Non-Interventional Post-Authorisation Safety Study Protocol

Study ID: 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

Medicinal product:	ITULAZAX
Active substance:	12 SQ-Bet Betula verrucosa (12-Bet)
EU PAS register number:	To be registered after OPRC approval
Product reference:	Not applicable
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 703845-342
Marketing authorisation holder:	ALK-Abelló A/S 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
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Document Status:	Final
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Version:	4.0

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List of abbreviations

AIT	Allergy immunotherapy
AE	Adverse event
ART	Antibody responder test
Bet	Betula verrucosa
CCSI	Company core safety information
CRF	Case report form
eCRF	Electronic case report form
FeNO	Fractionated exhaled nitrogen oxide
HDM	House dust mite
IEC	Independent ethics committee
IRB	Independent review board
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
NIS	Non-interventional study
PASS	Post-authorisation safety study
PFS	Pollen food syndrome
SAE	Serious adverse event
SCIT	Subcutaneous allergy immunotherapy
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SLIT	Sublingual allergy Immunotherapy
SLIT-drops	Sublingual allergy immunotherapy drops
SLIT-tablets	Sublingual allergy immunotherapy tablets
SQ	Standardised Quality
TRAE	Treatment-related adverse event
WHO	World Health Organisation

Protocol synopsis

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
Study ID:	NI-TT-01
Development phase:	IV, non-interventional post-authorization safety study (PASS)
Rationale and background:	In the clinical development programme the ITULAZAX was observed to be well-tolerated. However, no safety and tolerability data for the product from the use in a routine care setting are available. This non-interventional observational PASS is conducted in order to document the safety and tolerability of the ITULAZAX in real-life clinical practice.
Primary objective:	To investigate the safety and tolerability of the 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.
Study population:	The selection of patients is at the discretion of the investigator, enrolment can be offered to patients: - Who are prescribed ITULAZAX according to the current version of the approved national SmPC In addition, enrolment requires that a written informed consent by the patient is obtained before initiation of any study-related activities.
Study size:	A total of approximately 1000 adult patients are planned to be included in the study. A planned number of 50 investigators in Germany, 80 in the Netherlands, 10-12 in Denmark, 10-12 in Sweden, 10-12 in Norway, 10-12 in Finland are expected to participate.
Assessments:	At baseline: demographics, body measurements, previous and concomitant medication, medical history, concomitant diseases and medication baseline allergy symptoms, immunoglobulins (IgE, IgG4) and fractionated exhaled nitrogen oxide (FeNO), if routinely measured, first intake of SQ tree SLIT-tablet. All assessments shall only be performed if they are done routinely

	by the treating physician. At follow-up visits, since last visit: adverse events (AEs), allergy symptoms, symptoms of pollen food syndrome (PFS), symptomatic medication, antibody responder test (ART), if routinely performed in investigator's practise, FeNO, if done; first administration of other SLIT-tablets, if applicable.
Data sources:	Data will be entered by the physician in an electronic case report form (eCRF).
Statistical methods:	AEs as well as breakdown of AEs and treatment-related AEs (possibly related) according to seriousness, severity and causality will be summarised for AEs during administration (V1 to V4). AEs will be summarised by MedDRA System Organ Classes and MedDRA Preferred Terms displaying number of patients, frequency of patients having AEs as well as number of AEs. Missing data will not be replaced.
Product:	ITULAZAX
Country(ies):	Germany, Netherlands, Denmark, Sweden, Norway, Finland
Study milestones:	Planned first patient first visit: Mar 2020 Planned last patient last visit: Jun 2022 Planned final study report: Jun 2023

Amendments and updates

Amendments and updates of the protocol are summarised in Table 11.

Table 1 Amendments and updates of the protocol

Number	Date	Version	Description of document
1	10 Sep 2019	1.0	Final Protocol
2	13 Jan 2020	2.0	Table 2, Flow chart: Time frame V2, V3, V4 changed from 4-12 weeks to 1-3 months to be consistent with text above. Study milestones) updated (Section 3.3 and Synopsis): - Planned last patient last visit changed from Oct 2021 to Jun 2022 - Planned final study report changed from Oct 2022 to Jun 2023. Section 2.1: Treatment period corrected from 4 to 4-6 months aligned with Section 3.1 and Synopsis.

3	29 Apr 2020	3.0	- Study milestones, Planned first patient first visit updated to “Mar 2020” (Section 3.3 and Synopsis).
			- List of abbreviations: “MAH, Marketing authorization holder” added.
			- Section 3.2.2 Secondary endpoints: bullet 5 and 6, observation period adjusted to: “… the first 4-6 months of treatment”.
			- Section 4.2 Collection, recording and reporting of adverse events:
			  - Local safety contact persons/Germany: “Dr. Kerstin Lardong” deleted and replaced by: “Dr. Ilka Radüge and Prof. Dr. Eike Wüstenberg”
			  - Reference Safety information (RSI) document, changed to: “Assessment of expectedness of non-serious AEs and SAEs for submission purposes will be performed by the MAH according to the reference safety information which is the current approved Company Core Safety Information (CCSI). In case the CCSI is changed during the study, the expectedness assessment will be done acc. to the updated CCSI by the MAH.
			  - Pregnancy: 2nd paragraph, 2nd sentence “observed by the investigator or reported by the subject must be recorded and evaluated via the AE form and reported to ALK within 14 days of obtaining knowledge

			of the event via the AE form provided in the eCRF.” Deleted.
	28 May 2020	3.0	Section 4.2 Collection, recording and reporting of adverse events, paragraph “Reference Safety Information (RSI) document” deleted.
4	04 October 2022	4.0	Title page (page 1): Address of sponsor (street name) changed from: “Griegstr. 75, Haus 25” to “Friesenweg 38”.

Flow chart

A total number of maximum 4 visits was planned during the study; visit 1 (baseline), visit 2 (1-3 months after visit 1), visit 3 (1-3 months after visit 2) and visit 4 (final visit, 1-3 months after visit 3). Please refer to the flow chart in Table 2 for a summary and timing of planned visits, and the procedures planned at each visit.

Table 2 Flow chart

Visit ID	V1	V2	V3	V4
Time frame	Day 0	1-3 months after V1	1-3 months after V2	1-3 months after V3
Visit window	± 10 days	± 10 days	± 10 days	± 10 days
Informed consent	X			
Demography and body measurements	X			
Patient eligibility	X			
History of allergy (incl. PFS)	X			
Diagnostics, as far as available	X			
Previous (completed) immunotherapy(ies)	X			
Concomitant immunotherapy(ies)	X	X	X	X
Relevant previous and concomitant medication	X	X	X	X
Previous and concomitant illness	X	X	X	X
Allergy symptoms	X	X	X	X
PFS-symptoms	X	X	X	X
Symptomatic medication	X	X	X	X
Antibody Responder Test (ART), if performed		(X)	(X)	(X)
Handout of patient videos about AIT/side effects	(X)	(X)	(X)	(X)
Fractionated exhaled Nitric oxide (FeNO), if	(X)	(X)	(X)	(X)

performed				
First administration of ITULAZAX	X			
Assessment of AEs	X	X	X	X
Global assessment of tolerability at final visit			(X)	X
Study completion/withdrawal	(X)	(X)	(X)	X

1 Introduction

ITULAZAX achieved marketing authorization for sublingual allergy immunotherapy in adult patients with allergic rhinitis due to allergens from the birch homologous group in July 2019 in Denmark, Germany, Norway and Sweden, and in August 2019 in Finland and in the Netherlands after a clinical development program comprising clinical trials in phase 1 to 3. The current non-interventional PASS is conducted to record first data on safety and tolerability of ITULAZAX during routine treatment in real-life.

In the clinical development program ITULAZAX was observed to be well-tolerated. Most frequently reported adverse events were mild-to-moderate local allergic reactions related to the sublingual administration. As ITULAZAX is intended for treatment of an allergic disease by exposing the subject to the allergen, there is a risk that the treatment can trigger systemic allergic reactions. In rare cases, a systemic allergic reaction can develop into an anaphylactic reaction or shock. The risk of anaphylactic reactions is low and is mitigated through labelling with relevant precautions and guidance for treatment. To prevent the use of ITULAZAX in patients who are at increased risk of severe systemic allergic reactions, a number of risk minimisation measures have been introduced in the product information. While the most common adverse events experienced as pruritus and discomfort are inconvenient for the patient but do not impair the safety of the treatment, adverse events with severe swelling and/or systemic reactions observed in some patients treated with SLIT-tablets need the physician's particular attention. Therefore, in this non-interventional observational PASS, the safety and tolerability of ITULAZAX will be evaluated in real life settings in allergological practice. The study will gain initial experience with the treatment of adult patients with ITULAZAX under routine conditions of everyday practice.

1.1 Background

The clinical development program for ITULAZAX comprised 4 clinical trials in Phase 1 to 3.

Trial TT-01 was a randomized, multiple dose, dose escalation, double-blind, placebo-controlled trial in phase 1 investigating the safety of ITULAZAX in adult subjects with birch pollen-induced rhinoconjunctivitis (with or without asthma) conducted in Denmark including 70 subjects [1].

Trial TT-02 was a randomized, parallel-group, double-blind, placebo-controlled, multinational trial in phase 2 conducted in Europe (DK, FIN, LT, NL, NO, PL, SE) to investigate the dose-related efficacy and safety including 637 subjects [2].

Trial TT-03 was a randomized, double-blind trial conducted to determine the optimal dose for clinical efficacy of ITULAZAX in an environmental exposure chamber (EEC) including 219 subjects [3].

TT-04 was the pivotal trial in phase 3 to demonstrate efficacy and safety of ITULAZAX including 634 subjects [4].

In trial TT-01 doses up to 12 SQ-Bet were considered suitable for home-treatment, trial TT-02 showed a dose-response effect for doses of 2 to 12 SQ-Bet and trial TT-03 identified 12 SQ-Bet as optimal dose.

Trial TT-04 was a randomized, double-blind, placebo-controlled trial with 634 randomised subjects (aged 12-65 years) with moderate-to-severe allergic rhinoconjunctivitis despite use of symptom-relieving medication. Subjects were randomized 1:1 to active or placebo treatment. The primary endpoint was the average daily allergic rhinoconjunctivitis total combined score (TCS) during the BPS analysed for subjects with diary data during the BPS. Secondary endpoints included average daily symptom score (DSS) during the birch pollen season (BPS), average TCS and DSS during the entire tree pollen season (TPS) and average daily medication score (DMS) in the BPS and TPS. The primary and secondary endpoints demonstrated statistically significant and clinically relevant effects of ITULAZAX compared with placebo. Relative differences for the BPS from placebo were 40% for the TCS, 37% for DSS and 49% for DMS (all $p< 0.0001$). For the TPS relative differences were 37% for the TCS, 33% for DSS and 47% for the DMS (all $p< 0.0001$).

The trial demonstrated the efficacy and safety of ITULAZAX versus placebo during the BPS and TPS in adolescents and adults with birch pollen-induced allergic rhinoconjunctivitis.

In general, treatment was well tolerated. The most frequently reported treatment-related adverse events (TRAEs) were mild-to-moderate local reactions related to sublingual administration of the tablet, the most common events were oral pruritus and throat irritation. Twenty-five (8%) subjects in ITULAZAX group discontinued the trial because of 98 AEs. These were mainly characterised as irritation or swelling in the mouth or throat of mild or moderate intensity.

The safety and tolerability during routine treatment in real life will be investigated in this Non-interventional-PASS.

The safety and tolerability profile and expected frequencies according to the clinical trials with ITULAZAX are described in the Summary of Product Characteristics (SmPC), [5].

1.2 Rationale

This is a non-interventional PASS in adults to investigate the safety and tolerability of ITULAZAX in the real-life setting in Germany, the Netherlands, Denmark, Sweden, Norway and Finland. The use of ITULAZAX is performed according to normal clinical practice and according to the SmPC. The number of patients to be included in the study will add to the existing safety data for ITULAZAX. The decision of the physician to prescribe SLIT with ITULAZAX is taken independently from the inclusion of the patient in the study.

2 Study objectives

2.1 Primary objective

The primary objective of the study is:

- To investigate the safety and tolerability of ITULAZAX in adults (18-65 years of age) allergic to tree treated with ITULAZAX in the first 4-6 months of treatment in a real-life setting.

3 Investigational plan

3.1 Overall study design

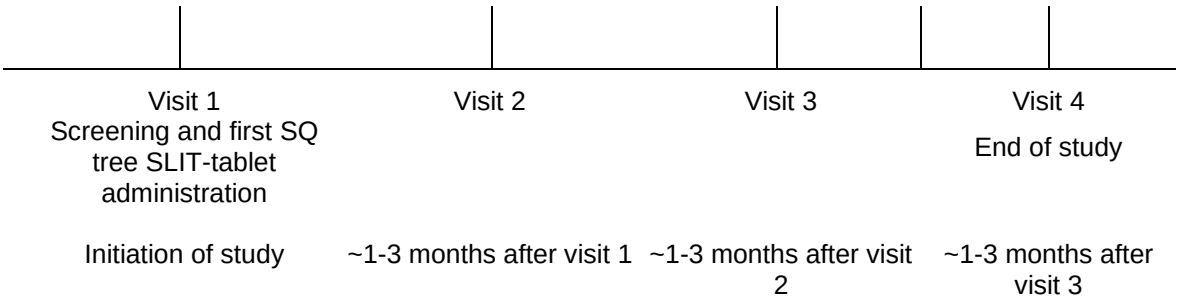
This is a non-interventional, observational, multi-site, open-label, multi-national PASS to investigate the safety and tolerability of ITULAZAX in adult patients in a real-life setting in Germany, the Netherlands, Denmark, Sweden, Norway and Finland.

A total number of approximately 1000 patients (aged 18-65 years) are planned to be enrolled and to be prescribed ITULAZAX in accordance with the nationally approved SmPC [5] and normal clinical practice.

The study will be initiated in November 2019 and the patients are planned to be followed for 4-6 (4 on average) months. A total number of 3-4 visits with approximately 1-3 months in between are planned (Figure 1).

The study is a non-interventional PASS based on the investigator's prescription of ITULAZAX, for which reason the number of visits and the duration between the visits are only intended as a guide.

Figure 1 Study design



3.2 Endpoints

3.2.1 Primary endpoint

Sum of pre-specified local adverse drug reactions (including lip swelling/oedema, mouth oedema, palatal oedema, swollen tongue/oedema, oropharyngeal swelling (oedema, pharyngeal oedema/throat tightness), laryngeal oedema).

3.2.2 Secondary endpoint(s)

- Number of treatment related AEs
- Number of systemic reactions
- Number of non-local adverse drug reactions
- Number of serious AEs (SAEs)
- Sum of pre-specified local adverse reactions (as specified in the primary endpoint) within the first 4-6 months of treatment in patients with history of Pollen Food Syndrome (PFS)
- Adherence to the first 4-6 months of treatment.

3.3 Study milestones

The planned dates for study milestones are summarised in Table 3.

Table 3 Study milestones

Planned first patient first visit:	Mar 2020
Planned last patient last visit:	Jun 2022
Planned final study report	Jun 2023

For PASS incl. below milestones:

Milestone	Planned date
Start of data collection	March 2020
End of data collection	June 2022
Registration in the EU PAS register	September 2019
Final report of study reports	June 2023

3.4 Discussion of design

Aim of the study is to gain information on safety and tolerability and to confirm the known safety profile of ITULAZAX from the clinical development program within a real-life setting.

As this is a non-interventional PASS, potential confounding factors cannot be ruled out. Data collection will reflect routine clinical practice rather than mandatory assessments at pre-specified time points. This may have an impact on the amount of data and the interpretation. Since this is an open-label design, the knowledge of active treatment may affect both investigator-perceived and patient-reported data. The recording of data by physicians in an eCRF allows immediate access to the data and processing of queries.

The strength of the study is that it is able to generate data on safety and tolerability for treatment with ITULAZAX in the real-life setting and in real-life patients with demographics and disease-related characteristics consistent with populations seen in clinical practice.

The sum of pre-specified local adverse drug reactions (including lip swelling/oedema, mouth oedema, palatal oedema, swollen tongue/oedema, oropharyngeal swelling (oedema, pharyngeal oedema/throat tightness, laryngeal oedema) as primary endpoint and number of treatment-related AEs, number of systemic reactions, number of non-local reactions, number of

serious AEs (SAEs), sum of pre-specified local adverse drug reactions within the first 4 months of treatment in the group of patients with data on Pollen food syndrome (PFS) and adherence to the first 4 months of treatment are suited to address the safety and tolerability in real-life as objective of the study

3.5 Study population

A total of approximately 1000 adult patients are planned to be included in the study. A planned number of 50 investigators in Germany, 80 in the Netherlands, 10-12 in Denmark, 10-12 in Sweden, 10-12 in Norway, 10-12 in Finland are expected to participate.

The decision to initiate treatment with ITULAZAX will be made at the discretion of the investigator before and independently from the decision to include the patient in the study.

The patients will not receive compensation for their participation.

3.5.1 Selection criteria

At the discretion of the investigator, enrolment can be offered to patients:

- Who are prescribed ITULAZAX according to the nationally approved SmPC

In addition, enrolment requires that a written informed consent is obtained before any study-related activities.

3.5.2 Patient discontinuation

The patients will be advised that he/she have the right to discontinue from the study at any time without prejudice.

Furthermore, the patient may also be discontinued from the study at the discretion of the investigator, e.g. in case of AEs or treatment discontinuation.

In case of discontinuation, the investigator should attempt to collect any outstanding data, if possible. The investigator should inquire about the reason for discontinuation (adverse event, non-compliance with protocol or other) and specify this in the case report form (refer to Section 4).

3.6 Treatments

3.6.1 Product

The patients will be treated with commercially available SQ tree SLIT-tablets according to routine clinical practice, the nationally approved SmPC [5].

ITULAZAX is an oral lyophilisate and is a standardised allergen extract from birch pollen. The strengths of ITULAZAX is 12 SQ-Bet per oral lyophilisate.

The sponsor will not pay for any medication (including ITULAZAX) or medical care received by the patient during or after their participation in the study.

3.7 Visit schedule and procedures

The study flow chart is presented in Table 2**Error! Reference source not found.**. The following section will describe the procedures to be performed at the individual visits. For details concerning the timing of each visit, please refer to the flow chart (Table 2**Error! Reference source not found.**).

3.7.1 Visit 1 (baseline)

The following procedures should be performed at visit 1:

- Obtain personally signed informed consent before any study-related activities.
- Demographics (age, sex, pregnancy, ethnic origin)
- Body measurements (height, weight)
- Evaluation of patient eligibility
- History of allergy
- Allergy in need of treatment with allergy immunotherapy (trees; grass, rye; house dust mite (HDM); animal hair/dander; weed; other)
- Age of patient at first occurrence of allergic reactions to tree pollen
- Age of patient when tree pollen allergy was diagnosed
- Clinical manifestation of tree pollen allergy (rhinitis, conjunctivitis, asthma, atopic dermatitis, other)
- Concomitant allergies, currently not in need for treatment (grass, rye, HDM, animal hair/dander, weed, other)
- Pollen food syndrome (yes/no, if yes triggers: apple, hazelnut, carrot, celery, celery root, other (to be specified))
- Diagnostics for allergy, data from the last 12 months, if available (birch, hazel, alder, tree mix, grass, HDM, other/ SPT, CAP-RAST, other)
- Allergy symptoms in the last season before ITULAZAX (nose, eyes, bronchial, skin)
- Symptoms of the pollen food syndrome in the last season before ITULAZAX
- Symptomatic medication used in the last season before ITULAZAX (antihistamines (conjunctival), antihistamines (nasal), antihistamines (oral), corticosteroids (nasal), corticosteroids (inhaled), corticosteroids (oral), short-acting ß$_2$-agonists (inhaled, SABA, long-acting ß$_2$-agonists (inhaled), LABA, others)
- Previous (completed) immunotherapy (ies), (Allergen, trade name/generic name, type, start/end date)
- Switch from ongoing allergy immunotherapy (AIT) to SQ tree SLIT-tablet (yes/no, if yes: allergen, trade name/generic name, type, start/end date)
- Concomitant immunotherapy (ies), (Allergen, trade name/generic name, type, start/end date, if SLIT relation to SQ tree SLIT-tablet, ongoing)
- Relevant previous and concomitant medication (trade name/generic name, indication, dose/day, start/end date, ongoing)
- Immunoglobulins (sIgE/sIgG4: not done/done, if done result (kU/L))

- If applicable and done in routine use: Fractional exhaled nitric oxide (FeNO) (Generally FeNO used (yes/no), If yes performed at start of study? (not done/done), if done result (ppb FeNO)).
- If applicable and done in routinely use: Patient video (shown for information on SLIT-tablet treatment (no/not shown later in the study/yes, before the first administration, after first administration)
- First administration of SQ tree SLIT-tablet (date/time of application, anti-allergic premedication applied (no/yes), AEs (no/yes, if yes document on AE pages)
- First administration of other SLIT-tablets, allergen 1, allergen 2 (date/time of application, anti-allergic premedication applied (no/yes), AEs (no/yes, if yes document on AE pages), if applicable
- Assessments of AEs after first administration of ITULAZAX
- Assessments of AEs after first administration of the other SLIT-tablet, if applicable
- Schedule date for visit 2

3.7.2 Visit 2

The following procedures should be performed at visit 2:

- Assessment of AEs since last visit (incl. FU-information on previous AEs)
- Pregnancy (yes, no)
- Changes in relevant concomitant diseases and medical treatments
- Adherence estimate (average frequency of tablet intake, reasons for not taking the tablet)
- Allergy symptoms since last visit (nose, eyes, bronchial, skin)
- PFS-symptoms since last visit
- Symptomatic medication since last visit
- If applicable and done in routinely use: Antibody Responder Test (ART), (ART generally applied, if yes results IgE, IgG4, neg./pos., ART score)
- If applicable and done in routinely use: Fractional exhaled nitic oxide (FeNO) (result (ppb FeNO), if performed).
- If applicable and done in routinely use: Patient video
- First administration of other SLIT-tablets, allergen 1, allergen 2 (date/time of application, anti-allergic premedication applied (no/yes), AEs (no/yes, if yes document on AE pages), if applicable
- Schedule date for visit 3

3.7.3 Visit 3

The following procedures should be performed at visit 3:

- Assessment of AEs since last visit (incl. FU-information on previous AEs)

- Pregnancy (yes, no)
- Changes in relevant concomitant diseases and medical treatments
- Adherence estimate (average frequency of tablet intake, reasons for not taking the tablet)
- Allergy symptoms since last visit (nose, eyes, bronchial, skin)
- PFS-symptoms since last visit
- Symptomatic medication since last visit
- If applicable and done in routinely use: Fractional exhaled nitic oxide (FeNO) (result (ppb FeNO), if performed).
- If applicable and done in routinely use: Patient video
- If applicable and done in routinely use: Antibody Responder Test (ART), (ART generally applied, if yes results IgE, IgG4, neg./pos., ART score)
- First administration of other SLIT-tablets, allergen 1, allergen 2 (date/time of application, anti-allergic premedication applied (no/yes), AEs (no/yes, if yes document on AE pages), if applicable
- Schedule date for visit 4 (if applicable)

3.7.4 Visit 4 (final visit)

The following procedures should be performed at visit 4:

- Assessment of AEs since last visit (incl. FU-information on previous AEs)
- Pregnancy (yes, no)
- Changes in relevant concomitant diseases and medical treatments
- Adherence estimate (average frequency of tablet intake, reasons for not taking the tablet)
- Allergy symptoms since last visit (nose, eyes, bronchial, skin)
- PFS-symptoms since last visit
- Symptomatic medication since last visit
- If applicable and done in routinely use: Fractional exhaled nitic oxide (FeNO) (result (ppb FeNO), if performed).
- If applicable and done in routinely use: Patient video
- First administration of other SLIT-tablet (date/time of application, anti-allergic premedication, AEs), if applicable
- If applicable and done in routinely use: Antibody Responder Test (ART), (ART generally applied, if yes results IgE, IgG4, neg./pos., ART score)
- Global assessment on tolerability by physician and patient

3.8 Assessments

3.8.1 Demographics

Demographic parameters are: age, gender, ethnic origin (not in NL), pregnancy.

3.8.2 Body measurements

Height and weight.

3.8.3 Previous and concomitant medication

The following previous and concomitant medication will be recorded:

Relevant concomitant medication, symptomatic anti-allergic medication used in the last season before ITULAZAX: antihistamines (conjunctival); antihistamines (nasal); antihistamines (oral); corticosteroids (nasal); corticosteroids (inhaled); corticosteroids (oral); short-acting ß$_2$-agonists (inhaled); SABA, long-acting ß2-agonists (inhaled), LABA, others (please specify).

3.8.4 Medical history

History of allergy

Allergy (in need of treatment with AIT): trees (birch, hazel, alder), grass/rye, HDM, animal hair/dander, weed, other.

Age of the patient at first occurrence of allergic reactions to tree pollen (years).

Age of the patient when the tree pollen allergy was diagnosed (years).

Clinical manifestation of the tree pollen allergy: rhinitis, conjunctivitis, asthma, atopic dermatitis, other.

Concomitant allergies (currently not in need of treatment): grass/rye, HDM, animal hair/dander, weed, other.

Pollen food syndrome (yes/no), if yes: first occurrence of oropharyngeal symptoms (year), if yes, triggers: hazelnut, other nuts, celery, carrot, other vegetable, apple, other fruit, celery root, other spices, other foods.

Diagnostics for allergy (data from the last 12 months, if available)

Birch, hazel, alder, tree mix, grass/rye, HDM, other: skin prick test (date, positive/negative/not assessed), CAP-RAST (date, positive/negative/not assessed, measured as kU/L or CAP class), other test (date).

Birch-specific IgE and IgG4, if determined

Previous and concomitant diseases

Relevant previous and concomitant diseases, e.g. hypertension.

Symptomatic medication used in the last season before ITULAZAX

Antihistamines (conjunctival/nasal/oral), corticosteroids (nasal/inhaled/oral), short-acting ß2-agonists (SABA), long-acting ß2-agonists (LABA), others.

Previous (completed) immunotherapy(ies)

Allergen, trade name/generic name, type of allergy immunotherapy (SCIT/SLIT-drops/SLIT-tablets), start/end date.

Switch from ongoing AIT to SQ tree SLIT-tablet (yes/no).

Concomitant immunotherapy(ies)

Yes/no, if yes (allergen, trade name/generic name, type of AIT (SCIT/SLIT-drops/SLIT-tablets), date, if SLIT: relation of administration to SQ tree SLIT-tablet, therapy ongoing.

Baseline allergy symptoms

Allergy symptoms in the last season before ITULAZAX at nose, eyes, bronchi, skin (none/mild/moderate/severe).

Symptoms of the pollen food syndrome in the last season before ITULAZAX: no PFS; PFS, but no symptoms; PFS, symptoms after which food (specify food).

Symptom (none/mild/moderate/severe): itchy lips/tongue/oral mucosa, burning of the tongue, swelling of lips/tongue/oral mucosa/larynx, inflammation of tongue/oral mucosa.

Symptom (none/mild/moderate/severe): eye/nose/perioral skin, wheeze, dyspnoea, nausea/vomiting, gastrointestinal disorders, collapse/shock, other.

PFS confirmed by apple challenge (yes/no): if yes, severity of reaction.

Antibody Responder Test (ART), after ≥4 weeks

ART generally applied by physician (yes/no), if yes result (IgE, kU/L; IgG4, mg A/L), ART score (0-10).

Fractional exhaled Nitric Oxide (FeNO)

FeNO generally measured by physician (yes/no), if yes result: FeNO (ppb).

3.8.5 Initiation of Treatment

First intake of SLIT-tablet

First administration of the SQ tree-SLIT-tablet: Date/time of first administration, pre-medication given (no/yes, if yes preparation time (minutes, seconds before SQ tree SLIT-tablet intake), AEs after first administration of SQ tree SLIT-tablet

3.8.6 Follow-up (visits 2-4)

History since last visit (AEs since last visit, follow-up information on previously documented AE since last visit, pregnancy, change in medical treatment(s) of concomitant disease(s) since last visit

Allergy symptoms since last visit (none/mild/moderate/severe) nose symptoms, eye symptoms, bronchial symptoms, skin symptoms

Symptoms of the PFS since last visit, if applicable

Symptomatic medication since last visit

ART, FeNO measurements, if routinely performed

First administration of other-SLIT-tablets: date/time of first administration, pre-medication given (no/yes, if yes preparation time (minutes, seconds before SQ tree SLIT-tablet intake), AEs after first administration of SQ tree SLIT-tablet, if applicable

Global assessment of tolerability by physician and patient (very good/good/moderate/poor).

4 Adverse events

4.1 Definitions

4.1.1 Adverse event definitions

An adverse event (AE) is any untoward medical occurrence in a patient or study subject administered a product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product.

The following are not considered AEs:

- Pre-planned procedures (documented as concomitant illness in the CRF at screening) unless the condition for which the procedures were planned has worsened from the first study related activity after the subject has signed the informed consent form.
- Pre-existing conditions found as a result of screening procedures.

4.1.2 Serious adverse event definitions

A serious adverse event (SAE) is any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening[a]
- Requires in-patient hospitalisation[b]
- Results in persistent or significant disability or incapacity[c]
- Is a congenital anomaly or birth defect

- Is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed).
- Suspected transmission of infectious agent via a medicinal product

a) This refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
b) The term hospitalisation is used when a subject:
   - Is admitted to a hospital or in-patient, irrespective of the duration of the physical stay or
   - Stays at the hospital for treatment or observation overnight
c) A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity or quality of life

A non-serious AE is any AE that does not meet the definition of an SAE.

4.1.3 Adverse event assessment definitions

Severity

The severity of an AE is assessed by the investigator using the following definitions:

- Mild: No or transient symptoms, no interference with the patient's daily activities.
- Moderate: Marked symptoms, moderate interference with the patient's daily activities.
- Severe: Considerable interference with the patient's daily activities, unacceptable.

Causality assessment

The causal relationship between an AE and the treatment is assessed using the following definitions:

- Possible: A causal relationship is conceivable and at least reasonable possible.
- Unlikely: The event is most likely related to a different aetiology than the medicinal product.

Outcome

The outcome of an AE is assessed by the investigator using the following definitions:

- Recovered: fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first study-related activity after the patient signed the informed consent.
- Recovered with sequelae: as a result of the AE the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be classified as an SAE.
- Not recovered: the patient's condition has not improved and the symptoms are unchanged at the time of study completion.
- Fatal: event that results in death.

- Unknown: the patient's condition is unknown. This term should only be used when no other definition is possible, e.g. the patient is lost to follow-up.

4.2 Collection, recording and reporting of adverse events

All AEs are systematically collected in this study from the patient has signed informed consent and until end of study defined as last visit 4. These events must be recorded and evaluated via the AE form in the eCRF by the investigator. The investigator should record the diagnosis if available and if not available the symptoms should be recorded separately.
Specific additional reporting requirements are applicable for SAEs and pregnancy related events as further described below. The additional information must be provided according to requested timelines by fax/email to the local affiliate of ALK via:

	Germany	Denmark, Norway, Sweden, Finland	Netherlands
E-Mail	arzneimittelsicherheit@alk-abello.de	drugsafety@alk.net	DrugSafetyNL@alk.net
Fax number	0049 40 70 38 45 5530	0046 850 109 313	0031 36 5397 841
Emergency phone number	0049 40 70 38 45 333	DK: 0045 38 16 70 70 NO: 0047 99 44 60 40 SE: 0046 300 185 45 FI: 00358 9 5842 2120	00 31 69836404
Local safety contact persons	Anja Krieg, Stufenplanbeauftragte Dr. Ilka Radüge, Prof. Dr. Eike Wüstenberg (beide stellv. Stufenplanbeauftragte)	Åsa Åman, NPPV Ann-Mari Eriksson, deputy NPPV	Anton Antonakoudis, NPPV Thuy Hilali-Nguyen, Leonard van der Zwan, deputy NPPVs

If requested, please forward supporting documents to ALK via fax or via e-mail to the appropriate local affiliate (contact details see above). Please state the trial ID (NI-TT-01) and the subject and site ID on all documents.

IMPORTANT: Any information that could reveal the identity of the trial subject must be hidden or removed in the source documentation. Also, information that is not relevant for the subject and the subject's condition must be hidden or removed.

ALK informs the competent authorities and independent ethics committees (IECs) about AEs reported in the study in accordance with local requirements in force.

SAEs

- All SAEs must be reported to ALK via the SAE form provided in the eCRF within 24 hours of obtaining knowledge of the event.
- SAEs must be followed until the outcome of the event is "recovered", "recovered with sequelae", "death" and until all queries have been resolved. For cases of chronic conditions and cancer, follow-up until "recovered", "recovered with sequelae" or

"death" is not required. After the subject has completed the study, these cases can be closed with "not recovered".

- The investigator must report follow-up information on SAEs to ALK within 24 hours of obtaining the follow-up information, using the SAE form provided in the eCRF.

Pregnancy

- Female subjects must be advised to notify the investigator immediately if they become pregnant.
- The investigator must report all pregnancies to ALK.
- Subjects will be informed that the investigator will report any pregnancy during the study to ALK and that the subject will be asked to provide information about her pregnancy, delivery and health of her infant until the age of one month.

Information on pregnancy and follow up should be reported within 14 calendar days of obtaining the information, using the pregnancy form provided in the eCRF.

Technical complaints

Any technical complaint related to the trial product (ITULAZAX) must be reported to the local contact in each of the participating countries as soon as possible after awareness by the investigator. For local contact details please refer to section 4.2.
The information must be accompanied by samples or a picture of the item and specify if the technical complaint is accompanied by an adverse event.

4.2.1 Adverse events after study completion

AEs occurring after end of study which the investigator considers to be related to the product should be reported to ALK either through normal reporting routes for spontaneous reports or using the fax number/email address listed in Section 4.2.

5 Data management

5.1 Data collection

Data generated by the study site and relevant for the study will be recorded in the eCRF.

The participating ALK affiliates will supply sites with access to the eCRF and will make arrangements to train the site staff in the use of the eCRF. There will be no access to the eCRF without documented training in the system.

All eCRF data must be verified and approved by an investigator at the site.

5.2 Data processing

Data will be entered in the eCRF and corrections made by the investigator according to the specification of the eCRF system used. Data managers will prepare queries for implausible or missing data and request investigators for correction or addition.

5.3 CRF

Data generated by the trial site and relevant for the trial will be recorded in the eCRF.

The sponsor or its representative will supply sites with access to the eCRF. The sponsor will make arrangements to train the site staff in the use of the eCRF. There will be no access to the eCRF without documented training in the system.

All eCRF data must be verified and approved by an investigator at the site.

The data manager for the study will review the eCRF for completeness and accuracy and instruct the personnel at the study site to make any required corrections or additions according to an eCRF guideline.

The information entered into the database is systematically checked and errors or omissions will result in queries, which will appear in the eCRF for resolution.

Concomitant medications entered into the database will be coded using the World Health Organisation Drug Reference List (WHO Drug, version Q1 2019 or higher).

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 22.0 or higher).

When the database has been declared to be complete and accurate, the database will be locked. The database must be available in an English version. This applies to both the database variables and the data in the database. Note that especially AE descriptions (verbatim text) must be translated from local language (if reported so) into English.

5.4 Query handling

Query handling at the trial site will be performed according to the guidelines for the eCRF system. Queries are created by programmed validation checks according to an edit check specification. Queries will also be created based on manual data checks.

All data changes/query decisions are created with an audit trail capturing the old information, the new information, identification of the user making the correction, the date the correction was made, and the reason for change.

5.5 Database lock

When the database has been declared to be complete and accurate, the database will be locked and data will be unblinded. All accesses to the eCRF will be set as “ready only”. CRAs and non-sponsor staffs “read only” accesses will be revoked from the eCRF, when PDF files are received at site.

If changes to trial data become necessary after database lock this must be performed according to the current ALK SOP.

A data archive for the site subject data files are produced and sent to the site.

The investigator must sign and date the data archive approval form and send it back to the sponsor.

6 Quality control

6.1 Recording of data and retention of documents

The participating ALK affiliates will comply with Good Pharmacovigilance Practice (GVP), [6] and relevant national legislation related to archiving of study documentation.

The investigator must maintain source documents for each patient in the study (e.g. all demographic and medical information).

ALK is responsible for a central secure archive to be maintained for the orderly storage and expedient retrieval of all documentation pertaining to the study. An index shall be prepared to identify the archived contents, to identify their location, and to identify by name and location any material that by their general nature are not retained in the study archive. Access to the archive shall be controlled and limited to authorised personnel only.

The archive should be maintained for at least five years after final report or first publication of the study results, whichever comes first.

7 Statistical methods

7.1 Sample size and power considerations

All data will be summarised by descriptive statistics. No formal statistical tests will be performed. No formal sample size calculation will be done. The sample size of approximately 1000 subjects follows empirical considerations and is based on a need to detect enough AEs to evaluate the safety profile of ITULAZAX in the real-life setting.

7.2 Definition of analysis sets

All patients with at least one administration of ITULAZAX will form the All-Patients-treated set (Safety Set).

7.3 Baseline characteristics

Demographics and other baseline characteristics will be displayed with summary statistics (i.e. number of patients, minimum, maximum, mean, median, 25% and 75% percentiles) and frequency tables for categorical variables.

7.4 Safety analysis

AEs as well as breakdown of AEs and treatment-related AEs (possibly related) according to seriousness, severity and causality will be summarised for AEs during administration (V1 to V4).

AEs will be summarised by MedDRA System Organ Classes and MedDRA Preferred Terms displaying number of patients, frequency of patients having AEs as well as number of AEs.

Missing data will not be replaced.

8 Protection of human subjects

8.1 Ethics and regulatory procedures

8.1.1 Informed consent

All patients must provide informed consent in accordance with the origins of the Declaration of Helsinki [7] and the applicable laws of the country. The written informed consent must be obtained before any study-related activities are performed.

It is the responsibility of the principal investigator or a sub-investigator to obtain the written informed consent from the patient.

The investigator must explain the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail and provide and the processing of the patient`s data recorded according to applicable law [8] the subject with a copy of the information sheet and the consent form. Information to a subject can be delegated to a nurse, but the investigator must be available for questions and both the nurse and the investigator must sign the consent form to document this.

The patient must be given sufficient time to consider the study before deciding whether to participate. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The patient must sign and date the informed consent form before he/she enters the study (i.e. before any study-related activity). The investigator must give a copy of the signed informed consent to the patient. The investigator should keep the original.

If information becomes available that may be relevant to the subject's willingness to continued participation in the study, the subject information sheet will be updated by the affiliate of the respective country and approved by an IEC/IRB and the Competent Authorities. The patient must be informed in a timely manner about the updated subject information sheet and written informed consent must be obtained.

8.1.2 Independent Ethics Committee (IEC)/Institutional Review Board (IRB)/data protection

Before initiation of this study, the protocol, the proposed subject information sheet and informed consent form and other information to patients as well as other documents required, must be reviewed by a properly constituted IEC/IRB and provided to the national (and local, if applicable) regulatory authority.

A signed and dated statement that the protocol and the subject information sheet/informed consent form have been approved by the IEC/IRB and the regulatory authority must be obtained by the affiliate of the respective country before study initiation.

8.1.3 Protocol amendments

Substantial changes to this protocol require a protocol amendment that must be signed off by the countries involved and be approved by IEC/IRB and/or regulatory authorities as applicable before implementation.

The requirements for approval of the substantial changes should in no way prevent any immediate action from being taken by the investigator or by the affiliate of the respective country in the interest of preserving the safety of all patients included in the study.

If an approval is not required, the amendment must be reported to the regulatory authority for their information.

8.2 Premature discontinuation of study

The affiliate of the respective country reserves the right to terminate the study under the following conditions:

- Safety concerns

If the study is prematurely terminated or suspended, the investigator should promptly inform the patients. Furthermore, the investigator and/or the affiliate of the respective country should promptly inform the pertinent IEC/IRBs and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

8.3 Statement of compliance

This study must be carried out in compliance with the protocol, which is designed to ensure adherence to the Declaration of Helsinki, as described in:

- The Declaration of Helsinki (1964, and its amendments and subsequent clarifications) (World Medical Association 1996), [8].

8.4 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information, data and materials whether in oral, written, graphic, electronic or other form provided by ALK or a third party acting on behalf of or at the instruction of ALK in strict confidentiality.

Study documents provided by ALK (protocol, CRFs, questionnaires and other material) should be stored appropriately to ensure their confidentiality. The information provided by ALK to the investigator may not be disclosed to others except as expressly authorised by this protocol or the non-interventional PASS agreement or with the prior written consent of ALK.

The investigator may disclose confidential information to employees of the investigator, hospital authorities and IECs/IRBs on a need-to-know basis and only if the aforementioned parties are bound or obligated by provisions of confidentiality no less strict than imposed upon the investigator under this protocol or the non-interventional PASS agreement. Further, the investigator may disclose confidential information set out in the protocol to the extent necessary to obtain informed consent from patients who wish to participate in the study.

Any data, results, reports, findings, discoveries and any other information developed or collected during this study shall be regarded as ALK's confidential information until published.

Financial disclosure from the investigators will be obtained before the study.

8.5 Data protection

By signing this protocol, the investigator recognises that certain personal identifying information with respect to the investigator and all sub-investigators and trial site personnel, may be used

and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

Name, address, telephone number and email address

Hospital or clinic address and telephone number

Curriculum vitae or other summary of qualifications and credentials

Financial disclosure information

Other professional documentation

Consistent with the purposes described above, this information may be transmitted to ALK, affiliates and ALK representative, in the investigator's country and other countries, including countries that do not have laws protecting such information.

Additionally, the investigator's name and business contact information may be included when reporting certain SAEs to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multi-site trial, in order to facilitate contact between investigators, ALK may share an investigator's name and contact information with other participating investigators upon request.

9 Reporting of results

9.1 Study report

The overall study report and country reports will accurately and completely summarise the study objectives, methods, results, and interpretation of the findings.

The national coordinating investigators will review and sign the study report.

All involved investigators will receive the synopsis study report upon finalisation.

9.2 Progress report and interim report of study results (PASS)

The progress report is meant to include relevant information to document the progress of the study, for example the number of patients who have entered the study, the number of exposed patients or the number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may include an interim report of study results.
The interim report of study results is meant to include results of any planned interim analysis of study data.
Upon request from a national competent authority progress reports for PASS imposed as an obligation or conducted voluntarily shall be submitted to the competent authorities of the Member states in which the study is conducted.

9.3 Publication of results

ALK retains exclusive ownership of all data, results, reports, findings, discoveries and any other information developed or collected during this study and ALK shall have the exclusive right to use all such information for any purpose, including, but not limited to, use of the results and data either in the form of CRF (or copies of these), or in the form of a report, with or without

comments and with or without analysis, in order to submit them to the regulatory authorities of any country.

By signing the investigator agreement, the investigator agrees that the results of this study may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

It is envisaged that the findings of this study, including sub-analysis, and if relevant the epidemiology of the screened population and the selection process, will, in due time and by mutual agreement, be published in international journals, theses and/or presented at scientific meetings or symposia. All presentations and publications must be reviewed by ALK prior to public presentation or submission. For multi-site studies, it is mandatory that the primary publication is based on data from all study sites, analysed as stipulated in the protocol. Authorship is based on the International Committee of the Medical Journal Editors “Uniform Requirements” (Vancouver Declaration).

If the number of authors is restricted, selection will be based on fulfilment of 1) involvement in the development of the protocol, 2) being coordinating investigators, and 3) being top recruiters.

Investigators participating in multi-site studies agree not to present data gathered from one study site or a group of study sites before the primary publication has been accepted for publication unless formally agreed by all other investigators and the affiliates of the participating countries.

ALK shall be provided with copies of any proposed publication or presentation at least 60 days in advance of the submission of such proposed publication or presentation to a journal, editor, or other third party. ALK has the right to review and comment on any such publication or presentation within 60 days of receipt but cannot prevent publications of findings. The investigator agrees that all reasonable comments made by ALK will be incorporated into the publication. Furthermore, the investigator agrees that the investigator shall, at ALK's request exclude or delete any confidential information, except study results generated hereunder, from the proposed publication or presentation.

ALK will review the presentations and publications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that the confidential information is not being inadvertently divulged and provide any relevant supplementary information. Upon ALK's request, the investigator shall delay a publication or presentation for 6 months from ALK's receipt of the publication or presentation to permit ALK to file a patent application or take other steps as necessary to protect the confidential information (including study results of ALK).

10 Reference list

(1) Birk AO, Andersen JS, Villesen HH, Steffensen MA, Calderon MA. Tolerability of the SQ tree SLIT tablets in adults. Clin Ther 2017;39:1858-1867.

(2) Mäkelä MJ, Gyllfors P, Valovirta E, Steffensen MA, Grønager PM, Savolainen J, Winther L. Immunotherapy with the SQ tree SLIT-tablet in adults and adolescents with allergic rhinoconjunctivitis. Clin Ther 2018; 40:574-586.

(3) Couroux P, Ipsen H, Stage BS, Damkjær JT, Steffensen MA, Salapatek AM, Lund K, Würtzen PA. A birch sublingual allergy immunotherapy tablet reduces rhinoconjunctivitis symptoms when exposed to birch and oak and induces IgG4 to allergens from all trees in the birch homologous group. Allergy 2019;74:361-369.

(4) Biedermann T, Kuna P, Panzner P, Valovirta E, Andersson M, de Blay F, Thrane D, Jacobsen SH, Stage BS, Winther L. The SQ tree SLIT-tablet is highly effective and well tolerated: results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2019;143:1058-1066.

(5) SmPC ITULAZAX, 2019 ALK Denmark.

(6) European Medicines Agency, Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies, 9 October 2017 - EMA/813938/2011 Rev 3

(7) World Medical Association. The Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects First adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification, 2002 (Washington). 1996.

(8) REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)