history of PFS, e=1,232 pre-specified local ADRs were reported (as specified in the primary endpoint) in 35.5% of total patients.

Other safety results

- In 46.7% of total patients, AEs were reported at first administration of ITULAZAX® (day 1 of treatment). In 41.3% of total patients, the AEs were assessed as mild, in 10.1% moderate, and in 1.7% severe.
- In 45.9% of total patients, AEs at first administration were assessed as related to treatment with ITULAZAX® and were, thus, ADRs. In 40.9%, ADRs were assessed as mild, in 9.6% moderate, and in 1.4% severe; in 3 (0.3%) patients, ADRs at first administration of ITULAZAX® were assessed as serious (SADRs).
- The proportions of patients with AEs and ADRs were higher in the patient groups with PFS compared to those without.
- At first administration of ITULAZAX® during current pollen exposure to tree pollen vs no exposure, AEs were reported in 28.6% vs 50.6% of total patients.
- During follow-up, the proportion of patients with AEs was 36.4% in V2, 20.7% in V3, and 12.0% in V4.
- Follow-up information on previously documented AEs became available at later visits in 17.7% of total patients.
- The proportion of patients with AEs was 61.7% during the entire course of treatment with ITULAZAX®. Again, the presence of PFS caused a higher AE rate when stratifying by clinical manifestation of allergy.
- The most frequently reported AEs during the entire course of treatment with ITULAZAX® were in MedDRA SOCs: gastrointestinal disorders (45.8%), followed by respiratory, thoracic and mediastinal disorders (31.4%), and general disorders and administration site conditions (13.7%).
- The corresponding three most common symptoms (PTs) across all SOCs of AEs were oral pruritus (24.5%), throat irritation (16.6%), and paraesthesia oral (8.4%).
- Of total patients, 53.5% reported a mild, 23.9% a moderate, and 6.6% a severe AE during the entire course of treatment.
- AEs after single administration of ITULAZAX® were reported in 52.8% of total patients and in 73.8% after coadministration of ITULAZAX® and GRAZAX® during the entire course of the study.
- Five pregnancies became known during follow-up and four of five women reported a normal delivery with a healthy child. One woman experienced a miscarriage/late spontaneous abortion that was not assessed as related to treatment with ITULAZAX®.

Other results – At first administration of ITULAZAX®

- Treatment was initiated in most patients (52.4%) between September and November 2020 or 2021.
- The time of administration was in 59.9% of patients in the morning.
- The first ITULAZAX® tablet was administered in 11.7% of patients within the tree pollen season.
- Anti-allergic premedication immediately prior to first administration of ITULAZAX® was administered in 22.0% of patients.
- The video on SLIT-tablet treatment was watched by 15.0% of patients during the 30 minutes waiting time after first intake of ITULAZAX®.
- Other SLIT (tablets/drops) with other allergens than tree pollen was first administered with initiation of ITULAZAX® in 3.5% of patients.

Other results – Follow-up visits

Secondary endpoint

- Most of total patients with at least one follow-up visit adhered to the administration of the ITULAZAX® tablet in the first 4-6 months of treatment: 94.5% reported an average intake of 6-7 times/week.

Further results

- Overall, 1,021 patients completed V2, 948 patients V3, and 816 patients V4.
- Pregnancy has become known in 0.4% of total patients with all pregnancies being documented at V3.
- 6.5% of total patients prematurely discontinued the study during follow-up visits (V2-V4).
- Changes in concomitant diseases during V2-V4 were reported in 4.9% of patients.
- In 7.4% of patients, changes in medical treatment(s) of concomitant disease(s) occurred during V2-V4.
- In 46.3% of the total patients, other SLIT (tablets/drops) with other allergens than tree pollen allergens were administered during follow-up visits.
- Other SLIT (tablets/drops) than ITULAZAX® with other allergens than tree pollen allergens were administered first during any follow-up visit in 32.8% of total patients.
- 12.6% of total patients experienced AEs after first administration of the other SLIT than tree pollen allergens during the follow-up visits.
- The main reason for not taking a tablet every day was reported to be ‘forgotten’ (61.3%), AEs (17.5%), and medical reasons (9.7%).
- All patients suffered from any type of allergy symptoms in the course of the study, with 99.7% of patients reporting nasal symptoms, 96.2% eye symptoms, 57.0% bronchial symptoms, and 27.5% skin symptoms at any time during the course of the study.
- For more than half of patients either ‘PFS, but no symptoms’ (50.0%) or ‘PFS, symptoms after’ consumption of a specific food (4.3%) was reported at the individual last visit.
- Most patients with PFS symptoms reacted to apple (45.5%), carrot (15.9%), tree nuts (11.4%), or peanut (5.4%) at the individual last visit. PFS symptoms to any other food were recorded in 61.4% of patients with PFS symptoms.
- Oral antihistamines (87.7%), nasal corticosteroids (65.6%), and conjunctival antihistamines (49.4%) were used most frequently as symptomatic medication in the overall course of the study.
- Any symptomatic medication was used in 64.2% of patients at their respective last visit.
- In 10.0% of total patients the Antibody Responder Test (ART; ALK, Denmark) was part of the practice routine, but in none of the patients the ART was applied during follow-up.
- FeNO was measured in 8.7% of patients and the mean FeNO value was 26.1 ppb during follow-up visits (V2-V4).
- 15.9% of patients watched the patient information video on SLIT-tablet treatment at any time during V1-V4.

Study termination

- The tolerability of ITULAZAX® was assessed by the patient to be ‘very good’ or ‘good’ in 82.7% of total patients.
- The tolerability of ITULAZAX® was assessed by the physician to be ‘very good’ or ‘good’ in 85.6% of total patients.
- The treatment was recorded to be continued after study termination in 83.8% of total patients; treatment was discontinued in 16.2%.
- The main reasons for discontinuation of the study were reported to be AEs in 8.5% of total patients, in 2.4% loss to follow-up, and in 1.7% non-compliance.
- The overall mean duration of study participation until the date of last intake/study termination was 156.6 days.

Conclusions

In conclusion, ITULAZAX® (12 SQ-Bet) was well tolerated in a large number of tree pollen allergic patients during the first 4-6 months of treatment in the real-life setting. No new safety concerns were identified in this study during daily at-home sublingual administration of the tablet after the first dose has been tolerated under medical supervision in the clinic. A number of 1,685 local ADRs were experienced by 53.3% of total patients during the entire course of treatment with ITULAZAX®. In total, ADRs were reported by 57.7% of patients, assessed as severe in 4.7% and classified as serious (SADRs) in 0.7%. In most of the patients the severity of ADRs were assessed as mild (50.2%) or moderate (19.8%). Local ADRs were most frequently coded as MedDRA PTs oral pruritus (Gastrointestinal disorders) and throat irritation (Respiratory, thoracic and mediastinal disorders) and were related to the sublingual administration of the tablet. This was in line with the safety profile reported in the SmPC.

A higher frequency of patients experiencing ADRs was observed for coadministration of the two tablets ITULAZAX® and GRAZAX® compared with the administration of ITULAZAX® as the only tablet.

In a subgroup of patients exposed to tree pollen at the first administration of ITULAZAX® according to the physician's assessment, no increase in the frequency of patients with ADRs was observed.

Overall, similar profiles of ADRs were observed in placebo-controlled clinical trials with ITULAZAX® and in the NI-TT-01 study with comparable or lower frequencies of the MedDRA PTs. ADR levels differed in patient groups with ARC as only clinical manifestation and patient groups with ARC and additional manifestations (ARC+AA, ARC+PFS, ARC+AA+PFS, and ARC+AD±AA±PFS). The safety profile observed in this PASS confirms the safety profile established by the controlled clinical trial TT-04.

Regarding effectiveness of treatment with ITULAZAX®, the proportion of patients with PFS, but without symptoms at the last visit of the study, was higher (50.0%) compared with baseline (9.3%) suggesting a potential beneficial effect of treatment. Symptoms and use of symptomatic medication were observed to be improved vs baseline assessments suggesting effectiveness in real-life and confirming the efficacy data by the controlled clinical trial TT-04.

Date of the report

09 JUN 2023