EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 June 2025
EMADOC-1700519818-2235109
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Palforzia

International non-proprietary name: Defatted powder of Arachis hypogaea L., semen (peanuts)

Procedure No. EMA/VR/0000256580

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Submission deadline	21 March 2025	27 February 2025	☐
☐	Validation	7 April 2025	11 March 2025	☐
☐	Start date	8 April 2025	8 April 2025	☐
☐	CHMP Rapporteur AR	12 May 2025	12 May 2025	☐
☐	PRAC Rapporteur AR	19 May 2025	16 May 2025	☐
☐	PRAC comments	23 May 2025	n/a	☐
☐	CHMP comments	26 May 2025	n/a	☐
☐	Updated PRAC Rapporteur AR	27 May 2025	n/a	☐
☐	Updated CHMP Rapporteur AR	28 May 2025	27 May 2025	☐
☐	PRAC outcome	3 June 2025	3 June 2025	☐
☐	Start of CHMP written procedure	3 June 2025	3 June 2025	☐
☒	CHMP Outcome	5 June 2025	5 June 2025	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Stallergenes submitted to the European Medicines Agency on 27 February 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.3.b	C.I.3.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	Variation type II

Update of section 4.8 of the SmPC in order update the description of Eosinophilic esophagitis cases occurring in Palforzia clinical trials following CHMP request in EMEA/H/C/004917/P46/011 concerning report from study ARC008. The RMP version 1.3 has also been submitted. In addition, the MAH took the opportunity to bring minor updates to the SmPC following the PEI linguistic review.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The MAH updated Module 2.5 Clinical Overview as well as Module 2.7.4 Clinical Safety by implementing additional data available following the completion of the long-term follow-on safety study ARC008 for eligible subjects, who participated in previous AR101 clinical studies. Likewise, missing data on study ARC005 had also been inserted – if not already done so. In addition, updates to the SmPC have been incorporated. Updates were requested by CHMP following assessment of the P46 procedure for the assessment of the CSR of ARC008 study (Procedure EMEA/H/C/004917/P46/011), were the CHMP requested an update of safety data, particularly regarding adverse events of clinical interest (e.g., cases of treatment-related Eosinophilic esophagitis (EoE)) occurring in Palforzia clinical trials (19 September 2024 - EMA/465576/2024).

Palforzia, an oral desensitization immunotherapy, was authorised on 17 December 2020 through the centralised procedure. It was first approved in children aged 4 to 17 years with a confirmed diagnosis of peanut allergy. On December 19th, 2024 indication was extended to children aged 1 to 3 years based on final results from study ARC005 conducted in toddlers. On 15th of April 2024, the MAH submitted in accordance with Article 46 of Regulation (EC) No1901/2006 the completed multicenter, open-label, Study ARC008 in subjects who participated in prior Palforzia studies. Study ARC008 (EudraCT: 2017-001334-26) is not included in the PIP EMEA-001734-PIP01-14. This study aims to determine the safety and tolerability during longer-term administration of Palforzia and follow-up observation after the last dose of Palforzia. Study ARC008 was planned as the longest clinical trial for Palforzia and included a large number of patients (planned study duration as per CSR approx. 10 years with approx. 950 subjects. Final enrolment of 911 participants, final duration from November 2017 (First subject dosed), last subject visit 27 April 2023. Final database lock 12 Oct 2023).

In Mar 2024 and Jan 2025 the summary of clinical safety (SCS) has been updated to incorporate the final data from studies ARC004, ARC011, ARC005 and ARC008. Following this completion, the focus is laid on the assessment of safety data concerning *adverse events of clinical interest* such as systemic allergic reaction (including anaphylaxis) and EoE (see EMEA/H/C/004917/P46/011). Anaphylaxis and EoE are important identified risks of AR101 treatment as described in the risk management plan.

Overall, 8/98 [1-3 y.o.] subjects (8.2%) and 149/944 [4-17 y.o.] subjects (15.8%) had 1 or more systemic allergic reactions. Only patients from the [4-17 y.o.] group had at least 3 events (16/944, 1.7%) and 1.1% (10/944) anaphylaxis (the severe subset of all systemic allergic reactions). 188/220 (85.5%) anaphylactic reactions had been described to be triggered by the study product, in opposite to other food allergens (28/220) 12.7% or nonfood allergen (11/220). In toddlers, three events in 2 subjects (2.0%) in the AR101 group were considered related to study treatment and 6 events by other food allergen. In addition, a non-serious event of severe anaphylaxis was observed in a 2-year old male patient during up-dosing (dose of 3 mg) in study ARC008.

Considering the overall population according to the current indication, 16 AR101-treated subjects overall experienced anaphylaxis (the severe subset of all systemic allergic reactions) in 4 studies, including 5 subjects in the controlled studies ARC003 and ARC007, and 5 in the open-label follow-on studies ARC004 and 6 subjects in open-label follow-on study ARC008. Five subjects aged 4-17 years experienced anaphylaxis during up-dosing at 6, 40, 80, and 120 mg and 10 during maintenance treatment. Ten of these 16 subjects who experienced anaphylaxis had potential cofactors. Common cofactors were exercise and nonspecific viral infections.

The newly added data from study ARC008 make clear that the risk for developing anaphylaxis (the severe systemic allergic reaction) remains even after years of being on treatment. Among 908 patients with a mean exposure to AR101 of 3.19 years and a maximum exposure of 10.2 years, severe treatment-emergent systemic allergic reaction (anaphylactic reaction) occurred in 6 subjects overall (0.7%), 5 of whom were between 4 and 17 years old. Two of these subjects, experienced anaphylaxis after being on treatment for over 3 or even 5 years, respectively (on day 1127 and day 1760 day, see Table 2.5-29).

Focusing on EoE, updated data revealed that EoE was diagnosed in 21 (before 12) subjects in the overall clinical development program of AR101 in children aged 4 to 17 years (plus one case in a 33 years old subject, leading to 22 cases at all). In 17/21 cases EoE was related to the study product. In 19/21 cases biopsies were performed, leading to 15/21 cases of biopsy-confirmed plus treatment related EoE in children aged 4 to 17 years (Table 2.5-40). The diagnosis of two of the related cases was not confirmed by biopsy. Of all biopsy-confirmed (20/22) and related (18/22) cases, improvement was reported in 73.3% of subjects (11/15) under 18 years of age after AR101 treatment discontinuation.

The updated data underlines that the manifestation of EoE is observed during any AR101 treatment period and that the risk for EoE seems to remain over time. As such, in 8/22 observed cases, EoE was diagnosed during up-dosing, and in 14/22 cases during maintenance. Occurrence was observed even after 4-5 years/ after up to 1515 or even 1856 total days of AR101 treatment. The youngest subject, which developed EoE was 4 years of age.

Interestingly, anaphylaxis and the development of EoE are to a certain extent opposed to each other: EoE is assumed to be triggered by peanut protein (AR101) and improves in most cases after AR101 treatment discontinuation, whereas in opposite the frequent consumption of peanut protein (AR101) is assumed to maintain (and probably increase or consolidate) a certain tolerance level of protein intake in peanut allergic subjects.

These updated data underline the importance of monitoring and the assessment of reported events associated with the use of Palforzia - although no new safety information that would change the benefit-risk assessment has been observed. The remaining risk of anaphylaxis (the severe subset of all systemic allergic reactions) – although on treatment for years - raises questions. Generally, a longer treatment is thought to be associated with at least maintaining (and probably increasing or consolidating) a certain tolerance level of protein. Still, based on this data treatment compliance or

coherence or possibly additional co-factors are not tangible. Although the frequency is low, education and training of patients remains important. In addition, information on GI events, including EoE need to be reflected constantly. Currently, still many uncertainties regarding the occurrence of non-IgE mediated gastrointestinal diseases exist. In terms of EoE, if OIT may serve as trigger for induction, or for pre-existing subclinical EoE to become symptomatic, remains open.

The proposed amendments to the Summary of Product Characteristics (including update of section 4.8) and to the Risk Management Plan (RMP) are agreed and in line with updates listed above.

The benefit-risk balance of Palforzia remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.3.b	C.I.3.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	Variation type II

Update of section 4.8 of the SmPC in order update the description of Eosinophilic esophagitis cases occurring in Palforzia clinical trials following CHMP request in EMEA/H/C/004917/P46/011 concerning report from study ARC008. The RMP version 1.3 has also been submitted. In addition, the MAH took the opportunity to bring minor updates to the SmPC following the PEI linguistic review.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexe I and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

In clinical studies, 15 out of 1 319 subjects, aged 1 to 17 years, were diagnosed with biopsy-confirmed eosinophilic oesophagitis while receiving PALFORZIA compared with 0 of 409 subjects receiving placebo. After discontinuation of PALFORZIA, symptomatic improvement was reported in 11 of 15 subjects. In 7 subjects with available follow-up biopsy results, eosinophilic oesophagitis was resolved in 4 subjects and improved in 3 subjects. All events were diagnosed in subjects aged 4 – 17 years.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Palforzia was authorised on 17 December 2020 through the centralised procedure (CP). It was first approved in children aged 4 to 17 years with a confirmed diagnosis of peanut allergy. On December 19th, 2024 indication was extended to children aged 1 to 3 years. On 15th of April 2024, the MAH submitted a completed paediatric study for Palforzia (Study ARC008) in accordance with Article 46 of Regulation (EC) No1901/2006.
Study ARC008 (EudraCT: 2017-001334-26) is not included in the PIP EMEA-001734-PIP01-14. It is a multicenter, open-label, longer-term study of Palforzia characterized oral desensitization immunotherapy in subjects who participated in a prior Palforzia study. This long-term study aims to determine the safety and tolerability during longer-term administration of Palforzia and follow-up observation after the last dose of Palforzia. The study ARC008 was planned as the longest clinical trial for Palforzia and included a large number of patients (planned study duration as per CSR approx. 10 years with approx. 950 subjects. Final enrolment of 911 participants, final duration from November 2017 (First subject dosed), last subject visit 27 April 2023).
Following assessment of the P46 procedure for the assessment of the CSR of ARC008 study (Procedure EMEA/H/C/004917/P46/011), the CHMP requested a revision of all treatment-related Eosinophilic esophagitis (EoE) cases occurring in Palforzia clinical trials mentioned in the SmPC of Palforzia.
Now, this Type II C.I.3.b variation for PALFORZIA (defatted powder of Arachis hypogaea L., semen (peanuts)) has been submitted to update section 4.8 of the SmPC correspondingly.

The RMP version 1.3 has also been submitted.

In addition, the MAH took the opportunity to bring minor updates to the SmPC following the PEI linguistic review during variation EMEA/H/C/004917/11/0014/G.

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

The MAH updated Module 2.5 Clinical Overview as well as Module 2.7.4 Clinical Safety by implementing additional data available following the completion of the long-term follow-on safety study ARC008 for eligible subjects, who participated in previous AR101 clinical studies. Likewise, missing data on study ARC005 had also been inserted – if not already done so.

In Mar 2024 and Jan 2025 the summary of clinical safety (SCS) has been updated to incorporate the final data from studies ARC004, ARC011, ARC005 and ARC008, which are now complete and have been reported.

The 7 studies involved 1319 subjects aged 1 to 17 years who received at least 1 dose of AR101 study product. The studies currently include the following:

- Four completed, randomized, double blind, placebo controlled, phase 3 studies, ARC003 (Europe and North America), ARC005 (Europe and North America), ARC007 (North America only), and ARC010 (Europe only)
- Three uncontrolled, follow on studies, ARC004 (final database lock 15 Oct 2019), ARC008 (final database lock 12 Oct 2023), and ARC011 (final database lock 12 Nov 2019).

SAFETY POPULATIONS

The following strategy was taken to follow the safety profile in children aged 1 to 17 years:

- Controlled population (4–17 y.o.): 841 subjects treated with AR101 and 335 subjects treated with placebo from 3 controlled studies (ARC003, ARC007, ARC010).
- Integrated safety population (4–17 y.o.): 944 subjects aged 4–17 years treated with AR101 (in ARC003, ARC004, ARC007, ARC010, ARC011).
- Controlled population (1–3 y.o.): 98 subjects treated with AR101 and 48 subjects treated with placebo in the controlled study ARC005.
- Updated combined controlled population (hereafter, controlled population [1-17 y.o.]): 939 subjects treated with AR101 and 383 subjects treated with placebo from the 4 controlled studies (ARC003, ARC007, ARC010, ARC005).

The integrated safety populations are considered representative of the larger, real-world, peanut-sensitive patient population that is likely to be treated with and benefit from AR101. The integrated safety data in the population of children aged 4 to 17 years was the primary focus of the initial clinical overview.

In addition, data from the now-completed follow-on study ARC008 has been included. According to the indication, only patients 1-17 y.o. first exposed to AR101 and receiving a daily dose of the product are considered in the update.

Please note: Updates had been made in correspondence of the above mentioned safety populations, of study ARC008 (in a separate section), as well as of adverse events in children aged 1 to 17 years (covering all studies, including ARC005 and ARC008) throughout Module 2.5 and 2.7. Discussion below is focused on those modifications in which changes were made to the individual safety population for the aspects on chronic or recurrent GI adverse events, including eosinophilic esophagitis (EoE), and events of systemic allergic reaction, including anaphylaxis (described below).

Anaphylaxis and EoE are important identified risks of AR101 treatment as described in the risk management plan.

For reporting the study results, anaphylaxis is considered only the severe subset of all systemic allergic reactions regardless of trigger (study product, food allergen, other allergen). The term systemic allergic reaction is used for anaphylactic reaction events of any severity and the term anaphylaxis is used to distinguish anaphylactic reaction events that were severe. All systemic allergic reaction events are summarized regardless of severity or trigger.

EoE is a chronic immune-mediated inflammatory disease of the esophagus. The baseline risk for EoE in the target population for AR101 is elevated, given this patient population consists of patients with atopic disease, a known risk factor for development of EoE. Published literature suggests a 2.5% to 7.3% prevalence of biopsy-confirmed EoE emerging during OIT in patients with food allergy (Hill, 2017), with symptoms resolving promptly upon cessation of OIT. It remains unclear whether OIT induces EoE or causes pre-existing subclinical EoE to become symptomatic, or whether it is unrelated to disease onset in some cases.

BRIEF DESCRIPTIONS OF THE METHODOLOGY FOR DATA COLLECTION AND EVALUATION OF SAFETY DATA

Summaries of adverse events include only treatment-emergent adverse events, defined as onset after the first dose of study product (AR101 or placebo) and up to 30 days after the last dose of study product. Symptoms recorded as part of a food challenge were not included. All adverse events in subjects aged 4 to 17 years were classified by system organ class and preferred term using MedDRA version 19.1. In toddlers aged 1 to 3 years, adverse events were classified by system organ class and preferred term using MedDRA version 21.1.

6.2. Results

ADVERSE EVENTS OF CLINICAL INTEREST

Anaphylaxis is an important identified risk of AR101 treatment as described in the risk management plan.

Anaphylaxis in subjects aged 4 to 17 years

Sixteen AR101-treated subjects overall experienced anaphylaxis (severe systemic allergic reaction) in 4 studies, including 5 subjects in the controlled studies ARC003 and ARC007, and 5 in the open-label follow-on study ARC004 and 6 subjects in open-label follow-on study ARC008 (Table 2.5-29). Among them, only 1 subject was younger than 4 years old and experienced a non-serious anaphylaxis during up-dosing, at 3 mg (Note from the Rapporteur: it is noted that in Module 2.5 and 2.7 30mg was mentioned, however this is assumed to be a typo and 3 mg is correct). Five subjects aged 4-17 years experienced anaphylaxis during up-dosing at 6, 40, 80, and 120 mg and 10 during maintenance treatment. According to Table 2.5-29, there seem to be more anaphylactic reactions in study ARC007 during up-dosing. However, this may be associated with slightly different inclusion and exclusion criteria for study eligibility.

All subjects recovered, and none required prolonged hospital admission or required intensive support. Eleven subjects interrupted or down-dosed study treatment and 3 discontinued from their study. Ten of the 16 subjects who experienced anaphylaxis had potential cofactors. Common cofactors were exercise and nonspecific viral infections. In ARC008 study, among 908 patients with a mean exposure to AR101 of 3.19 years and a maximum exposure of 10.2 years, severe treatment-emergent systemic allergic reaction (anaphylactic reaction) occurred in 6 subjects overall (0.7%), 5 of whom were between 4 and 17 years old.

Five (5) additional cases of severe anaphylaxis in patients aged 4–17 years have been reported in ARC008 (Table 2.5-29), one case each originated from ARC003 and ARC007, and three cases were from the ARC010 study.

Table 2.5-1: Summary of Subjects With Anaphylaxis (Integrated Safety Population, 4 to 17 Years)

Study	Age	Sex	Serious	Period, Study Day	Dose	Epi Use
ARC003	15	F	Yes	300 mg/day, 284	300 mg	Yes
ARC004	4	F	No	300 mg/day, 389	300 mg	Yes
ARC004	5	F	No	300 mg/day, 458	240 mg	No
ARC004	13	F	No	300 mg/day, 389	300 mg	Yes
ARC004	14	F	No	300 mg/day, 444	300 mg	Yes
ARC004	5	F	No	300 mg/day, 471	300 mg	Yes
ARC007	10	M	No	Up-dosing, 70	40 mg	Yes
ARC007	17	M	No	Up-dosing, 64	6 mg	Yes
ARC007	14	F	No	Up-dosing, 104	120 mg	No
ARC007	14	F	No	Up-dosing, 72	80 mg	Yes
ARC008	8	M	No	300 mg/day, 1760	300 mg	No
ARC008	11	M	No	300 mg/day, 196	300 mg	Yes
ARC008	12	M	No	Up-dosing, 170	160 mg	No
ARC008	14	M	Yes	300 mg/day, 1127	300 mg	Yes
ARC008	7	F	No	300 mg/day, 523	300 mg	Yes

Source: ISS Listing 14.3.2.6 (updated February 2025)
Study day is from the first day of treatment.
Epi, epinephrine, F, female; M, male.

Safety in subjects aged 1 to 3 years

On ARC005 eight subjects experienced a total of 9 serious adverse events. The events were considered by the investigators to be unrelated to study treatment.

In ARC008, five (5) additional patients aged 1 to 3 years experienced a total of 7 serious adverse events in the follow-on study ARC008. None of them was considered related to treatment

In addition, a non-serious event of severe anaphylaxis was observed in a 2-year old male patient during up-dosing (dose of 3 mg) in study ARC008.

OVERALL

Data from the 1 322 subjects of the controlled population [1-17 y.o] (939 AR101-treated and 383 placebo treated) were collected during 4 controlled studies (ARC003, ARC007, ARC010, ARC005).

In addition, data from the follow-on study ARC008 is analysed.

Systemic allergic reaction, including anaphylaxis

Overall, 8 [1-3 y.o.] subjects (8.2%) and 149 [4-17 y.o.] subjects (15.8%) had 1 or more systemic allergic reactions of any severity. Only patients from the [4-17 y.o.] group developed at least 3 or more events (11 (1.2%) 3 events; 5 (0.5%) > than 3 events) and only patients (10, 1.1%) from the [4-17 y.o.] group developed severe anaphylactic reactions (anaphylaxis) (Table 2.5-38, not shown).

In the [1-3 y.o.] group, 1/3 of the events were triggered by the study product and 2/3 by other food allergens. In the [4-17 y.o.] group, most systemic allergic reactions (> 80%) were considered triggered by study product and 12.7% were triggered by other food allergens (Table 2.5-38, not shown).

Considering the overall population (including studies ARC003, ARC004, ARC007, ARC008) according to the current indication, **16** cases of anaphylaxis have been reported (Table 2.5-29).

CHRONIC OR RECURRENT GI ADVERSE EVENTS INCLUDING EOSINOPHILIC ESOPHAGITIS (EoE)

GI adverse events of clinical interest included chronic or recurrent GI adverse events that resulted in study discontinuation, including EoE. Patients with EoE or other eosinophilic GI disease, chronic, recurrent, or severe gastroesophageal reflux disease, or dysphagia or recurrent GI symptoms were excluded from AR101 clinical studies, and subjects who developed biopsy-documented EoE were discontinued from studies. Subjects with chronic or recurrent GI adverse events in AR101 clinical studies were to be evaluated monthly for 6 months, including completing the Pediatric Eosinophilic Esophagitis Symptom Scores version 2.0 (PEESS v2.0) questionnaire (Franciosi, 2011).

EOSINOPHILIC ESOPHAGITIS (EoE)

EoE is an important identified risk of any OIT, including AR101 treatment.

The phase 2 studies ARC001 and ARC002 were not included in the integrated safety population. Here **2 subjects** in the phase 2 studies ARC001 (1 subject, 002-008) and ARC002 (1 subject, 005-509) were described of suffering from EoE.

EoE was diagnosed in **5 of 944 subjects** (0.5% overall) in the controlled and integrated safety populations aged 4 to 17 years. EoE was considered treatment-related in 3 of the subjects. The severity of EoE was considered mild in 2 subjects, moderate in 2 subjects, and severe in 1 subject. All 5 subjects with EoE discontinued the study, including 1 who was discontinued due to no longer meeting eligibility criteria.

In the open-label, long-term follow-on study **ARC008,** in which subjects had been included who participated in previous AR101 clinical studies **13 cases of EoE** had been reported (including 9 biopsy-confirmed and product-related EoE). Clinical review of all the cases of EoE indicated that the onset of clinical symptoms was typically with dysphagia, vomiting, or both. The diagnosis of EoE was confirmed by biopsy in all but two cases in ARC008, which were diagnosed based on clinical features.

Across **all** AR101 clinical **studies, 22 subjects were diagnosed with EoE (**21 subjects 1-17 y.o. at enrolment). For **18 cases, the investigators considered the EoE to be related to the study product** (17 subjects 1-17 y.o.)**:** 2 subjects in the phase 2 studies ARC001 (1 subject) and ARC002 (1 subject), 1 subject in study ARC003 (008-006), 2 subjects in study ARC004 (including 1 adult), 2 subject in study ARC007, and **11 subjects in study ARC008** of whom 9 were confirmed by biopsy (Table 2.5-40).

Of **all** biopsy-confirmed (20/22) and related (18/22) cases, improvement was reported in 73.3% of subjects (11/15) **under 18** years of age after AR101 treatment discontinuation. No events were diagnosed in subjects aged 1-3 years.

Adapted summary based on Table 2.5-40: Summary of Subjects With Eosinophilic Esophagitis (All Studies) as of 07 Jun 2024

Table 2.5-40: Summary of Subjects With Eosinophilic Esophagitis (All Studies) as of 07 Jun 2024

	Study Subject Age at enrolment / Age at start of event / Sex	Study Period/Total Days AR101	Event Dose (mg)	Severity	Related (18 Yes; 4 No)	Biopsy Proven (20 Yes; 2 No)
1	**ARC001** 4 /4 / M	Up-dosing/20	12	Mild	Yes	Yes
2	**ARC002** 8 / 8/ M	Maintenance/1059	950	Moderate	Yes	Yes
3	**ARC003** 10 / 11/ M	Up-dosing/186	200	Mild	Yes	Yes
4	**ARC004** 13 / 13 /F	Up-dosing/49	12	Severe	No	Yes
5	Adult 33 / 34 / F	Maintenance/543	200	Severe	Yes	Yes
6	9 /10 / M	Maintenance/399	300	Moderate	Yes	Yes
7	**ARC007** 9 / 10 /M	Up-dosing/138	40	Moderate	Yes	Yes
8	17 / 17 /M	Up-dosing/141	80	Mild	No	Yes
9	6 / 7 /M	Up-dosing/28	4	Moderate	Yes	Yes
10	**ARC008** 16 /18 / F	Maintenance/1515	300	Moderate	Yes	Yes
11	14 /14/ M	Maintenance/798	160	Moderate	No	Yes
12	8 / 10/ M	Maintenance/579	160	Severe	Yes	No
13	13 / 14 / F	Maintenance/385	160	Moderate	Yes	No
14	17 / 18 / M	Maintenance/662	240	Moderate	Yes	Yes
15	11 / 13/ F	Maintenance /949	300	Moderate	Yes	Yes
16	13 / 14 / F	Up-dosing/231	160	Moderate	Yes	Yes
17	15 / 16 / M	Up-dosing/136	40	Moderate	Yes	Yes
18	6 / 8 / M	Maintenance/1189	300	Moderate	Yes	Yes
19	8 / 8 / M	Maintenance/1856	300	Mild	Yes	Yes
21	10 / 13 / M	Maintenance/1215	300	Mild	Yes	Yes
22	17 / 19 / M	Maintenance/1216	300	Severe	No	Yes
22	13 / 14 / M	Maintenance/252	200	Mild	Yes	Yes

Table 2.5-40: Modified from Source: Listing 14.3.2.2, Listing 14.3.2.3 (update February 2025)

OVERALL

Eosinophilic esophagitis

EoE was initially diagnosed in **5** of 944 [4-17 y.o.] subjects (0.5% overall). EoE was considered treatment-related in 3 of the subjects. The 5 subjects in the integrated population with a diagnosis of EoE are listed in Table 2.5-31. EoE was not diagnosed in any [1-3 y.o.] subject (Table 2.5-39).

As of the latest data cut off, including data from the completed follow-on study ARC008, EoE was observed in **21** [1-17 y.o.] subjects overall, and was considered treatment-related in 17 of the cases.

In 19 cases biopsies were performed, leading to 15 cases of biopsy-confirmed plus treatment related EoE (Table 2.5-40). The diagnosis of two of the related cases was not confirmed by biopsy.

In addition, one case of biopsy-confirmed EoE, related to study product, was observed in a 33-year old female patient during maintenance in study ARC004.

POST-MARKETING SAFETY REPORTS

Finally, the MAH included the latest available PSUR in 2.5.5.7.

As of the DLP of 30-Jan-2024, a total of 3591 patients cumulatively received at least one dose of PALFORZIA®, of which 1944 patients received at least one dose of PALFORZIA® during the reporting interval of the last 1-year periodic safety update report (PSUR) (interval from 31-Jan-2023 through 30-Jan-2024).

Table 2.5-2: Numbers of ADR from post-marketing data sources

Period	Number of serious ADR	Number of non-serious ADR	Total
Interval (31-Jan-2023 to 30-Jan-2024)	65	810	875
Cumulative (31-Jan-2020 to 30-Jan-2024)	147	3909	4056

Source: PSUR6 (31-Jan-2023 to 30-Jan-2024)

No new significant safety information that would be relevant for the benefit-risk assessment of PALFORZIA® was identified based on the review of the published literature during this reporting interval.

6.3. Discussion

The MAH updated previous summaries of safety data by implementing additional data available following the completion of the long-term follow-on safety study ARC008. Especially the previous missing update of safety data concerning *Adverse events of clinical interest* such as systemic allergic reaction (including anaphylaxis) or EoE, was criticised in Procedure EMEA/H/C/004917/P46/011. This especially, because anaphylaxis and EoE are important identified risks of AR101 treatment as described in the risk management plan.

SAFETY CONCLUSIONS

Safety data to support the proposed AR101 dosing regimen in children aged 4 to 17 years were provided by a total of 944 subjects who received at least 1 dose of AR101. No new safety concerns were identified.

As described before (but not re-mentioned above), the incidence of treatment-related adverse events was highest during up-dosing and decreased over a year of maintenance treatment at 300 mg/day. Most treatment-related adverse events were mild or moderate in severity. 149/944 subjects (15.8%) had 1 or more systemic allergic reactions. Sixteen patients from the [4-17 y.o.] group had at least 3 events
(16, 1.7%) and 10 subjects suffered from anaphylaxis (10, 1.1%) (Table 2.5-38). 188/220 anaphylactic reactions had been described to be triggered by the study product, in opposite to other food allergens (28) or nonfood allergen (11) (Table 2.5-38).

Most subjects with systemic allergic reaction (any severity) continued treatment with AR101.

The newly added data from study ARC008 make clear that the risk for developing an anaphylactic reaction remains even after receiving the study product for a long time. Among 908 patients with a mean exposure to AR101 of 3.19 years and a maximum exposure of 10.2 years, severe treatment-emergent systemic allergic reaction (anaphylactic reaction) occurred in 6 subjects overall (0.7%), 5 of whom were between 4 and 17 years old. Two of these subjects, experienced anaphylaxis after over 3 or even 5 years, respectively (on day 1127 and day 1760 day, see Table 2.5-29).

While discussing anaphylaxis in subjects aged 4 to 17 years, the MAH included the following sentence "Among them, only 1 subject was younger than 4 years old and experienced a non-serious anaphylaxis during up-dosing, at 30 mg". This sentence is irritating as the chapter is about children older 4 years of age. In addition, an up-dosing step of 30 mg is not part of the general up-dosing scheme. A typo is assumed (3mg instead of 30mg).

For toddlers aged 1 to 3 years, safety data was available for 98 subjects who received at least 1 dose of AR101, including 87 subjects who received the maintenance dose of 300 mg/day (study ARC005). For detailed summary of safety conclusion, please see Procedure No. EMEA/H/C/004917/II/0014/G. In short, the pattern of adverse events in this lower age group was consistent with that seen in the 4 to 17 years age group. However, the intensity of the adverse events appeared to be less severe in these younger subjects (51.0% of adverse events classified as mild in toddlers aged 1 to 3 years compared to 39.5% of adverse events classified as mild in children aged 4 to 17 years). No subject had an adverse event that was life-threatening or led to death. Overall, 8/98 [1-3 y.o.] subjects (8.2%) had 1 or more systemic allergic reactions. Fewer subjects discontinued due to adverse events in the 1 to 3 years group compared to the older children (6.1% compared to 11.4%). There were no study discontinuations due to systemic allergic reactions in toddlers aged 1 to 3 years compared to 15 subjects (1.6%) treated with AR101 in the 4 to 17 age group. All events in toddlers aged 1 to 3 years occurred during up-dosing and maintenance. Three events in 2 subjects (2.0%) in the AR101 group were considered related to study treatment and 6 events by other food allergens. In addition, a non-serious event of severe anaphylaxis was observed in a 2-year old male patient during up-dosing (dose of 3 mg) in study ARC008.

Focusing on EoE, updated data revealed that EoE was diagnosed in 21 (before 12) subjects in the overall clinical development program of AR101 in children aged 4 to 17 years (plus one case in a 33 years old subject, leading to 22 cases at all). In 17/21 cases EoE was related to the study product. In 19/21 cases biopsies were performed, leading to 15/21 cases of biopsy-confirmed plus treatment related EoE in children aged 4 to 17 years (Table 2.5-40). The diagnosis of two of the related cases was not confirmed by biopsy. EoE was not diagnosed in any toddler aged 1 to 3 years in either treatment group in study ARC005 and study ARC008.

After study product discontinuation, symptomatic improvement was reported in 13 of 18 subjects (all ages; with or without biopsy-proven diagnosis) with EoE related to study product.

The discrepancy between previously reported cases of EoE was explained by the MAH not in the updated module 2, but in the Application Form (0055) - Response to validation Query. Here the following scientific rational for the change is stated:

The figures previously presented in the SmPC on EoE cases and total number of patients exposed to Palforzia were extracted from the work of Dr Caroline Nilsson et al. published in 2021 in a peer-reviewed journal (Nilsson, Caroline, et al. "Onset of eosinophilic esophagitis during a clinical trial program of oral immunotherapy for peanut allergy." The Journal of Allergy and Clinical Immunology: In Practice 9.12 (2021): 4496-4501.). This paper reported the incidence of EoE among subjects aged 4-55 years, in Palforzia clinical trials (including 2 phase 2 trials, 5 completed phase 3 trial and 1 ongoing phase 3 trial), regardless of whether the cases were deemed related to the study product.

At the time of publication, ARC008 and ARC005 studies had not yet been completed, which explains the difference in the total number of patients exposed to Palforzia and the number of EoE cases….

The updated data underlines that the manifestation of EoE is observed during any AR101 treatment period. As such, in 8/22 observed cases, EoE was diagnosed during up-dosing, and in 14/22 cases during maintenance. Occurrence was observed even after 4-5 years/ after up to 1515 or even 1856 total days of AR101 treatment. The youngest subject, which developed EoE was 4 years of age.

The overall updates of the MAH are acknowledged. Discrepancies were sufficiently explained.

The remaining risk of anaphylaxis (the severe subset of all systemic allergic reactions) – although on treatment for years - raises questions. Generally, a longer treatment is thought to be associated with at least maintaining (and probably increasing or consolidating) a certain tolerance level of peanut protein. Still, based on this data treatment compliance or coherence or possibly additional co-factors is not tangible. Although the frequency is low, education and training of patients remains important. In addition, information on GI events, including EoE need to be reflected constantly. Currently, still many uncertainties regarding the occurrence of non-IgE mediated gastrointestinal diseases exist. In terms of EoE, if OIT may serve as trigger for induction, or for pre-existing subclinical EoE to become symptomatic, remains open.

7. PRAC advice

Not applicable.

8. Risk management plan

The MAH submitted an updated RMP version 1.3, date of final sign off 14 Feb 2025 with this application. The (main) proposed RMP changes were the following:

- The marketing authorisation holder and the QPPV have been changed.
    - The current MAH is Stallergenes
- Part I: Product overview
    - Update of the sections: *Indication in the EEA* and *Dosage in the EEA* as indication has been extended to children aged 1 to 3 years
- Part II: Module SI - Epidemiology of the indication and target population
    - Update of the MA dates
- Module SVII - Identified and potential risks
    - Update of the safety concerns characterisation with ARC008 data
- Part III: Pharmacovigilance Plan (including post-authorisation safety studies)
    - Update with ARC008 data

ARC008

ARC008 was an international, open-label, longer-term study for subjects from ARC002, ARC004, ARC005, ARC007, ARC010, and ARC011 to evaluate patients who have received as much as 5-years total treatment and a subsequent 1-year follow-up observation.

For details, please see the section 6.2 Clinical Safety aspects.

The updated parts of the RMP are presented below:

PART I: PRODUCT OVERVIEW

The marketing authorisation holder has been changed. The former MAH was Aimmune Therapeutics, the current MAH is Stallergenes.

The section *Indication in the EEA* has been updated as indication was recently extended to children aged 1 to 3 years. Palforzia is now indicated for the treatment of patients aged 1 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older.

The section *Dosage in the EEA* has been updated and it now shows dosages for patients 1 to 3 years old and 4 to 17 years old.

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the indication and target population

The date when the conversion of the Palforzia EU centralised procedure to Great Britain Marketing Authorisation was validated by the Medicines and Healthcare products Regulatory Agency (MHRA) has been amended. In addition, the launch date in France has been amended.

The dates when Palforzia indication was extended to children aged 1 to 3 years have been added (in the US July 26th, 2024, and in Europe December 19th, 2024).

Part II: Module SIII – Clinical trial exposure

The module Clinical trial exposure has been updated with information that the ARC008 study has been completed. In the previous version of the risk management plan, ARC008 was already completed but as the clinical study report was under preparation it was still considered an ongoing study at that time.

Part II: Module SV – Post-authorisation experience

As of 30 January 2024, Palforzia is marketed for use in the US, EU (Germany, Austria, and France), Switzerland and the UK. Sweden has been deleted from this list.

Part II: Module SVII – Identified and potential risks

The table SVII.3.1. Presentation of important identified risks and important potential risks has been updated concerning the important identified risks.

- Important Identified Risk 1: Anaphylaxis/systemic allergic reactions
  Information on systemic allergic reactions in the study ARC008 has been added to the sections *Evidence source and strength of evidence* and *Characterisation of the risk*.
- Important Identified Risk 2: Eosinophilic oesophagitis
  The sections *Evidence source and strength of evidence* and *Characterisation of the risk* were updated with the data from ARC008. The number of reports of eosinophilic oesophagitis in the section *Impact on the risk-benefit balance of the product* was updated.
- No updates have been done to the table presenting important potential risk or missing information.

Part II: Module SVIII – Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Anaphylaxis/systemic allergic reactions Eosinophilic oesophagitis
Important potential risks	Possible rebound after discontinuation of treatment
Missing information	Use during pregnancy Impact on long-term immune-mediated reactions

The safety concerns remain unchanged.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.2 Additional pharmacovigilance activities

The milestone dates of the study ARC008 were updated.

III.3 Summary table of additional pharmacovigilance activities

The summary table was updated regarding the study ARC008.

- The study ARC008 was marked as completed.
- The safety concerns addressed by ARC008 were updated: *Possible rebound after discontinuation of treatment* and *Impact on long-term immune-mediated reactions* were deleted from the table. The safety concerns Anaphylaxis/systemic allergic reactions and Eosinophilic oesophagitis remained unchanged.
- The due dates for ARC008 were updated.

Ongoing and planned additional pharmacovigilance activities

Study name Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Phase 3, open label longer-term follow on for AR101 studies (ARC008) Completed	To evaluate safety and tolerability, maintenance of desensitization, and effects on immunologic parameters after longer-term administration of PALFORZIA and follow-up observation after treatment discontinuation	Anaphylaxis/systemic allergic reactions Eosinophilic oesophagitis	Protocol amendment 6	Dated 22 December 2020
			Last patient last visit	18 April 2023
			Study end date	27 Apr 2023
			CSR	19 Mar 2024
Post- marketing pregnancy registry Ongoing in US and EU	To monitor pregnancy outcomes in pregnant women exposed to PALFORZIA ascertained by spontaneous reporting	Use during pregnancy	Protocol version 0.0	Dated 24 February 2020
			Protocol amendment 1.0	Dated 16 March 2021
			Annual registry reports	The data lock is based on the IBD and submission coincides with the PSUR cycle
			1st annual registry report	October 2021 with 2nd PSUR
			2nd annual registry report	October 2022 with 4th PSUR
			Final study report	June 2025

Study name Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Effectiveness evaluation of PALFORZIA educational materials Planned	The key study objectives are to evaluate: • Healthcare professional's understanding and retention of core educational material messages • Parent/caregiver's (1-3 year-old patients) understanding and retention of core educational messages • Parent/caregiver's (4-11 year-old patients) understanding and retention of core educational messages • Patient's (12-17 years old) understanding and retention of core educational messages • Monitor adherence to educational materials distribution plan	Anaphylaxis/ systemic allergic reactions Eosinophilic oesophagitis	Planned start of data collection	June 2022
			Final study report	June 2027

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The risk minimisation measures remain unchanged.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

The summary of the risk management remain unchanged.

ANNEXES

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

The study ARC008 has been moved from ongoing studies to completed studies.

ANNEX 4 – Specific adverse drug reaction follow-up forms

The name of the MAH have been changed in the specific adverse drug reaction follow-up forms.

8.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

9. Changes to the Product Information

As a result of this variation, section(s) 4.8. Undesirable effects, and 5.1 Pharmacodynamic properties of the SmPC are being updated to implement the final results of EoE cases from all 9 clinical trials. Present details focus only on biopsy-confirmed cases related to the study product, including those in patients whose biopsy-confirmed diagnosis occurred well after the end of the studies (SmPC 4.8. Undesirable effects).

The MAH further takes this opportunity to bring the following minor updates to the SmPC following the PEI linguistic review during variation EMEA/H/C/004917/11/0014/G (see Annex 2):

- Update of a number in the clinical efficacy section (5.1 Pharmacodynamic properties): the initial number was not correct potentially due to a human error in reformulating the text, which may have originally presented only the two arms rather than the overall population.
- Table 12 in the clinical efficacy section (5.1 Pharmacodynamic properties):
    - Addition of the notes 1 and 4 in the table: the notes 1 and 4 were missing (probably previously deleted by mistake)
    - Deletion of 'Not Applicable" in the legend below the table:
        - the information 'Not Applicable' made the Table 12 consistent with Table 13. Indeed, since none of the results in Table 12 were "Not Applicable," this additional abbreviation is superfluous and can be removed without affecting the document's readability or comprehension.

The Package Leaflet (PL) was not affected by the changes.

9.1.1. Quick Response (QR) code

NA

9.1.2. Additional monitoring

NA

10. Request for supplementary information

Not applicable