LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Alutard SQ Timotej
(*Phleum pratense* pollen)

SE/H/2145/01-03/MR

This module reflects the scientific discussion for the approval of Alutard SQ Timotej. The procedure was finalised on 2021-10-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Alutard SQ Timotej, 10 000 SQ-E/ml, 100 000 SQ-E/ml, Up-dosing pack, Suspension for injection *(English names: Alutard SQ Phleum pratense, 10 000 SQ-U/ml, 100 000 SQ- U/ml).*

The active substance is allergen, Phleum pratense pollen. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Alutard SQ Timotej, 10 000 SQ-E/ml, 100 000 SQ-E/ml, Up-dosing pack, Suspension for injection, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, ALK-Abelló A/S, applies for a marketing authorisation in AT, DE, NL through this mutual recognition procedure with Sweden acting as reference member state (RMS). The product was first approved through a National Procedure.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
Standard animal studies on primary, secondary and safety pharmacodynamics have not been performed with Alutard SQ Phleum pratense. However, considering the specificity of the pharmacological action, the fact that humans have been naturally exposed (although not the s.c. route) to the allergens contained in Alutard SQ Pleum pratense, and the extensive clinical experience no further animal studies are considered necessary to evaluate the pharmacological properties of the Alutard SQ Phleum pratense.
The Alutard SQ Timotej allergen extract is adsorbed to aluminium hydroxide resulting in a slow release. The delayed release of allergens potentially reduces the risk of inducing systemic reactions and prolong the stimulation of the immune system.

Pharmacokinetics
The lack of non-clinical pharmacokinetic studies of Alutard SQ Timotej is acceptable since systemic absorption of grass pollen allergen is unlikely.

Regarding the aluminium content (see further comments Toxicology), it is concluded that AIT with Alutard SQ Phleum pratense contributes to the body burden of life-time accumulated aluminium. When considering the total body burden over a presumed lifetime, the increase by Alutard SQ treatment over 3-years-time gives a minor contribution to the total exposure. However, there is a theoretical risk of aluminium accumulation in patients at high risk i.e. patients with renal dysfunction and patients concomitantly treated with other aluminium containing drugs (e.g. antacids). A benefit risk analysis should be performed before AIT is initiated in risk groups (see SmPC section 4.4 and 4.8).

Toxicology
The non-clinical toxicity studies were performed before the concept of GLP was introduced and can therefore not be judged according to the present standard. However, the studies were performed up to the standard of that time at a quality level considered satisfactory, and the results are judged as reliable. In addition, in light of the clinical safety data base, the data is of extremely limited value.

Single dose toxicity data demonstrated a wide margin between the maximum human therapeutic dose and the dose administered i.v. in mice. Repeated dose toxicity data showed no adverse effects in mice or rats at a dose that corresponds to 100x the maximum human dose per kg.

The vast clinical experience does not indicate any genotoxic or carcinogenic potential of Phleum pratense pollen allergen extract. Furthermore, the Phleum pratense pollen allergen extract was negative in both the bacterial reverse mutation assay and in the mouse lymphoma assay.

Effects on reproduction have not been studied. However, data from the repeated dose toxicity studies and the vast clinical experience does not indicate any risk to male or female reproduction.

No acute high concentration of aluminium is anticipated in the blood stream after injection of Alutard SQ and thus no acute toxicity. With regard to chronic effects, the body burden of aluminium accumulated over a lifetime is increased by AIT, although resulting in only a minor contribution to the total body burden over a presumed lifetime. Based on these data, it is therefore concluded that the aluminium content in Alutard SQ Timotej does not normally pose a risk to the patient. A benefit risk analysis should, however, be performed before AIT is initiated, especially in certain population groups such as patients with renal dysfunction and young children, as stated in SmPC section 4.4 and 4.8. See also Pharmacokinetics and Safety in special groups and situations/ Extrinsic factors/Aluminium.

Environmental Risk Assessment (ERA)
The active substance is a mixture of proteins of natural origin and therefore not considered to pose a

risk to the environment.

IV. CLINICAL ASPECTS

Introduction

The Alutard SQ Phleum pratense drug product obtained the first marketing authorisation (MA) in Denmark in March 1982. It was nationally approved in Sweden in 1990 and is currently marketed for the treatment of specific IgE-mediated allergic diseases caused by *Phleum pratense* (timothy grass) pollen.

Pharmacokinetics
Clinical trials investigating the pharmacokinetic profile and metabolism of Alutard SQ Phleum pratense have not been performed. This is in accordance with the EMA 2008 guideline on clinical development of products for allergy immunotherapy.

Pharmacodynamics
To support pharmacodynamic and the immunological responses to AIT the MAH has submitted 11 trials.

The most accessible and robust markers of AIT are the changes in allergen-specific antibody concentrations that occur as a result of treatment. Since allergen-specific antibodies of non-IgE isotypes will compete with IgE for allergen binding, an increase in allergen-specific antibodies can be directly correlated to reduced effector cell activation and indirectly to T-cell activation through inhibition of facilitated allergen presentation (assessed in the Aasbjerg and Schmid trials). Increased expression of allergen-specific IgG4 furthermore reflects the AIT-induced cellular changes towards protective Th1 and regulatory responses (assessed in the UK-18 and Varney/Walker/Durham/Wachholz trials).

Even though, two of the 11 studies did not demonstrate an expected pattern for the IgE as a response to AIT (i.e study UK21 trial and Francis trial) six other trials did so (Østerballe/Djurup/Mosbech, UK22, Schmid and Aasbjerg trial respectively). In addition, all studies that measured IgG4 response (n=8; Table 1) demonstrated a positive increase in line with the expected pattern following AIT.

Overall, it is considered that the studies presented by the MAH supports that Alutard SQ *Phlenum pratense* results in an expected autoimmune immunological response.

*Table 1**Trials supporting immunological response for Alutard SQ Phleum pratense***

Trials investigating only Alutard SQ *Phleum pratense*	
Description	**Immunological parameters**
UK22 trial (see Table 2)	IgE, IgG4, IgE-blocking factor, IgE-FAB
UK21 trial (see Table 2)	IgE

UK 18 trial (see Table 2)	Basophils, neutrophils, eosinophils, mast cells. T cells (CD3), IL-2 receptor positive cells (CD25), IL-5 mRNA-expressing cells, IFN-γ mRNA cells
Varney/Walker/Durham/Wachholz trial (see Table 2)	Allergen-IgE binding to B cells by IgG antibodies, T cells (CD3), IL-4 mRNA+ cells, CD4+ T lymphocytes, eosinophils, IFN-γ mRNA cells
Francis trial (see Table 2)	IgE, IgA, IgG4
Østerballe/Djurup/Mosbech tria l (see Table 2)	IgE, IgG, IgG1, IgG2, IgG3, IgG4, anti-IgG antibodies
Schmid trial (see Table 2)	IgE, IgE-blocking factor, basophil sensitivity, FAB-inhibition, basophil activation test (BAT)
Aasbjerg trial (see Table 2)	IgE, IgG4, IgE-blocking factor, facilitated antigen presentation (FAP), basophil activation test (BAT)
Trials investigating Alutard SQ or ALK7 grass mixes	
Dolz trial (see Table 2)	IgE, IgG
Zenner trial (see Table 2)	IgE, IgG4
SHX0562 trial (see *Table 2*)	IgE, IgG4, other non-IgE subtype antibodies (termed IgX)

IV.1 Clinical efficacy

IV.1.1 Background and overview of clinical efficacy (by the MAH)

The clinical efficacy of Alutard SQ *Phleum pratense* is well-defined, having been used by the applicant over many years in adults and children. Data from trials investigating Alutard SQ *Phleum pratense* provide direct evidence of the efficacy of the product.

In addition, data from trials investigating other Alutard SQ or ALK7 (identical to the 10,000 SQ-U strength of Alutard SQ) single grass species or grass mixes are considered supportive in this dossier under the principle of homologous groups (EMEA 2008a). These products are all produced using allergens extracted from one or more grasses from the Pooideae homologous group (Lorenz et al. 2009) using the same extraction process and formulation of the finished product.

To demonstrate the clinical efficacy of Alutard SQ *Phleum pratense* a total of 12 trials where ALK was the sponsor or provided material and/or financial support are presented in this summary of clinical efficacy (*Table 2*):

• 6 trials investigating only Alutard SQ *Phleum pratense*.
• 2 trials investigating Alutard SQ *Phleum pratense* and Alutard SQ *Betula verrucosa*.
• 4 supportive trials investigating Alutard SQ or ALK7 grass mixes.

The efficacy of Alutard SQ *Phleum pratense* has been shown using a number of different methods. The most commonly used methods were rhinoconjunctivitis symptom scores and medication scores (both used in 10 trials). These methods were co-primary endpoints in some of the newer trials or were secondary endpoints in other trials. Despite the frequent use of these methods, the details around the

types of symptoms and medication collected, the collection period and how the data was presented were unique to each of the trials.

Other commonly used methods included skin prick tests (8 trials) and conjunctival provocation tests (6 trials). Again, there were differences in the doses and diluents used for the testing between trials as well as differences in the criteria for a positive test. For skin prick testing most trials only assessed immediate/early responses, while a few trials also assessed late (6 hours) skin responses.

Since grass pollen allergy can have a significant effect on a person's daily life, the effect of Alutard SQ *Phleum pratense* on quality of life has also been investigated in 3 of the trials.

Overall, the 12 trials demonstrate the clinical efficacy of Alutard SQ *Phleum pratense* in reducing the rhinoconjunctivitis symptoms of the subjects.

Table 2 Clinical trials to demonstrate the efficacy of Alutard SQ Phleum pratense

Description	Treatment and dose	Location in Module 5
Trials investigating only Alutard SQ *Phleum pratense*		
UK22 trial		
Evaluation of efficacy and safety of 2 doses (10,000 SQ-U and 100,000 SQ-U) of Alutard SQ *Phleum pratense* in adult subjects with moderate/severe seasonal allergic rhinoconjunctivitis double-blind, placebo-controlled 1 year treatment	Alutard SQ *Phleum pratense* in doses of 10,000 SQ-U, 100,000 SQ-U or placebo	**UK22 Integrated clinical trial report**
UK21 trial		
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* in children with seasonal allergic asthma double-blind, placebo-controlled 2 years treatment	Alutard SQ *Phleum pratense* 100,000 SQ-U or placebo	**UK21 Integrated clinical trial report**
UK18 trial		
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* in adult subjects with severe seasonal allergic rhinoconjunctivitis with asthma double-blind, placebo-controlled 2 years treatment	Alutard SQ *Phleum pratense* 100,000 SQ-U or placebo	Published papers: **Walker et al 2001**
Varney/Walker/Durham/Wachholz trial *		
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* in adult subjects with severe seasonal allergic rhinoconjunctivitis with or without mild asthma double-blind, placebo-controlled 1 year treatment + 3 years following completion of initial trial	Alutard SQ *Phleum pratense* 100,000 SQ-U or placebo	Published papers: **Varney et al 1991** **Walker et al 1995** **Durham et al 1996** **Durham et al 1999**
Francis trial		
Evaluation of efficacy of Alutard SQ *Phleum pratense* in adult subjects with moderate/severe seasonal allergic rhinitis double-blind, placebo-controlled 1 year treatment	Alutard SQ *Phleum pratense* 100,000 SQ-U or placebo	Published paper: **Francis et al 2008**
Østerballe/Djurup/Mosbech trial		
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* versus purified extract with two major allergens (Ag19 and Ag25) in subjects (adults and adolescents) with seasonal allergic rhinoconjunctivitis with or without asthma 3 years treatment + 6 years follow-up	Alutard SQ *Phleum pratense* or purified extract with two major allergens (Ag19 and Ag25)	Published papers: **Østerballe 1980** **Østerballe 1982a** **Østerballe 1982c** **Djurup & Østerballe 1984** **Mosbech & Østerballe 1988**

Description	Treatment and dose	Location in Module 5
Trials investigating Alutard SQ *Phleum pratense* and Alutard SQ *Betula verrucosa*		
Winther trial		
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* and *Betula verrucosa* in adult subjects with seasonal allergic rhinoconjunctivitis Double blind 2 years treatment	Alutard SQ *Phleum pratense* and *Betula verrucosa* 100,000 SQ-U	Published papers: **Winther et al 2000a** **Winther et al 2000b**
PAT trial		
Evaluation of efficacy of Alutard SQ *Phleum pratense* and *Betula verrucosa* in reducing the risk of asthma in children with seasonal allergic rhinoconjunctivitis 3 years treatment + 7 years follow-up	Alutard SQ *Phleum pratense* and *Betula verrucosa* 100,000 SQ-U	Published papers: **Möller et al 2002** **Niggemann et al 2006** **Jacobsen et al 2007**
Trials investigatingAlutard SQ or ALK7 grass mixes		
Dolz trial		
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense, Dactylis glomerata, Lolium perenne* in subjects (adults and adolescents) with seasonal asthma and/or rhinoconjunctivitis double-blind, placebo-controlled 3 years treatment	Alutard SQ *Phleum pratense, Dactylis glomerata, Lolium perenne* 100,000 SQ-U or placebo (rush up-dosing with aqueous extract, maintenance with Alutard SQ *Phleum pratense, Dactylis glomerata, Lolium perenne*)	Published paper: **Dolz et al 1996**
Zenner trial		
Evaluation of efficacy and safety of ALK7 6-grass mix + rye in subjects (adults and adolescents) with seasonal allergic rhinoconjunctivitis double-blind, placebo-controlled 1 year treatment	ALK7 6-grass mix + rye 1000 SE (equals 10,000 SQ-U) or placebo	Published paper: **Zenner et al 1997**
Klimek trial		
Evaluation of efficacy and safety of ALK7 6-grass mix + rye in subjects (adults and adolescents) with seasonal allergic rhinoconjunctivitis 1 year treatment	ALK7 6-grass mix + rye 1000 SE (equals 10,000 SQ-U)	Published paper: **Klimek et al 2005**
SHX0523 trial		
Evaluation of quality of life and compliance of Alutard SQ 5-grass mix + rye in subjects with seasonal allergic rhinoconjunctivitis Open label, single arm 3 years treatment	Alutard SQ 6-grass mix + rye 100,000 SQ-U	**SHX0523 Integrated clinical trial report**

*21 subjects were exposed to Alutard SQ *Phleum pratense* for more than 3 years in the first follow-up trial (**Walker et al. 1995**), and 16 subjects were exposed to Alutard SQ *Phleum pratense* for a further 3 years in the second follow-up trial (**Durham et al. 1999**). 16 subjects were therefore exposed for up to 6 years.

IV.1.2 Summary of results of individual studies

For detailed presentations and assessments of the included trials, see Clinical AR.

IV.1.2.1 Trials investigating only Alutard SQ Phleum pratense

- **UK22 trial**

Objective and design: The objective of this trial was to evaluate the efficacy and safety of two doses (10,000 SQ-U and 100,000 SQ-U) of Alutard SQ Phleum pratense in subjects with moderate/severe seasonal allergic rhinoconjunctivitis inadequately controlled with standard drug therapy.

Up-dosing consisted of a minimum of 15 injections over 8 weeks (2 injections on one day separated by 30minutes, once weekly); maintenance injections were administered every 6 ± 2 weeks.

Results: Rhinoconjunctivitis quality of life questionnaire (RQLQ) had a baseline to season change in placebo of 2.29, 1.81 for low dose and 1.40 for high dose. Minimal important difference is 0.5 which was shown when comparing high dose with placebo ($p<0.001$). Although the difference was "only" 0.48 when comparing low dose to placebo, it was statistically significant ($p=0.027$). The difference between the low and high dose was also statistically different ($p=0.027$).

- **UK21 trial**

Objective and design: The objective of this trial was to evaluate the efficacy and safety of Alutard SQ Phleum pratense in children with seasonal allergic asthma.

39 subjects (3-16 years of age) were randomised to receive Alutard SQ Phleum pratense 100,000 SQ-U or placebo in a 1:1 ratio.

Results: The rhinoconjunctivitis symptom scores were lower for the Alutard SQ group compared to the placebo group, although these differences were not statistically significant. However, Alutard SQ Phleum pratense was shown to have a significant effect on reducing the reactivity to grass pollen in the skin (skin prick test), conjuctiva (conjunctival provocation test) and lungs (bronchial provocation test).

- **UK18 trial**

Objective and design: The objective of this trial was to evaluate the efficacy and safety of Alutard SQ Phleum pratense 100,000 SQ-U in subjects with severe seasonal allergic rhinoconjunctivitis with asthma.

Results: The results showed statistically significant better outcome in the Alutard group compared to placebo. The difference in RQLQ reached clinically relevant difference (0.5 points, $p=0.02$).

- **Varney/Walker/Durham/Wachholz trial**

Objective and design: The objective of the initial trial (and first follow-up trial) was to evaluate the efficacy and safety of Alutard SQ Phleum pratense in subjects with severe summer hay fever not responding adequately to standard pharmacotherapy.

The objective of the second follow-up trial was to evaluate the long term clinical efficacy and safety of specific immunotherapy with Alutard SQ Phleum pratense in subjects with severe summer hay fever.

Results: Overall total symptom and medication scores were statistically significant better in the Alutard group compared to placebo, and the results were maintained throughout the 3-4-years study period. A sustained effect was also observed for at least 3 years after completion of treatment.

- **Francis trial**

Objective and design:

The objective of the trial was to evaluate the efficacy of Alutard SQ Phleum pratense in subjects with moderate/severe seasonal allergic rhinitis.

Results: Alutard treatment led to reduction in skin prick test and symptoms. Furthermore, subjects receiving immunotherapy also required significantly ($p < 0.05$) greater concentrations of P. pratense allergen to elicit conjunctival symptoms on provocation testing (32,182 ± 7432 SQ-U/mL) than subjects receiving placebo (2760 ± 440 SQ-U/mL).

- **Østerballe/Djurup/Mosbech trial**

Objective and design: The objective of the trail was to evaluate the efficacy and safety of ALK-depot SQ (Alutard SQ) Phleum pratense versus purified extract with two major allergens (Ag19 and Ag25).

Results: The Alutard group reported fewer symptoms and lower medication scores compared with the control groups. The results sustained during seasons 2 and 3.

IV.1.2.2 Trials investigating Alutard SQ Phleum pratense and Alutard SQ Betula verrucosa

- **Winther trial**

Objective and design: The objective of the trial was to compare side-effects to birch- and grass-pollen extracts in adult subjects with a history of severe birch- and grass-pollen allergy. Furthermore, the trial aimed to identify parameters predictive of systematic reactions. The participants received either Alutard SQ Betula verrucosa or Phleum pratense.

Results: Both groups showed improvement in symptoms but annual differences in pollen counts contributed to different symptom severity.

- **PAT trial**

Objective and design: The objective of the trial was to determine whether specific immunotherapy can prevent the development of asthma and reduce bronchial hyperresponsiveness in children with seasonal allergic rhinoconjunctivitis to birch and/or grass pollen.

Following a baseline season (season 0), 205 children (6-15 years of age) were randomised to treatment with Alutard SQ (Phleum pratense and/or Betula verrucosa) or control medication for 3 years.

Results: Significant improvements in conjunctival sensitivity, bronchial hyperresponsiveness and symptom VAS scores were recorded following immunotherapy compared with control treatment. Immunotherapy treated children also had significantly fewer asthma symptoms. Seven years after the end of this treatment the significant improvements in rhinoconjunctivitis and conjunctival sensitivity persisted and the preventive effect on asthma development was sustained.

IV.1.2.3 Trials investigating Alutard SQ or ALK7 grass mixes

- **Dolz trial**

Objective and design: The objective of this trial was to evaluate the efficacy and safety of Alutard SQ Phleum pratense, Dactylis glomerata, Lolium perenne in subjects with seasonal asthma and/or rhinoconjunctivitis.

Results: Alutard SQ group showed statistically significant improvement in all variables compared to placebo.

- **Zenner trial**

Objective and design: The objective of this trial was to evaluate the efficacy and safety of ALK7 6-grass mix + rye in subjects with seasonal allergic rhinoconjunctivitis. The maximum dose equalled 10,000 SQ-U.

Results: Overall symptom score was improved compared to placebo (p=0.020).

- **Klimek trial**

Objective and design: The objective of this trial was to compare the efficacy and safety of short-term immunotherapy (6-grass + rye up to doses equalling 10000 SQ-U) with symptomatic drug treatment.

Results: Overall symptoms and medication scores were statistically significantly lower in the group receiving immunotherapy as compared with the group receiving anti-allergic drugs alone.

- **SHX0523 trial**

Objective and design: The objective of the trial was to explore the effect of specific immunotherapy on disease-specific and general QoL and compliance in a large group of subjects treated by allergists.

Results: The RQLQ was evaluated for 1093 subjects. RQLQ (scale 0 to 6) improved from 2.91 before treatment to 1.05 after 3 years ($p < 0.0001$). This change is greater than the minimal important difference of 0.5.

IV.1.3 Comparison and analyses of results across studies

Grass pollen allergy is prevalent in all ages and the different studies included patients from 2 to 71 year, with some differences between studies. Most of the trials were performed in subjects with moderate and/or severe rhinoconjunctivitis, in some stratification was done based on asthma. All subjects had positive SPT to grass or positive specific IgE.

Although some of the methods used were similar, the designs of the trials included in this application differ significantly, and direct comparisons and analyses across trials are not possible.

With some variations, rhinoconjunctivitis symptoms were collected in 10 of the trials. In 9 of those, Alutard SQ or ALK7 resulted in significant reduction in symptom score compared to comparator or baseline.

Rhinoconjunctivitis medicine was an endpoint in 10 of the trials. The majority of studies showed statistically significant decrease in medicine use when treated with Alutard compared to placebo.

Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was used in three trials, showing statistically significant improvement in the Alutard group compared to placebo. The validated minimal clinical difference of 0.5 was reached in several analyses.

IV.1.4 Comparison of results in sub-populations

Two of the trials, UK21 and PAT, included only children from 3 to 16 years old. UK21 showed a numerically better improvement in asthma-related endpoints during pollen season in the active treatment group but the difference did not reach statistical significance. However, skin prick test, conjunctival provocation test and bronchial provocation test showed significant improvement when treated with Alutard (see also section IV.1.2.1). PAT showed significant improvements in symptoms, including asthma, with sustained superiority to control treatment after 3 and 5 years (see also section IV.1.2.1).

Use of Alutard SQ *Phleum pratense* in paediatic population is reflected in SmPC section 4.2. The wording was agreed between member states in the Paediatric worksharing procedure (DK/W/005/pdWS/001). In this procedure, the MAH submitted the UK21 trial (investigating safety and efficacy), the UK23 trial (investigating safety) and PAT trial (investigating efficacy).

In five of the other trials (i.e the Østerballe/Djurup/Mosbech, the Dolz, the Zenner, the Klimek and the SHX0523 trial respectively) children and adolescents <18 years were included. No separate analyses by age were conducted in these trials, but there were no apparent differences between children/ adolescents and adults in these trials. See section IV.1.2.1 and IV.1.2.2.

No trials have been conducted in subjects older than 65 years of age, only a small number of elderly peopled were included in one of the trials. No conclusions can be drawn but there are no indications that the efficacy would change dramatically at that certain age.

No trials have been conducted in pregnant women and the EAACI guideline on Allergic rhinoconjunctivitis (Roberts et al. 2018) states that allergy immunotherapy should not be initiated during pregnancy but may be continued during pregnancy if the already initiated treatment has been tolerated well.

IV.1.5 Analysis of clinical information relevant to dosing recommendations

Subcutaneous immunotherapy with Alutard SQ Phleum pratense is carried out in two phases: an up-dosing period followed by a maintenance period, with a maximum recommended maintenance dose of 100,000 SQ-U.

The 15-week up-dosing schedule has been recommended since Alutard SQ Phleum pratense was granted the first MA in 1982 and was based on clinical practice at the time.

The recently approved 7-week up-dosing schedule provides an up-dosing schedule with fewer treatment visits. The safety of this up-dosing schedule was investigated in the AL-X-01 trial (AL-X 01 integrated clinical trial report).

The trials included in this summary used different up-dosing schedules, from “rush-up” dosing to once weekly up-dosing, all with an acceptable safety profile. Up-dosing should always be adjusted to the patient’s tolerance and is thus limited by safety while the efficacy of the treatment is mainly linked to the repeated doses of the maintenance dose during 3 to 5 years. The goal is to attain a maintenance

dose of 100,000 SQ-U, but this dose may have to be adjusted, based on local and/or general tolerability.

IV.1.6 Persistence of efficacy and/or tolerance effects

Allergy immunotherapy affects the pathophysiological mechanism of allergic disease and has in trials been showed to have effect up to 7 years after completion of the maintenance period of 3-5 years.

IV.1.7 Assessor's overall conclusions of clinical efficacy

The MAH has submitted 12 studies to support the efficacy of Alutard SQ *Phleum pratense* (timothy). Six of the trials investigate only *Phleum pratense*, 2 studies investigate *Phleum pratense* and *Betula verrucosa* (birch), and the remaining supportive trials investigate Alutard SQ or ALK7 grass mixes.

As timothy is part of the same homologous group as other grasses, extrapolation from studies with grass mixes is acceptable according to the Guideline on allergen products: Production and quality issues (EMEA/CHMP/BWP/304831/2007). Thus, studies with grass mixes may be used for support of efficacy of Alutard SQ *Phleum Pratense*.

Grass pollen allergy is prevalent in all ages and the different studies included patients from 2 to 71 year, with some differences between studies. Most of the trials were performed in subjects with moderate and/or severe rhinoconjunctivitis, in some stratification was done based on asthma. All subjects had positive SPT to grass or positive specific IgE.

Rhinoconjunctivitis symptom score was used as an efficacy endpoint in 10 of the trials. While most of the trials collected daily eye, nose and lung/chest symptoms on a 0-3 severity scale (3 being the most severe), the exact symptoms and/or the method of analysis were different for each trial. In 9 of those trials, Alutard SQ or ALK7 resulted in significant reduction in symptom score compared to comparator or baseline.

Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was used in three trials. It has a validated minimal clinical difference of 0.5. The value 0 represents no impairment while 6 is severely impaired and showed statistically significant improvement in the Alutard group compared to placebo.

Rhinoconjunctivitis medicine was an endpoint in 10 of the trials. The majority of studies showed statistically significant decrease in medicine use when treated with Alutard compared to placebo.

Thus, the presented studies support efficacy on variables affected by IgE-mediated allergy to pollen of timothy.

Two of the trials, UK21 and PAT, included only children from 3 to 16 years old. UK21 showed a numerically better improvement in asthma-related endpoints during pollen season in the active treatment group but the difference did not reach statistical significance. However, skin prick test, conjunctival provocation test and bronchial provocation test showed significant improvement when treated with Alutard. PAT showed significant improvements in symptoms, including asthma, with sustained superiority to control treatment after 3 and 5 years. In the SmPC it is stated that AIT is not suitable for children under the age of 5 and that there are limited efficacy data in children >5 years of age. The wording was agreed between member states in the Paediatric worksharing procedure (DK/W/005/pdWS/001).

No trials have been conducted in subjects older than 65 years of age, only a small number of elderly peopled were included in one of the trials. No conclusions can be drawn but there are no indications that the efficacy would change dramatically at that certain age.

No trials have been conducted in pregnant women and the EAACI guideline on Allergic rhinoconjunctivitis (Roberts et al. 2018) states that allergy immunotherapy should not be initiated during pregnancy but may be continued during pregnancy if the already initiated treatment has been tolerated well. This is reflected in the SmPC.

Subcutaneous immunotherapy with Alutard SQ Phleum pratense is carried out in two phases: an up-dosing period followed by a maintenance period, with a maximum recommended maintenance dose of 100,000 SQ-U.

The 15-week up-dosing schedule has been recommended since Alutard SQ *Phleum pratense* was granted the first MA in 1982 and was based on clinical practice at the time.

The recently approved 7-week up-dosing schedule provides an up-dosing schedule with fewer treatment visits. The safety of this up-dosing schedule was investigated in the AL-X-01 trial (AL-X 01 integrated clinical trial report) and assessed in national procedure 5.4.3-2019-38077.

The trials included in this summary used different up-dosing schedules, from “rush-up” dosing to once weekly up-dosing, all with an acceptable safety profile. Up-dosing should always be adjusted to the patient’s tolerance and is thus limited by safety while the efficacy of the treatment is mainly linked to the repeated doses of the maintenance dose during 3 to 5 years. The goal is to attain a maintenance dose of 100,000 SQ-U, but this dose may have to be adjusted, based on local and/or general tolerability.

The submitted studies support the currently approved posology of Alutard SQ *Phleum pratense*.

IV.2 Clinical safety

IV.2.1 Introduction

To demonstrate safety of Alutard SQ *Phleum pratense* in treating rhinoconjunctivitis in clinical trials, a total of 15 trials (*Table 3*) in which ALK was the sponsor or provided material and/or financial support are included in this summary of clinical safety:

- 7 trials investigating only Alutard SQ *Phleum pratense* (900 subjects on Alutard SQ *Phleum pratense* and 163 subjects on placebo)
- 1 trial investigating Alutard SQ Phleum pratense and Alutard SQ *Betula verrucosa* (26 subjects on Alutard SQ *Phleum pratense* and 26 subjects on Alutard SQ *Betula verrucosa*)
- 7 supportive trials investigating Alutard SQ or ALK 7 grass-mixes (1876 subjects treated with Alutard SQ or ALK 7 grass-mixes and 111 subjects on placebo)

The trials are different in design, including differences in posology and target populations, which make them unsuitable for pooling and direct comparisons.

Table 3 Overview of data sources to demonstrate the safety of Alutard SQ Phleum pratense

Description	Treatment and dose	Subjects	Location in Module 5
Trials investigating only Alutard SQ Phleum pratense			
UK22 trial			
Evaluation of efficacy and safety of 2 doses (10,000 SQ-U and 100,000 SQ-U) of Alutard SQ *Phleum pratense* in adult subjects with moderate/severe seasonal allergic rhinoconjunctivitis 1 year treatment duration	Alutard SQ *Phleum pratense* in doses of 10,000 SQ-U, 100,000 SQ-U or placebo	410 subjects; 203 subjects treated with 100,000 SQ-U, 104 subjects treated with 10,000 SQ-U and 103 subjects treated with placebo 18-60 years	**UK22 Integrated clinical trial report**
UK22 Follow-on trial			
Evaluation of long-term safety of Alutard SQ *Phleum pratense* in subjects with seasonal allergic rhinoconjunctivitis not responding adequately to anti-allergic drugs (an open-label follow-on safety trial of the UK22 trial) 2-3 years treatment duration	Alutard SQ *Phleum pratense* 10,000 SQ-U and 100,000 SQ-U	334 subjects; all subjects received active treatment 19-60 years	**UK22FO Integrated clinical trial report**
UK21 trial			
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* in children with seasonal allergic asthma 2 years treatment duration	Alutard SQ *Phleum pratense* 100,000 SQ-U or placebo	39 subjects. 33 subjects completed; 16 on active treatment and 17 on placebo 3-16 years	**UK21 Integrated clinical trial report**
UK18 trial			
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* in adult subjects with severe seasonal allergic rhinoconjunctivitis with asthma 2 years treatment duration	Alutard SQ *Phleum pratense* 100,000 SQ-U or placebo	44 subjects; 22 subjects on active treatment and 22 on placebo 22-64 years	Published paper: **Walker et al 2001**
Varney/Walker/Durham/Wachholz trial *			
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* in adult subjects with severe seasonal allergic rhinoconjunctivitis with or without mild asthma 1 year + 3 years following completion of initial trial	Alutard SQ *Phleum pratense* 100,000 SQ-U or placebo	40 subjects; 21 on active treatment and 19 on placebo 19-52 years	Published papers: **Varney et al 1991** **Walker et al 1995** **Durham et al 1999**

Description	Treatment and dose	Subjects	Location in Module 5
UK23 trials			
Evaluation of safety of Alutard SQ *Phleum pratense* in adults, adolescents and children, suffering from seasonal allergic rhinoconjunctivitis due to grass pollen not responding to pharmacotherapy 3 years	Alutard SQ *Phleum pratense* 10,000 SQ-U and 100,000 SQ-U	*Adult/adolescents trial:* 338 subjects enrolled; 321 subjects treated, all on active treatment 13-61 years *Children trial:* 81 subjects on active treatment 5-16 years	**UK23A Integrated clinical trial report** **UK23P Integrated clinical trial report**
Østerballe/Djurup/Mosbech trial			
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* versus purified extract with two major allergens (Ag19 and Ag25) in subjects (adults and adolescents) with seasonal allergic rhinoconjunctivitis with or without asthma 3 years + 6 years follow-up	Alutard SQ *Phleum pratense* or purified extract with two major allergens (Ag19 and Ag25)	40 subjects; 20 subjects on active treatment with Alutard SQ *Phleum pratense* and 20 subjects on active treatment with purified extract with two major allergens (Ag19 and Ag25) 15-43 years	Published papers: **Østerballe 1980** **Østerballe 1982b**
Trials investigating Alutard SQ *Phleum pratense* and Alutard SQ *Betula verrucosa*			
Winther trial			
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense* and *Betula verrucosa* in adult subjects with seasonal allergic rhinoconjunctivitis 2 years	Alutard SQ *Phleum pratense* and *Betula verrucosa* 100,000 SQ-U	52 subjects; 26 subjects on active treatment with Alutard SQ *Phleum pratense* and 26 subjects on active treatment with Alutard SQ *Betula verrucosa* 18-52 years	Published papers: **Winther et al 2000b**
Trials investigating Alutard SQ or ALK7 grass mixes			
AL-X-01 [#]			
Safety and tolerability of shortened up-dosing with Alutard SQ 12-16 weeks treatment duration	Alutard SQ 6-grasses and rye, birch, or HDM mix	341 subjects enrolled, 340 treated grass-11: N=85, grass-7: N=85, tree-7: N=87, HDM-7: N=83	**AL-X-01 Integrated clinical trial report**

Description	Treatment and dose	Subjects	Location in Module 5
Dolz trial			
Evaluation of efficacy and safety of Alutard SQ *Phleum pratense, Dactylis glomerata, Lolium perenne* in subjects (adults and adolescents) with seasonal asthma and/or rhinoconjunctivitis 3 years	Alutard SQ *Phleum pratense, Dactylis glomerata, Lolium perenne* 100,000 SQ-U or placebo (rush up-dosing with aqueous extract, maintenance with ALK-depot SQ (Alutard SQ) *Phleum pratense, Dactylis glomerata, Lolium perenne*)	30 subjects. 28 subjects completed; 18 on active treatment and 10 on placebo 15-35 years	Published paper: **Dolz et al 1996**
Zenner trial			
Evaluation of efficacy and safety of ALK7 6-grass mix + rye in subjects (adults and adolescents) with seasonal allergic rhinoconjunctivitis 1 year	ALK7 6-grass mix + rye 1000 SE (equals 10,000 SQ-U) or placebo	86 subjects; 45 on active treatment and 41 on placebo 16-53 years	Published paper: **Zenner et al 1997**
SHX0562 trial			
Evaluation of pharmacodynamic efficacy and safety of an intraseasonal short-time up-dosing schedule for Alutard SQ 6-grass mix + rye 1 year	Alutard SQ 6-grass mix + rye 10,000 SQ-U or placebo	148 subjects. 112 on active treatment and 36 on placebo 18-65 years	**SHX0562 Integrated clinical trial report**
Klimek trial			
Evaluation of efficacy and safety of ALK7 6-grass mix + rye in subjects (adults and adolescents) with seasonal allergic rhinoconjunctivitis 1 year treatment duration	ALK7 6-grass mix + rye 1000 SE (equals 10,000 SQ-U)	48 subjects; 24 subjects on active treatment and 24 subjects in control group 15-50 years	Published paper: **Klimek et al 2005**
PMS-AL-H-01 trial			
Evaluation of tolerability of intra-seasonal subcutaneous immunotherapy with Alutard SQ grass in patients with grass pollen induced allergic rhinoconjunctivitis. 7 months	Alutard SQ 6-grass mix and rye 10,000 SQ-U during grass pollen season and increased to 100,000 SQ-U after pollen season	250 subjects; adults and children 5-73 years	**PMS-AL-H-01 Integrated clinical trial report**
SHX0523 trial			
Evaluation of quality of life and compliance of Alutard SQ 6-grass mix + rye 3 years	Alutard SQ 6-grass mix + rye 100,000 SQ-U	1257 subjects on active treatment. 2-71 years	**SHX0523 Integrated clinical trial report**
Post-marketing data			

Description	Treatment and dose	Subjects	Location in Module 5
Periodic safety update reports (PSURs)	-	-	**5.3.6 Reports of post-marketing experience**

* 21 subjects were exposed to Alutard SQ *Phleum pratense* for more than 3 years in the first follow-up trial (**Walker et al. 1995**), and 16 subjects were exposed to Alutard SQ *Phleum pratense* for a further 3 years in the second follow-up trial (**Durham et al. 1999**). 16 subjects were therefore exposed for up to 6 years

AL-X-01 trial investigated 7-week and 11-week up-dosing schedules.

IV.2.2 Patient exposure

Patient exposure in clinical trials

In the 15 clinical trials included in the summary of clinical safety, a total of 2, 776 subjects were exposed to Alutard SQ or ALK7 grass pollen products. In the 7 trials investigating only Alutard SQ *Phleum pratense* 900 subjects was exposed to Alutard SQ *Phleum pratense*.

21 subjects were exposed to Alutard SQ *Phleum pratense* for more than 3 years in the first follow-up trial (Walker et al. 1995), and 16 subjects were exposed to Alutard SQ *Phleum pratense* for a further 3 years in the second follow-up trial (Durham et al. 1999). 16 subjects were therefore exposed for up to 6 years.

No subjects above 65 years were included in the studies using *Phlenum pratense* only. However, the age range for trials investigating Alutard SQ or ALX-7 Grass mix included subjects above 65 years (*Table 3*).

In the pediatric population the age range varies from 3 to 16 years. Exposure and safety in the paediatric population is further discussed in section IV.2.7.

Post-marketing exposure

Patient exposure is presented in and based on sales figures and presented as treatment years (TY).

The cumulative post marketing exposure is estimated to 139, 004 TY for Alutard SQ *Phleum pratense* and 465,836 TY for Alutard SQ and ALK7 *Grass mix and other single grass species products* (604,839 TY in total) and covers the period 01-Jan-1995 to 31-Dec-2019, although it should be noted that exposure data prior to 2003 was not systematically collected.

IV.2.3 Adverse events

Summary of adverse events

An overall summary of adverse events has been presented for study UK-22, UK-22 follow-on trial, UK-21 trial and UK 23 trials. See Clinical AR for details.

The proportion of subjects with adverse event in these studies varies between 61% to 96% in the Alutard SQ *Phleum pratense* treatment groups.

In the placebo comparative UK22 trial, a similar proportion of subjects reported AEs in the placebo group (64%) as in the two Alutard SQ *Phleum pratense* groups (69.5 % in the 100,000 SQ-U N group and 61% in the 10 000 SQ-U N group).

Severe AEs were reported in 0-12.8% in the Alutard SQ *Phleum pratense* treatment groups. In the placebo comparative UK22 trial, a similar proportion of subjects reported severe AEs in the placebo group (11.7%) as in the two Alutard SQ *Phleum pratense* groups (12.8% in the 100,000 SQ-U N group and 10.6% in the 10 000 SQ-U N group).

Local and systemic allergic reactions

As expected for AIT treatment, local injection site reactions and systemic reactions were the most commonly observed AEs in all trials. These were primarily mild or moderate in intensity and the

subjects generally recovered quickly. An overall overview of local reactions and systemic reactions from trials specifically performed using Alutard SQ *Phleum pratense* is provided in Table 8.

An overall overview of local reactions and systemic reactions from two of the largest trials, UK22 and UK23 respectively is presented in Table 4 and Table 5.

Most of the local and systemic allergic adverse reactions occurs during the up-dosing phase (Table 8).

The proportion of subjects reporting allergic reactions was higher for subjects receiving higher doses compared to those receiving lower doses of injected allergens (trial UK 22; see Table 8).

In line with EMA guideline (CHMP/EWP/18504/2006) allergic side effects have been distinguished into immediate or delayed effects according to the time of appearance. However, to note is that the time of onset for "immediate" effects and definition of large local reactions differs between the trials but have been indicated study by study in the footnotes (Table 8).

See further discussion regarding safety in use of the pediatric population in section IV.2.7.

The risk for allergic reactions with Alutard SQ Timotej and recommendations regarding dose reductions in case of local and/or systemic reactions and general handling in case of allergic reactions are reflected in SmPC section 4.2. Handling specifically in case of severe systemic reactions is reflected in SmPC section 4.4. The overall risk for allergic reactions is reflected in SmPC section 4.8 and 5.1.

Table 6 Overview of local reactions and systemic reactions in trial UK22

	Alutard SQ *Phleum pratense* 100,000 SQ-U N (%) E	**Alutard SQ *Phleum pratense* 10,000 SQ-U N (%) E**	**Placebo N (%) E**	**Total N (%) E**
No. of subjects	203 (100%)	104 (100%)	103 (100%)	410 (100%)
Local reactions:				
No. of subjects with local reactions	118 (58.1%) 446	38 (36.5%) 117	25 (24.3%) 70	181 (44.1%) 633
Systemic reactions:				
No. of subjects with systemic reactions	150 (73.9%) 880	54 (51.9%) 318	48 (46.6%) 218	252 (61.5%) 1416

Table 7 Overview of local reactions and systemic reactions in trial UK23

	UK23P Alutard SQ *Phleum pratense* N (%) E	**UK23A Alutard SQ *Phleum pratense* N (%) E**
No. of subjects	81 (100%)	321 (100%)
Local reactions:		
No. of subjects with local reactions	65 (80%) 376	91 (28%) 191
Systemic reactions:		
No. of subjects with systemic reactions	64 (79%) 310	154 (48%) 533

Table 8 Local allergic reactions and systemic allergic reactions in trials performed with Phleum pratense

Trial	Treatment group	Subjects N	Phase - Time of onset		Local reactions N (%) E	Systemic reactions N (%) E
UK22 [a]	100,000 SQ-U	203	Up-dosing:	Early	20 (9.9%) 47	56 (27.6%) 166
				Delayed	106 (52.2%) 308	121 (59.6%) 498
			Maintenance:	Early	5 (2.5%) 6	14 (6.9%) 41
				Delayed	34 (16.7%) 72	44 (21.7%) 124
			Unknown:	Early	1 (0.5%) 1	7 (3.4%) 19
				Delayed	8 (3.9%) 12	18 (8.9%) 32
	10,000 SQ-U	104	Up-dosing:	Early	5 (4.8%) 8	17 (16.3%) 60
				Delayed	35 (33.7%) 88	46 (44.2%) 157
			Maintenance:	Early	3 (2.9%) 5	9 (8.7%) 33
				Delayed	9 (8.7%) 15	21 (20.2%) 57
			Unknown:	Early	0 (0.0%) 0	2 (1.9%) 3
				Delayed	1 (1.0%) 1	5 (4.8%) 8
	Placebo	103	Up-dosing:	Early	4 (3.9%) 5	13 (12.6%) 17
				Delayed	16 (15.5%) 31	37 (35.9%) 130
			Maintenance:	Early	3 (2.9%) 5	7 (6.8%) 11
				Delayed	14 (13.6%) 29	17 (16.5%) 50
			Unknown:	Early	0 (0.0%) 0	1 (1.0%) 2
				Delayed	0 (0.0%) 0	4 (3.9%) 8
UK22-FO [b, c]	100,000 SQ-U	334	Up-dosing:	Early	18 (5%) 30	28 (8%) 62
			Maintenance:	Early	58 (17%) 107	56 (17%) 130
			Missing:	Early	1 (<1%) 1	NA
UK18 [d]	100,000 SQ-U	22	Up-dosing		0 (0.0%) 0	NA (NA) 4
			Maintenance		0 (0.0%) 0	NA (NA) 3
	Placebo	22	Up-dosing		0 (0.0%) 0	NA (NA) 5
			Maintenance		0 (0.0%) 0	0 (0.0%) 0
Varney/Walker/ Durham/Walchholz [e]	100,000 SQ-U	21	Up-dosing		NA (NA) 28	NA (NA) 11
			Maintenance		NA (NA) 6	NA (NA) 0
UK23A [c, f]	100,000 SQ-U	321	Up-dosing		76 (24%) 146	141 (44%) 417
			Maintenance		33 (10%) 45	46 (14%) 116
Østerballe/Djurup/ Mosbech	100,000 SQ-U	20	Up-dosing		NA	NA (NA) 11
			Maintenance		NA	NA
Winther [g]	100,000 SQ-U	26	Up-dosing + Maintenance		NA (NA) 100	NA (NA) 41
Paediatric trials						
UK21 [h, i]	100,000 SQ-U	19	NA		8 (42%) 13	13 (68%) 25
	Placebo	19	NA		5 (26%) 11	7 (37%) 12
UK23P [c, j]	100,000 SQ-U	81	Up-dosing		61 (75%) 254	58 (72%) 219
			Maintenance		42 (52%) 122	28 (35%) 91

[a]Local reactions reported as; early local reaction >5 cm in diameter and delayed local reactions >8 cm in diameter. Systemic reactions were graded 0-4 according to EAACI (Malling & Weeke, 1993). Early local and systemic reactions occurred within 1 hour after injection, and late local and systemic reactions between 1-24 hours after injection.

[b]Early local and systemic reactions occurred within 1 hour after injection, and late local and systemic reactions between 1-24 hours after injection

[c]During study, all maintenance doses of Alutard SQ Phleum pratense were reduced to 10,000 SQ-U

[d] Local reactions defined as large reactions (>8×8 cm).

[e]Reported local reactions were all large reactions (>8x8 cm).

[f] Local reactions were defined as early (occurred 0-60 minutes after injection) or late (occurred between 1-24 hours after injection). Large local swelling was defined as >8 cm. Systemic reactions were graded 0-4 according to the EAACI (Malling & Weeke, 1993).

[g] Late Local reactions were reported (>8cm). Systemic reactions were graded according to the EAACI (Malling & Weeke, 1993).

[h]Local reaction: maximal diameter ≥8 cm at injection site. Systemic reaction: Any reaction occurring within 24 hours after injection i.e. rhinoconjunctivitis, flushing, feneralised pruritus, angiodema, urticaria, asthma or shortness of breath, and multiple symptoms terminating in anaphylactic shock.

[i]UK21 Integrated clinical trial report, Table 10-4 and Table 10-5

[j]local reactions were defined as early (occurred 0-60 minutes after injection) or late (occurred between 1-24 hours after injection). Large local swelling was defined as >8 cm. Systemic reactions were graded as follows; Grade 1/Mild (Itching, erythema, conjunctivitis, rhinitis), Grade 2/Moderate (Urticaria, angioedema, Wheeze not causing respiratory distress), Grade 3/Severe (Wheeze causing respiratory distress, stridor, hoarseness, pallor, hypotension), and Grade 4/Life threatening (Increasing respiratory distress despite medication, collapse, loss of consciousness, respiratory or cardiac arrest)

IV.2.4 Serious adverse events and deaths

Serious adverse events were reported in 9 of the 15 trials. In total 98 SAEs were reported in 77 subjects (2.6% of total subjects), of which 40 events in 31 subjects (1.2%) were assessed as related to Alutard SQ/ALK7 treatment. All related events were systemic allergic reactions.

In total, 21 SAEs were assessed as related to Alutard SQ *Phleum pratense* treatment in the seven clinical trials investigating only Alutard SQ *Phleum.* Approximately 50% (i.e. 11/21) of these SAEs were reported as anaphylactic reactions or anaphylactic shocks. According to data presented no related SAE were reported in the pediatric population in study UK21 or UK23P.

No fatal events have been reported in clinical trials that were considered related to the use of Alutard SQ Phleum pratense. Two deaths (brain neoplasm; drowning) considered unrelated to treatment were reported in the UK23A trial.

The risk for anaphylactic reactions and anaphylactic shocks is reflected in the SmPC (section 4.2, 4.3, 4.4 and 4.8).

IV.2.5 Discontinuations due to adverse events

Approximately 5-10% of the adult subjects in the larger studies i.e. UK22, UK22-FU and UK23, were withdrawn due to AEs. In most cases systemic allergic reactions including anaphylactic shock were the reasons for withdrawals. Lower doses of the IMP resulted in lower frequencies of withdrawal AEs (i.e 100,000 vs 10 000 SQ-U in study UK22). The frequency of withdrawals due to AEs in the paediatric population (study UK23P) were higher (12.3%) compared to the adults (6.8%).

IV.2.6 Laboratory findings

No clinical laboratory evaluations were reported

IV.2.7 Safety in special populations

Intrinsic factors
There was no safety analysis of subjects by gender or ethnic origin in the trials provided in this application. The MAH concludes that based on cumulative experience with allergy immunotherapy there is no reason to expect that any of these subgroups will be differentially impacted by treatment with Alutard SQ *Phleum pratense.* Exploration of safety data from the paediactric population is presented in the below section.

Paediatric population

In a paediatric work-sharing procedure 2010 (DK/W/005/pdWS/001) on grass pollen (*Phlenum pratense*) it was agreed that children under 5 years of age are normally not considered suitable candidates for hyposensitisation because acceptance and cooperation problems are more likely in this age group than for adults. For children > 5 years of age clinical data of efficacy were considered sparse and could not (at that time) prove efficacy. Data on safety did not reveal a higher risk than for adults (SmPC section 4.2).

The UK21 and UK23P trials were conducted in paediatric population; paediatric subjects were also included in trials AL-X-01 and SHX0523. In the Dolz trial, the Zenner trial, the Klimek trial, the Østerballe/Djurup/Mosbech trial, and the PMS-AL-H-01 trial, paediatric subjects <18 years were included, but no separate safety analyses on these subjects were conducted and are therefore not included here.

Overall, it could be concluded that the studies performed with Alutard SQ *Phlenum pratense* and/or Grass pollen demonstrates that the safety profile in the adolescents (> 12 years) are similar to adults (i.e. study AL-X-01, SHX0523). The safety profile in studies performed in children below 12 years (i.e. study UK21 and UK23P) indicated a similar AE profile as in adolescent, however, in study UK23 higher frequency of allergic adverse events was noted in the paediatric population aged 5-16 years compared to the adults. This difference is considered accepted with the current recommendation in the SmPC (section 4.2). Data on safety do not reveal a higher risk in children than for adults. This is also in line with the conclusion within the paediatric work-sharing procedure in 2010 (DK/W/005/pdWS/001).

Use of Alutard SQ *Phlenum pratense* and/or Grass pollen in children below 5 years is limited and not recommended because acceptance and cooperation problems are likely in this age group (DK/W/005/pdWS/001 reflected in SmPC section 4.2 and 4.4).

Use in the paediatric population is considered sufficiently reflected in SmPC section 4.2, 4.4 and 4.8.

Extrinsic factors

Aluminium
In Alutard products, aluminium in the form of aluminium hydroxide is added as an adjuvant.
The content of aluminium in the drug product depends on the strength, of which 4 varieties are produced for Alutard SQ. According to the European Pharmacopoeia monograph on Allergen Products (European Pharmacopoeia 2019), the acceptance criteria should be 80 – 120% of the stated amount of aluminium but not more than 1.25 mg (1250 µg) per human dose. The upper acceptance limit for Alutard SQ 100,000 SQ-U/mL (highest dose) is set to 1,250 µg/mL to comply with the restriction on maximum amount per dose specified in (European Pharmacopoeia 2019). The stated amount of aluminium per dose of Alutard SQ is thus below the specified maximum amount.

No events other than local reactions including allergic reactions to aluminium have been reported to ALK in which a causal relationship with aluminium adjuvant was suspected for either renally compromised patients or any other patient population. While the risk of aluminium accumulation

leading to undesirable effects in patients treated with Alutard SQ is plausible and relevant, it remains theoretical due to the lack of published case reports and post-marketing data. The risk for complication in due to content of aluminium in the product is reflected in SmPC section 4.4 and 4.8.

IV.2.8 Safety related to drug-drug interactions and other interactions

No interaction trials have been conducted in humans and no potential drug interactions have been identified from any source.

Concomitant treatment with symptomatic anti-allergy medications, e.g. antihistamines, corticosteroids or mast cell stabilisers may increase the patient's tolerance level towards the allergen injections. This should be considered at discontinuation of such medications.
Care and attention should be observed with concomitant use of tricyclic antidepressants, COMT inhibitors and monoamine oxidase inhibitors (MAOIs), since these might compromise emergency treatment with adrenaline.

This is reflected in SmPC section 4.5.

IV.2.9 Use in pregnancy and lactation

In accordance with the EAACI guideline on allergic rhinoconjunctivitis (Roberts et al. 2018) treatment with Alutard SQ *Phleum pratense* should not be initiated during pregnancy but may be continued during pregnancy if the already initiated treatment has been tolerated well. If treatment is continued during pregnancy, careful monitoring is recommended.

No clinical data are available for the use of Alutard SQ Phleum pratense during breast feeding. No effects on the breastfed infants are anticipated.

This is reflected in SmPC section 4.6

IV.2.10 Long-term safety

In the trials included, subjects were treated for up to 4 years (Varney/Walker/Durham/Wachholz trial). Long-term therapy has not raised any safety concerns.

IV.2.11 Safety in relation to dose regimen

No specific safety issues other than the known safety patten has been identified (in clinical trials or post-marketing) for the currently recommended up-dosing schedules used for Alutard SQ *Phleum pratense*.

IV.2.12 Post-marketing data

By 31-Dec-2019, ALK had received 1,021 individual case safety reports for Alutard SQ Phleum pratense corresponding to a frequency of 0.007 cases received per TY. 341 of the 1,021 received cases involved children (5-17 years of age). For Alutard SQ Grass mix and other single grass species products, a total of 2,634 cases were received (0.006 cases/TY).

The majority of the received non-serious adverse reactions for both Alutard SQ *Phleum pratense* specifically and for all Alutard and ALK7 grass products in general, were skin and injection site reactions or reactions related to the respiratory system.

For Alutard SQ *Phleum pratense*, 437 individual case safety reports were assessed overall as serious. For Alutard SQ Grass mix and other single grass species products, 879 individual case safety reports were assessed overall as serious.

Serious systemic allergic reactions (PT Anaphylactic reaction, PT Anaphylactic shock, PT Hypersensitivity, PT Type 1 Hypersensitivity) constitute the majority of the most commonly reported serious adverse reactions for Alutard SQ *Phleum pratense* (279 cases out of 437) as well as for other Alutard SQ and ALK7 grass products (487 cases out of 879).

No patients treated with Alutard SQ *Phleum pratense* or Alutard SQ and ALK7 grass mixes experienced a fatal outcome for any reported serious adverse event.
All the post-marketing most commonly reported non-serious and serious PTs and are reflected in the ADR table in SmPC section 4.8 except malaise. Malaise is covered by other listed terms (fatigue, discomfort).

Table 9 Tabulated list of adverse reactions (from SmPC section 4.8)

The adverse reactions are divided into groups according to the MedDRA convention 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), not known (cannot be estimated from the available data). Adverse drug reactions and frequencies in the table below are based on one clinical trial with Alutard SQ 6-grass mix and rye. Additional adverse reactions reported spontaneously from the market for Alutard SQ grass products are included in the table below.

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Immune system disorders	Common	Anaphylactic reaction
	Uncommon	Anaphylactic shock
Nervous system disorders	Not known	Dizziness, paraesthesia
Eye disorders	Common	Conjunctivitis, eye pruritus, eye swelling
	Uncommon	Eyelid oedema
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Ear pruritus
Cardiac disorders	Not known	Palpitations, tachycardia, cyanosis
Vascular disorders	Not known	Hypotension, pallor, flushing
Respiratory, thoracic and mediastinal disorders	Common	Cough, dyspnoea, nasal congestion, allergic rhinitis, sneezing, throat irritation, rhinorrhoea, nasal pruritus
	Not known	Bronchospasm, throat tightness, wheezing, asthma
Gastrointestinal disorders	Common	Diarrhoea, vomiting, nausea, abdominal pain
	Uncommon	Dyspepsia
Skin and subcutaneous tissue disorders	Common	Urticaria, pruritus, rash, erythema
	Uncommon	Swelling face, eczema
	Not known	Angioedema

Musculoskeletal and connective tissue disorders	Not known	Joint swelling, arthralgia
General disorders and administration site conditions	Very common	Injection site reaction*
	Common	Fatigue, chills, feeling hot, discomfort
	Not known	Chest discomfort, injection site hypertrichosis, sensation of a foreign body

* Injection site reactions may present events such as injection site pruritus/swelling/urticaria/ erythema/nodules/pain/bruising/haematoma/induration/inflammation/oedema/rash/warmth/ discolouration/papule, localised oedema, administration site pain, pain in extremity.

IV.2.13 Assessor's overall conclusions on clinical safety

To support safety for use of Alutard SQ *Phlenum pratense,* in the intended indication, the MAH has submitted 15 studies and/or publications. Eight of these trials have investigated Alutard SQ *Phleum pratense* alone in at least one treatment arm. Four of the trials conducted with Alutard SQ *Phlenum pratense* were placebo controlled (UK22, UK 21, UK 18 and the study by Varney /Walker/Durham/Wachholz) and two were conducted in children and adolescents (UK21 and UK23P).

All studies were conducted in subjects with seasonal allergic rhinoconjunctivitis (with or without asthma). Overall, most of the studies had a duration between 1 year up to 3 years. However, the trial by Østerballe/Djurup/Mosbech had a follow-up period of 6 years. In addition to data from clinical trials safety for the product is supported by clinical post-marketing experience from over 30 years.

Approximately, 900 subjects were exposed to Alutard SQ *Phleum pratense* in the 7 trials investigating only Alutard SQ *Phleum pratense.* In addition, approximately 2, 776 subjects have been exposed to Alutard *Grassmix* in the 8 supportive clinical studies and 139,004 treatment years post-marketing. Overall, the exposure of Alutard SQ *Phleum pratense* specifically and cross-reacting allergens is considered sufficient.

Local and systemic allergic adverse reactions are expected adverse events during treatment with immunotherapy. Most of these reactions occurs during the up-dosing phase. This pattern was also demonstrated for Alutard SQ *Phleum pratense* in the submitted studies. In two of the largest trials investigating Alutard SQ *Phleum pratense,* 58% (UK22) respectively 28% (UK23A) of the adult subjects treated with the 100 000 SQ-E/ml dosing and 80% in the pediatric population (UK23P) experienced local allergic reactions. The corresponding frequencies for systemic reactions were 74% (UK22) and 28% (UK23A) of the adults and 79% of the pediatric subjects (UK23P).

The frequencies of reactions were dose-dependent (study UK22) and most of these reactions occurred during the up-dosing phase. Treatment-related SAEs were rare (1.2% [n=31] of total subjects). All related SAEs were systemic allergic reactions.

Approximately 50% (i.e. 11/21) of the related SAEs in the clinical trials performed with Alutard SQ *Phleum pratense* only, were reported as anaphylactic reactions or anaphylactic shocks.

According to data presented no related SAE were reported in the pediatric population in study UK21 or UK23P. No fatal events have been reported in clinical trials that were considered related to the use of Alutard SQ *Phleum pratense.* Approximately 5-10% of the adult subjects in the larger studies i.e. UK22, UK22-FU and UK23, were withdrawn due to AEs.

Careful recommendations regarding dose reductions in case of local and/or systemic reactions and general handling in case of allergic reactions are reflected in SmPC (section 4.2, 4.3, 4.4 and 4.8). Overall, risk for allergic reactions with Alutard SQ *Phleum pratense* treatment is considered acceptable and manageable with the current SmPC text.

Studies performed with Alutard SQ *Phlenum pratense* and/or Grass pollen demonstrates that the safety profile in the paediatric population above 5 years is similar to the pattern in adults. However, in one study (UK23) higher frequencies of allergic adverse events were noted in the paediatric population aged 5-16 years compared to the adults. This difference is considered accepted with the current recommendation in the SmPC section 4.2. This wording is in line with the agreement within the paediatric work-sharing procedure (DK/W/005/pdWS/001) on grass pollen. Use of Alutard SQ *Phlenum pratense* and/or Grass pollen in children below 5 years is limited. Caution should be taken in case of use in this age group. This is reflected in SmPC section 4.2 (also in line with the agreed wording of 4.2 in the paediatric work-sharing procedure DK/W/005/pdWS/00 on grass pollen) and SmPC section 4.4. Overall, use of the product in the paediatric population is considered sufficiently reflected in SmPC section 4.2, 4.4 and 4.8.

Post-marketing, a total of 1,021 individual case safety reports (584 non-serious and 437 serious) for Alutard SQ *Phleum pratense* have been received by ALK (corresponding to a frequency of 0.007 cases received per TY). The PTs reported are all reflected in the SmPC section 4.8.

Overall, safety and specifically the risk for allergic reactions with Alutard SQ *Phlenum pratense* treatment is considered acceptable and manageable with current SmPC text.

IV.2.14 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Alutard SQ Grass.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP for Alutard SQ *Grass* was approved in 2020 within the national procedure 5.4.3-2019-38077. As timothy is part of the same homologous group as other grasses, extrapolation grass mixes is acceptable (EMEA/CHMP/BWP/304831/2007) and the Alutard SQ *Grass* the RMP for Alutard SQ Grass is applicible also for Alutard SQ *Phleum Pratense*.

The submitted Risk Management Plan, version 2.0 signed 31-Jan-2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The user test was accepted with the national variation 5.4.3-2020-43038, by a bridging to the user test carried out on the product Alutard SQ Honey Bee Venom (approved in procedure 5.4.3-2016-48005). Please find below the assessment of the user test.

"Assessment of the Bridging proposed by the applicant:

Content
The user test for the PIL of **Alutard SQ Honeybee Venom**, leaflet was assessed and accepted in the national variation 5.4.3-2016-48005.
The approved PIL of **Alutard SQ Honeybee Venom** has been compared by the applicant with the PIL of **Alutard SQ Phleum pratense** and the bridging report shows that the key safety messages are sufficiently similar.

Layout
The design and layout of PIL for **Alutard SQ Phleum pratense** will be the same as that for **Alutard SQ Honey BeeVenom** (national variation 5.4.3-2016-48005). The differences in the PL designs are minimal and do not affect the bridging strategy.

The content, wording and format of the two PLs are essentially similar. The proposed bridging regarding content and layout is considered acceptable."

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alutard SQ *Phlenum Pretense* is an allergy immunotherapy product indicated for patients with clinically relevant symptoms of IgE-mediated allergic disease caused by pollen from Phleum pratense (Timothy) and diagnosed with a positive skin prick test and/or specific IgE test to pollen from Phleum pratense.

The product was national approved in Sweden in 1990. Approved variations since then, that affected clinical aspects and the SmPC of the product are the variations 2122:2004/20259 (Change in dose recommendations); 2010/53592 (Paediatric information); 5.4.3-2019-38077 (7 step-up-dosing); 5.4.3-2019-38057 (update section 4.3, 4.4 and 4.6); 5.4.3-2019-38057 (update section 4.3, 4.4 and 4.6); 5.4.3-2020-42707 (update section 4.3, 4.4 and 4.6) and recently procedure 5.4.3-2020-43038 (Update of the dossier in preparation of an MRP application).

Pharmacodynamics

To support pharmacodynamic and the immunological responses to AIT the MAH has submitted 11 trials. Even though, two of the 11 studies did not demonstrate an expected pattern for the IgE as a response to AIT (i.e study UK21 trial and Francis trial) six other trials did so (Østerballe/Djurup/Mosbech, UK22, Schmid and Aasbjerg trial respectively). In addition, all eight studies that measured IgG4 response demonstrated a positive increase in line with the expected pattern

following AIT. Overall, it is considered that the studies presented by the MAH supports that Alutard SQ *Phlenum pratense* results in an expected autoimmune immunological response.

Clincial efficacy

In total, 12 studies have been submitted to support clincal efficacy. Six of the trials investigate only *Phleum pratense*, 2 studies investigate *Phleum pratense* and *Betula verrucosa* (birch), and the remaining supportive trials investigate Alutard SQ or ALK7 grass mixes.

Rhinoconjunctivitis symptom score was used as an efficacy endpoint in 10 of the 12 trials. In 9 of those trials, Alutard SQ or ALK7 resulted in significant reduction in symptom score compared to comparator or baseline. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was used in three trials and showed statistically significant improvement in the Alutard group compared to placebo. Rhinoconjunctivitis medicine was an endpoint in 10 of the trials. The majority of studies showed statistically significant decrease in medicine use when treated with Alutard compared to placebo.

The presented studies support efficacy on variables affected by IgE-mediated allergy to pollen of timothy.

Clinical Safety

The major risk with Alutard SQ Phlenum Pratense, as with immunotherapy in general, ADRs related to local and systemic allergic reactions (including anaphylactic shock/reactions). This is clearly demonstrated both from safety results in the clinical studies and from data originating from the MAHs safety database. The risks are sufficiently covered in the SmPC. Available safety data from Paediatric Article 45 procedure in 2010 and articles published after this procedure does not indicate additional risks related to the use of Alutard SQ in the paediatric population (above 5 years). This is reflected in SmPC section 4.4 and 4.8.

Use in children below 5 years

Limited data from clinical trials on the adverse events in children below 5 years is available. No conclusions can be drawn for this age group. Also, in the Paediatric Article 45 procedure in 2010 it was concluded that a risk-benefit analysis must be carefully considered when treating children below 5 years of age. This is reflected in the SmPC section 4.4.

Overall, the presented pre-clinical, quality and clinical data is considered sufficient to support a MRP article 5.3 known active substance application for Alutard SQ *Phlenum Pratense.*

The benefit-risk balance for Alutard SQ *Phlenum Pratense* is positive.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Alutard SQ Timotej, 10 000 SQ-E/ml, 100 000 SQ-E/ml, Up-dosing pack, Suspension for injection was positively finalised on 2021-10-26.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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