19 September 2024
EMA/465576/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Palforzia

Defatted powder of Arachis hypogaea L., semen (peanuts)

Procedure no: EMEA/H/C/004917/P46/011

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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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]**
☐	Start of procedure	29/04/2024	29/04/2024	☐
☐	CHMP Rapporteur Assessment Report	03/06/2024	04/06/2024	☐
☐	CHMP members comments	17/06/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20/06/2024	n/a	☐
☐	Request for supplementary information (RSI)	27/06/2024	27/06/2024	☐
☐	MAH's submission of responses	20/08/2024	20/08/2024	☐
☐	Re-start of procedure	21/08/2024	21/08/2024	☐
☐	CHMP Rapporteur Assessment Report	04/09/2024	04/09/2024	☐
☐	CHMP members comments	09/09/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	12/09/2024	12/09/2024	☐
☒	CHMP adoption of conclusions:	19/09/2024	19/09/2024	☐

[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

Administrative information

Procedure resources	
Rapporteur:	Name**:** Jan Mueller-Berghaus

Table of contents

1. Introduction

On 15th of April 2024, the MAH (Aimmune) submitted a completed paediatric study for Palforzia (Study ARC008) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

During the procedure the MAH (Aimmune) transferred the MA to a new MAH (Stallergenes).

2. Scientific discussion

2.1. Information on the development program

AR101 (brand name is Palforzia) is licensed as oral immunotherapy (OIT) for children aged 4 to 17 years with a confirmed diagnosis of peanut allergy to reduce the incidence and severity of allergic reactions, including anaphylaxis, after exposure to peanut. AR101 is also approved as maintenance of efficacy in patients with peanut allergy who turned age 18 years during therapy.

The development of AR101, known as Palforzia, for the paediatric population in treating peanut allergies adhered to the Paediatric Investigation Plan (PIP) EMEA 001734-PIP01- 14. As part of this agreed-upon PIP, six clinical studies were conducted, marking the successful completion of the PIP requirements. In June 2023, a favourable opinion from the Paediatric Committee (PDCO) was received regarding the full PIP compliance check.

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 completed on 27 April 2023 (last patient last visit: LPLV).

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).

2.2. Information on the pharmaceutical formulation used in the study

The MAH developed AR101 (brand name PALFORZIA) using a characterized OIT desensitization approach for patients with peanut allergy.

The AR101 drug substance (peanut [Arachis hypogaea] allergens) is sourced from raw shelled peanuts that are processed into food-grade, light roast, 12% defatted peanut flour. The drug substance contains approximately 50% peanut protein (w/w). The remaining components include primarily fats, carbohydrates, minerals, and moisture. The active ingredient of AR101 contains allergenic peanut proteins, a natural mixture of a variety of proteins termed Ara h 1 through Ara h 17. Of the allergenic proteins, Ara h 1, Ara h 2, and Ara h 6 are considered the most clinically important allergens (immunodominant).

AR101, characterized peanut (Arachis hypogaea) allergens, is used in a regimented OIT protocol that consists of daily administration of gradually increasing doses of peanut protein (AR101) until a target daily dose does not induce allergic symptoms. The AR101 dosing regimen is administered in 3 sequential periods: initial dose escalation, up dosing, and maintenance.

There is no specific paediatric formulation of Palforzia as the existing formulation is suitable for paediatric use.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study ARC008 (EudraCT: 2017-001334-26)

2.3.2. Clinical study

Study ARC008 (EudraCT: 2017-001334-26)

Description

Study ARC008 (EudraCT: 2017-001334-26) is a Phase 3, multicenter, open-label, longerterm investigation of Palforzia, an oral desensitization immunotherapy, focusing on participants from prior Palforzia studies. This specific study falls outside the scope of the PIP EMEA-001734-PIP01-14 and serves as a long-term assessment of Palforzia's safety and tolerability during extended administration, along with post-treatment follow-up.

The study was concluded on April 27, 2023 (Last Patient Last Visit: LPLV), and the database lock was finalized on October 12, 2023. The End of Trial Notification for study ARC008 was submitted in relevant participating countries.

Methods

As per CSR, in this phase 3, international, open-label, longer-term study of an AR101 regimen in children and adults with peanut allergy, included subjects entering ARC008 were prior participation in one of the MAH AR101 clinical studies. Because the dosing regimens and procedures in the parent studies were not uniform, subjects received AR101 in 1 of 5 treatment pathways in ARC008:

Treatment Pathway 1: for subjects who received and tolerated AR101 in a daily or non-daily regimen in the parent study (except study ARC005). These subjects underwent a Screening/Baseline visit, and eligible subjects entered the Extended Maintenance Period. Subjects who entered ARC008 on a dose > 300 mg daily switched to 300 mg daily on the first day of the Extended Maintenance Period. Subjects from parent study ARC004 on non-daily regimens who did not tolerate 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit DBPCFC switched to 300 mg daily on the first day of the Extended Maintenance Period. Subjects who received non-daily AR101 regimens in parent study ARC004 and who tolerated 600 mg peanut protein (1043 mg peanut protein cumulative dose) at the ARC004 Exit DBPCFC continued the non-daily AR101 regimen in the Extended Maintenance Period.

Treatment Pathway 2: for the following subjects:

- Subjects who did not complete their AR101 dosing regimen (e.g., up-dosing, maintenance) in an eligible parent study (except study ARC005).

- Subjects from parent study ARC004 who received a non-daily AR101 dosing regimen and who did not tolerate this regimen.

- Subjects from ARC004 who missed or withheld their non-daily AR101 dose for > 3 days, and subjects who received a non-daily AR101 dosing regimen and tolerated less than the 300 mg single dose of

peanut protein (443 mg cumulative) at the ARC004 Exit DBPCFC, if continued treatment with AR101 was determined to be safe per investigator judgment and after discussion with the medical monitor.

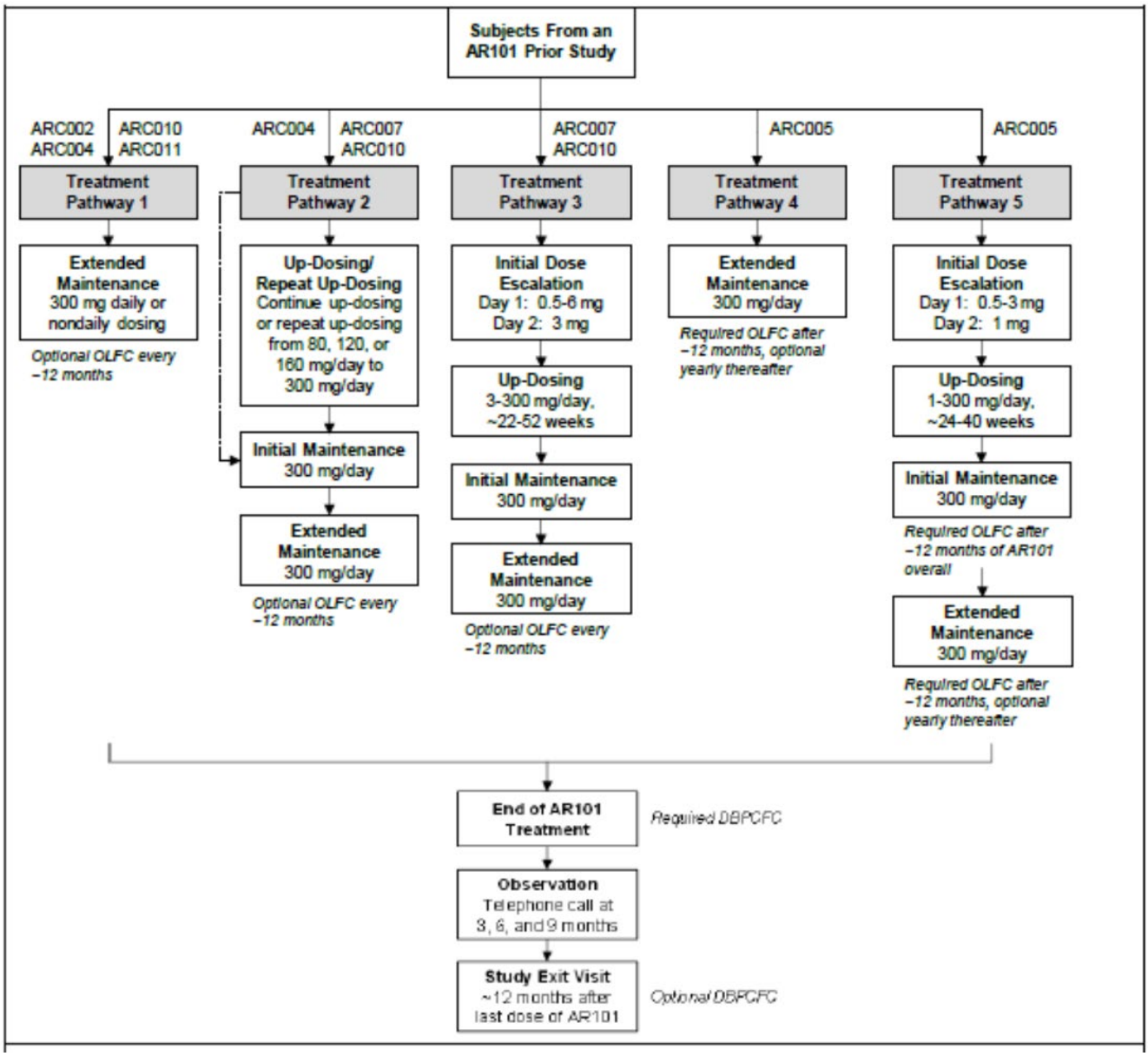
Subjects who did not complete their AR101 dosing regimen in an eligible parent study had a Screening/Baseline visit and continued the regimen in ARC008, proceeding through the applicable study periods until the End of Treatment visit. Subjects who entered ARC008 soon after completing the ARC004 Early Discontinuation visit had a Screening/Baseline visit, and eligible subjects started the Repeat Up-Dosing Period at a dose of 80, 120, or 160 mg daily (a decrease in AR101 dose of approximately 50% to 75%) at the discretion of the investigator. These subjects proceeded sequentially through the Initial Maintenance Period and Extended Maintenance Period. Subjects who completed the Repeat Up-Dosing Period or who tolerated AR101 300 mg daily for 2 weeks in ARC004 had a Screening/Baseline visit in ARC008 and then proceeded to the Initial Maintenance Period. Subjects who completed both the Repeat Up-Dosing and Initial Maintenance Periods or who received AR101 300 mg daily for at least 24 weeks in ARC004 had a Screening/Baseline visit in ARC008 and then proceeded to the Extended Maintenance Period. In addition, ARC004 subjects who tolerated the non-daily regimen in ARC004 but who subsequently did not tolerate the non-daily regimen after entering ARC008 Treatment Pathway 1 may have switched to Treatment Pathway 2 and started the Repeat Up-Dosing Period at the investigator's discretion.

Treatment Pathway 3: for subjects who received placebo in the parent study (except study ARC005). These subjects underwent a Screening/Baseline visit, and eligible subjects started the Initial Escalation Period with a dose of 0.5 mg. Subjects then proceeded sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period.

Treatment Pathway 4: for subjects who received AR101 and tolerated the 300 mg/day dose for at least 2 consecutive weeks before the exit DBPCFC in parent study ARC005. These subjects had a Screening/Baseline visit, and eligible subjects started the Extended Maintenance Period.

Treatment Pathway 5: for subjects who received placebo in parent study ARC005. These subjects had a Screening/Baseline visit, and eligible subjects started the Initial Escalation Period at a dose of 0.5 mg. Subjects then proceeded sequentially through the Up-Dosing Period, Initial Maintenance Period, and Extended Maintenance Period.

Figure 1: Treatment regimen in ARC008 as per CSR



Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; OLFC, open-label food challenge.

For subjects **in Treatment Pathway 1, 2, or 4,** initiation of AR101 in ARC008 occurred on the same day as or within 3 days after the Exit/Early Discontinuation visit in the parent study, unless specified otherwise in the parent study protocol. **For subjects in Treatment Pathway 3 or 5**, initiation of AR101 in ARC008 occurred on the same day as or within 10 days after the Screening/Baseline visit.

Treatment Pathway 2 only: Subjects who entered Treatment Pathway 2 in ARC008 soon after completing the ARC004 Early Discontinuation visit entered the Repeat Up-Dosing Period after the Screening/Baseline visit. Subjects who completed the Repeat Up-Dosing Period or who tolerated AR101 300 mg/day for 2 weeks in ARC004 proceeded to the Initial Maintenance Period after the ARC008 Screening/Baseline visit. Subjects who completed both the Repeat Up-Dosing and Initial Maintenance Periods or who received AR101 300 mg/day for at least 24 weeks in ARC004 proceeded to the Extended Maintenance Period after the ARC008 Screening/Baseline visit.

Subjects who developed safety or tolerability concerns while on daily treatment with AR101 in any Treatment Pathway had their dosing regimen adjusted per protocol. It was possible that a subject who

tolerated a non-daily regimen in the parent study entered ARC008 on Treatment Pathway 1 but subsequently developed safety or tolerability concerns during Extended Maintenance. Such subjects, per investigator judgment, switched from Treatment Pathway 1 to Treatment Pathway 2 to undergo Repeat Up-Dosing and continued maintenance dosing at 300 mg daily; alternatively, they could have been discontinued from the study. Other situations may have arisen where the investigator decided that it was in the best interest of the subject to switch to Treatment Pathway 2. All such cases were to be discussed with the medical monitor who must have agreed on the decision prior to switching. The most likely scenarios were as follows:

- Simple non-adherence: Subjects who missed more than 2 consecutive scheduled non-daily doses (eg, every other day dosing regimen, subject missed Monday and Wednesday doses) during any part of the study other than for treatment of an AE or a dispensing error.

- Medically necessary dose interruptions: Subjects who missed more than 4 consecutive scheduled non-daily doses due to medically indicated circumstances (eg, as part of the treatment for intercurrent AEs).

- Safety / tolerability concerns: Any subject on non-daily dosing who had 1 related serious adverse event (SAE), 1 related AE graded severe, 2 related AEs occurring on separate occasions, both graded moderate, or 3 consecutive doses judged "not tolerated," was be to transferred from Treatment Pathway 1 to Treatment Pathway 2 for safety reasons. Alternatively, they may have been discontinued from ARC008.

An internal team (safety risk management team) monitored safety for the study.

Additional information on End of treatment, Follow-up observation Period and Study Exit Visit, (as per protocol amendment 6.0):

End of Treatment Visit (All Treatment Pathways)

• Subjects in the US from prior studies ARC007 and ARC011 who have access to commercially available product will have the End of Treatment visit at their next scheduled study site (not remote) visit.

• Subjects in the US from prior studies ARC002 or ARC004 who have access to commercially available product may have the End of Treatment visit at their next scheduled study site (not remote) visit if so directed by the study sponsor when necessary for operational considerations.

• Subjects from prior study ARC005 will return to the study site for the End of Treatment visit when they complete at least approximately 3 years total of AR101 treatment including study ARC005 and AR101 is commercially available in their country, or discontinue early.

• All other subjects will return to the study site for the End of Treatment visit when they complete at least approximately 5 years total of AR101 treatment including all prior studies and AR101 is commercially available in their country, or discontinue early.

A DBPCFC will be performed at the End of Treatment visit; subjects who discontinue AR101 treatment early for safety reasons will not have the DBPCFC. All subjects will have telephone follow-up at least 14 days after the last dose of AR101 or last food challenge, whichever is last.

Follow-Up Observation Period (All Treatment Pathways)

The End of Treatment visit will be followed by a 12-month observation period. During observation, management of peanut allergy will be guided by the subject's physician.

Observation assessments will be conducted by telephone at 3, 6, and 9 months to enquire about the following:

- Current treatment plan (e.g., commercially available product, complete peanut avoidance, use of food equivalents for peanut oral immunotherapy, other investigational immunotherapy, other)
- Events of systemic allergic reactions, EoE, accidental/nonaccidental exposures to food allergens and their outcomes, use of epinephrine, hospitalizations (all causes), emergency department visits (all causes), and SAEs

Study Exit Visit (All Treatment Pathways)

The Study Exit visit will be conducted approximately 12 months after the last dose of AR101. An optional DBPCFC may be performed.

Duration of Treatment: The total duration of the study was expected to be approximately 10 years.

Study participants

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were prior participation in one of the following MAH AR101 clinical studies: ARC002, ARC004, ARC005, ARC007, ARC010, ARC011. Subject or guardian/parent who signed written informed consent form accordance with local institutional review board (IRB)/ethics committee (EC) guidelines, and written assent from as required by local IRB/EC guidelines. Sexually active females of childbearing potential had to use effective birth control.

Exclusion Criteria: Subjects were not eligible for inclusion in this study if they did not complete a minimum of 3 months of AR101 Maintenance in the parent study if subject was assigned to AR101 in that study (except for subjects in ARC004 who did not tolerate the non-daily AR101 dosing regimen, subjects in ARC007 or ARC010, or unless specified otherwise in the parent study). Subjects who were receiving or received within 5 years prior to Screening any type of peanut or other food allergen immunotherapy, except AR101 or unless allowed in the parent study, and except during the follow-up observation period in this study were not eligible for inclusion in this study. Subjects were to be excluded if they had to hypersensitivity to epinephrine, if they discontinued early from the parent study for any safety reason (with certain exceptions for subjects from study ARC004), or if they were in the build-up phase of immunotherapy for any non-food allergen, except during the follow-up observation period in this study.

Treatments

Test Product, Dose, and Mode of Administration

Study ARC008 has been performed using the currently approved paediatric formulation, pharmaceutical form and strengths of AR101as follows:

- PALFORZIA 0.5 mg oral powder in capsules for opening
- PALFORZIA 1 mg oral powder in capsules for opening
- PALFORZIA 10 mg oral powder in capsules for opening
- PALFORZIA 20 mg oral powder in capsules for opening
- PALFORZIA 100 mg oral powder in capsules for opening

• PALFORZIA 300 mg oral powder in sachet

AR101 is applied for an oral immunotherapy (OIT) desensitization approach. No formulations other than those already used in paediatric subjects were administered in the study; specifically, no extemporaneous formulations were applied. The contents of the AR101 capsules/sachets were mixed with a vehicle food, such as apple sauce, yogurt, pudding, or other palatable, age-appropriate food. The vehicle food must have been one to which the subject was not allergic.

The basic structure of the dose regimen consisted of a 2-day initial escalation at very low doses, followed by an up-dosing phase of dose escalations with a single dose level escalation occurring every 2 weeks, and then an initial maintenance phase followed by an extended maintenance phase. This dosing regimen was well tolerated and effective in previous studies (Burks, 2012), and the 300 mg target dose was well tolerated and had clinically important activity in the AR101 phase 3 studies.

In addition, the dosing regimen used in the Maintenance and Extended Maintenance Periods in this study was a 300 mg dose to be administered at the dosing interval that the subject last tolerated in a previous MAH-sponsored clinical study.

Objective(s), Outcomes/endpoints

The rationale for conducting ARC008 was as follows:

• To allow subjects who received placebo in MAH sponsored clinical studies with AR101 to receive AR101 drug product.

• To allow subjects who received AR101 in MAH sponsored clinical studies to continue treatment.

• To assess safety and tolerability during longer-term administration of AR101 and follow up observation after the last dose of AR101.

• To explore whether the level of desensitization to peanut protein was maintained or continued to increase after longer-term administration of AR101 and follow up observation after the last dose of AR101.

The primary objective of this study was to describe safety and tolerability during longerterm administration of AR101 and follow-up observation after the last dose of AR101.

A follow-up observation period after the last dose of AR101 was included to assess sustained clinical effect of AR101 treatment (ARC008-Report Body, section 9.2 Discussion of Study Design).

Outcomes/endpoints

There were no primary efficacy endpoints in this study.

Table 1: Study ARC008 – Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
• To describe safety and tolerability during longer-term administration of AR101 and follow-up observation after the last dose of AR101	• Frequency of adverse events (AEs). • Frequency of premature discontinuation of AR101 dosing due to AEs. • Frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs. • Frequency of AEs that lead to a change in treatment regimen. • Frequency of AEs that lead to early withdrawal. • Frequency of anaphylaxis. • Frequency of use of epinephrine as a rescue medication. • Frequency of accidental/non-accidental ingestion of peanut and other allergenic foods. • Frequency of AEs following accidental/non-accidental exposure to peanut and other allergenic foods. • Frequency of eosinophilic esophagitis (EoE).
Secondary	**Secondary**
• To assess the level of desensitization achievable through extended maintenance dosing of AR101	• Proportion of subjects tolerating each challenge dose in the open-label food challenge (OLFC) and the double-blind placebo-controlled food challenge (DBPCFC). • The maximum tolerated challenge dose at each food challenge. • Change in tolerated dose of peanut protein. • Maximum severity of symptoms in each food challenge. • Frequency of use of epinephrine as a rescue medication during the food challenges.
• To characterize the interaction of AR101 and asthma control or nasal allergy symptoms in subjects with a history of asthma and/or allergic rhinitis	• Change in peak expiratory flow (PEF). • Change in Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT) score. • Change in Total Nasal Symptom Score (TNSS).
• To evaluate subjects' QoL and treatment satisfaction during AR101 treatment on daily and non-daily treatment regimens	• Changes in food allergy quality of life (QoL) scores as measured by Food Allergy Quality of Life Questionnaires (FAQLQ), and the Food Allergy Independent Measure (FAIM) questionnaire.
• To evaluate parent/caregiver QoL during the child's treatment with AR101	• Change in Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire score.
Exploratory	**Exploratory**
• To evaluate effects on immunologic parameters after longer-term administration of AR101 and follow-up observation after the last dose of AR101	• Change in peanut-specific (ps) and peanut component-specific serum immunoglobulin G subclass 4 (IgG4). • Change in total, ps, and peanut component-specific serum immunoglobulin E (IgE). • Change in peanut skin prick test (SPT) mean wheal diameter.
• To evaluate changes in control of pre-existing asthma or atopic dermatitis in subjects from prior study ARC005	• Change in Test for Respiratory and Asthma Control in Kids (TRACK) and Eczema Area and Severity Index (EASI) scores.

As AR008 is an open-label, longer-term follow-on study of AR101 in subjects who participated in a previous AR101 clinical study, descriptive statistics were used to analyze the study data, and no formal hypothesis testing or sample size calculations were required. Therefore, the endpoints were not ordered in a statistical hierarchy.

In addition to food challenges, this study investigated potential surrogate immunologic tests to assess desensitization. Specifically, the utility of total, peanut-specific (ps), and peanut component-specific immunoglobulin E (IgE), and ps and peanut component-specific immunoglobulin G subclass 4 (IgG4) were to be explored as surrogate markers of peanut allergy or response to OIT.

Evaluation in terms of Desensitization

To measure the level of desensitization to peanut protein, **open-label food challenges (OLFC)** were to be conducted as follows:

• Treatment Pathways 1, 2, and 3: an optional OLFC was to be conducted at annual intervals beginning after 12 months in the Extended Maintenance Period.

• Treatment Pathway 4: an OLFC was required after the first 12 months in the Extended Maintenance Period and optional at annual intervals thereafter.

• Treatment Pathway 5: an OLFC was required at the End of Initial Maintenance and after the first 12 months in the Extended Maintenance Period, and optional at annual intervals thereafter.

It should be noted that "during the OLFC at the end of initial maintenance, single doses of peanut protein (3, 10, 30, 100, 300, 600, 1000, and 2000 mg) were conditionally tested using a food challenge mixture administered sequentially at 20- to 30-minute intervals. However, each OLFC during the Extended Maintenance Period was conducted over a single day and in keeping with accepted food challenge procedures, conditionally **tested 4 unblinded single doses** sequentially at 20- to 30-minute intervals: 300 mg, 600 mg, 1000 mg, and 2000 mg of peanut protein using a defatted peanut flour.

A **DBPCFC** was to be performed at the **End of Treatment visit** to assess desensitization after longer-term administration of AR101, and then an **optional DBPCFC** was to be performed after approximately 1 year of follow-up observation to assess continued desensitization. The highest single dose of the food challenges was 2000 mg peanut protein likewise.

Criteria for Evaluation in terms of Safety

All AEs were recorded from the time of signing of the informed consent form through at least 14 days after the last AR101 dose, 14 days after the last food challenge, or until resolution or stabilization of all AEs ongoing at the time dosing was stopped, whichever was later. The investigator was to treat subjects experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolved or their status stabilized.

Any new event or experience that was not present at Screening/Baseline or worsening of an event present at Screening/Baseline was reported as an AE. Any event that met the definition of an SAE was also to be reported to the study Safety Reporting Center. SAEs with a suspected causal relationship to AR101 which occurred within 30 days after the last AR101 dose, were to be reported to the sponsor. The following safety evaluations were also conducted: lung function (PEF), asthma (National Heart, Lung, and Blood Institute classification; ACT or C-ACT), and allergic rhinitis (TNSS).

CHMP comment

At submission, the MAH presented data on safety and tolerability during longer-term administration of AR101 and the level of desensitization achievable through extended maintenance dosing of AR101. This is acknowledged. However, no data or in parts only raw data is presented for the interaction of AR101 on asthma control or nasal allergy symptoms in correspondent subjects.

In terms of the request for supplementary information, data on QoL aspects were added, which describe that treatment resulted in improved subject-reported FAQLQ scores for subjects and parental

burden (for details see answers to question 8.3). Improvements in parent-reported FAQLQ scores were noted, though not clinically significant. Treatment with AR101 resulted in improved subject-reported and parent-reported Food Allergy Independent Measure (FAIM) scores.

Sample size

Number of Subjects (Planned and Actual):

Determination of Sample Size: The potential number of subjects who may have been enrolled in this study was approximately 950. The sample size was determined by the number of eligible subjects from each of the prior AR101 studies who participated in this study.

Randomisation and blinding (masking)

This was an open-label study. All subjects were treated with AR101, no blinding was performed. Subjects were assigned to 1 of 5 treatment pathways in this study depending on the parent study they entered from.

Statistical Methods

No formal statistical analysis were performed. This study was exploratory in nature; descriptive statistics were tabulated and reviewed to evaluate study endpoints. There were no planned applications of covariate adjustments or stratification.

Analysis Populations = Safety Population: all subjects who received AR101 during ARC008. The Safety Population was used for all analyses.

Data were analyzed by Precision for Medicine personnel. Statistical analyses are reported with tables, listings, and figures, presented in both rich text and pdf format, and using recommended ICH numbering. Output specifications for all tables, listings, and figures are in conformance with guidelines specified by the ICH in Appendix 7 of the Electronic Common Technical Document Specification (2008). All tables, data listings, summaries, and figures were generated using SAS for Windows, Release 9.4 or higher. The data cutoff date of final database lock of 12 October 2023 was used for analyses summarized in this report.

No interim data analyses were performed.

The following ad hoc analyses were conducted, and rationale for changes are included below:

Ad hoc Analyses Description	Rationale
Figures added to present the OLFC, DBPCFC, and immunoglobulin data	To present the OLFC, DBPCFC, and immunoglobulin results in graphical form.
Revision of the < 1 year column of total exposure and presenting data only for maintenance dosing during this period.	The original < 1 year column of total exposure data comprised 3 study parts: initial escalation, up-dosing, and early maintenance. The first 2 parts were already reflected in the initial escalation data and up-dosing data.
Inclusion of the baseline immunoglobulin data from the parent studies to use in change from baseline calculations.	Baseline immunoglobulin data collected during ARC008 were sparse and included both subjects who are continuing AR101 treatment from their parent study after different durations of AR101 treatment between studies, as well as subjects who received placebo in the parent study.
Addition of Treatment Pathways 1-3 and Treatment Pathways 4-5 data, where appropriate.	To provide additional detail on age subgroups.

Results

Participant flow

Subject Disposition:

Eligible subjects were prior participation in one of the parental AR101 clinical studies: ARC002, ARC004, ARC005, ARC007, ARC010, ARC011. A total of 911 subjects were screened and enrolled. Of those, 582 (63.9%) were assigned to Treatment Pathway 1, 27 (3.0%) to Treatment Pathway 2, 190 (20.9%) to Treatment Pathway 3, 72 (7.9%) to Treatment Pathway 4, and 40 (4.4%) to Treatment Pathway 5.

The Safety Population consisted of all subjects who received AR101 during ARC008. The Safety Population was used for all analyses. A total of 908 (99.7%) subjects received AR101 during ARC008 and were included in the Safety Population. The Safety Population comprised the following number of subjects by country: 590 in the US, 95 in United Kingdom, 67 in Canada, 48 in Germany, 36 in Ireland, 31 in Spain, 18 in France, 10 in Italy, 10 in Sweden, and 3 in Netherlands.

Subject Disposition (All Subjects)

	AR101
Number of subjects screened	911
Number of screen failures	0
Number of subjects enrolled	911
Safety population [1]	908 (99.7%)
Treatment Pathway	
1	582 (63.9%)
2	27 (3.0%)
3	190 (20.9%)
4	72 (7.9%)
5	40 (4.4%)
Initial ARC008 Dosing Regimen	
Daily	844 (92.6%)
Non-daily	64 (7.0%)
Unknown	3 (0.3%)
Entered initial escalation period [2]	229 (25.1%)
Entered up-dosing [3]	244 (26.8%)
Entered initial or extended maintenance period [4]	881 (96.7%)

Entered follow-up observation period [4]	134 (14.7%)
Did subject require follow-up due to chronic/recurrent GI symptoms?	
Yes	28 (3.1%)
No	883 (96.9%)
Completed all dosing as defined in the protocol	
Yes	194 (21.3%)
No	710 (77.9%)
Missing [5]	7 (0.8%)
Reason for early treatment discontinuation	
AE	26 (2.9%)
Allergen exposure	0
In clinic dosing symptom	1 (0.1%)
At home dosing event	8 (0.9%)
Chronic/recurrent GI AEs/symptoms	24 (2.6%)
Withdrew consent (unrelated to AE)	352 (38.6%)
Protocol violation	18 (2.0%)
Investigator decision (unrelated to AE)	13 (1.4%)
Sponsor decision	209 (22.9%)
Death	0
Lost to follow-up	18 (2.0%)
Pregnancy	0
COVID-19	3 (0.3%)
Other	38 (4.2%)
Completed study per protocol	
Yes	18 (2.0%)
No	478 (52.5%)
Missing [6]	415 (45.6%)
Reason for early study discontinuation	
AE	0
Allergen exposure	0
Chronic/recurrent GI AEs/symptoms	0
Withdrew consent (unrelated to AE)	86 (9.4%)
Protocol violation	2 (0.2%)
Investigator decision (unrelated to AE)	13 (1.4%)
Sponsor decision	349 (38.3%)
Death	0
Lost to follow-up	7 (0.8%)
Pregnancy	0
COVID-19	1 (0.1%)
Other	20 (2.2%)

Completed safety follow-up per protocol	
Yes	9 (1.0%)
No	514 (56.4%)
Missing [7]	388 (42.6%)
Reason for premature discontinuation from follow-up	
AE	0
Allergic AE	0
Dosing symptom	0
Chronic/recurrent GI AEs/symptoms	0
Withdrew consent (unrelated to AE)	3 (0.3%)
Protocol violation	1 (0.1%)
Investigator decision (unrelated to AE)	2 (0.2%)
Sponsor decision	0
Death	0
Lost to follow-up	5 (0.5%)
Pregnancy	0
COVID-19	0
Other	10 (1.1%)
Missing	493 (54.1%)

Source: Table 14.1.1
Denominators for percentages were based on total subjects screened for screen failure and based on number of enrolled subjects for all other percentages.
[1] Safety population included all subjects who received AR101 during ARC008.
[2] Treatment Pathways 3 and 5.
[3] Treatment Pathways 2, 3, and 5.
[4] All Treatment Pathways.
[5] Subjects in the 'Missing' category did not have 'End of Treatment' forms.
[6] Subjects in the 'Missing' category did not have Disposition - Study Exit forms.
[7] Subjects in the 'Missing' category did not have 'End of Follow-Up' forms.
Abbreviations: AE, adverse event; COVID-19, Coronavirus Disease 2019; GI, gastrointestinal.

CHMP comment:

Of 911 subjects, which were screened and enrolled, 582 (63.9%) were assigned to Treatment Pathway 1, 27 (3.0%) to Treatment Pathway 2, 190 (20.9%) to Treatment Pathway 3, 72 (7.9%) to Treatment Pathway 4, and 40 (4.4%) to Treatment Pathway 5. 908 (99.7%) subjects received AR101 during ARC008 and thus corresponded to the definition of the Safety Population.

As the study progresses, it becomes apparent that the number of participants is thinning out considerably.

The former known and described relatively high treatment effort in terms of treatment adherence and compliance in combination with possible interactions like uncomfortable "disgust" towards "peanut" might be regarded as major confounders which lead to treatment discontinuation, withdrew of consent or non-protocol compliance.

Based on the request for further details on subjects' disposition, the MAH explained that AR101 treatment discontinuations were mainly due to withdrawal of consent and sponsor's decision to terminate the study early. For study discontinuation, the main reason was sponsor's decision. It was further clarified that the high number of missing 'Disposition – Study Exit Form' was partly due to late introduction of this form with protocol amendment 6 (22 December 2020).

Additionally, the sponsor provided some further insight into reasons for withdrawal of consent. The reasons include (as already mentioned above) dislike of the study drug, transitioning to other forms of treatment and practical reasons.

For details of the additionally provided information, please refer to responses to questions 1 and 8.2.

Recruitment

Parental AR101 clinical studies: ARC002, ARC004, ARC005, ARC007, ARC010, ARC011.

Baseline data

Age was calculated relative to the date of informed consent in ARC008. The overall median age for the 908 subjects was 9.0 years. Median age in Treatment Pathways 1, 2, and 3 was 10.0 years each, and in Treatment Pathways 4 and 5 was 3.0 and 4.0 years, respectively.

At the time of informed consent, the majority of subjects in Treatment Pathways 1, 2, and 3 (95.5%, 96.3%, and 98.4%, respectively) were aged 4 to 17 years and the rest were aged ≥ 18 years. The majority of subjects (65.3%) in Treatment Pathway 4 were aged 1 to 3 years and the rest were aged 4 to 5 years. Subjects in Treatment Pathway 5 were aged either 1 to 3 years (47.5%) or 4 to 5 years (52.5%).

Most subjects were male (60.6%). Most subjects were white (78.4% subjects) and were not of Hispanic or Latino ethnicity (92.4%).

More subjects were enrolled in the US (65.0%) compared with Europe and Canada.

Table 2 Demographics (Safety Population)

	Treatment Pathway 1 (N = 580)	Treatment Pathway 2 (N = 27)	Treatment Pathway 3 (N = 189)	Treatment Pathway 4 (N = 72)	Treatment Pathway 5 (N = 40)	Overall (N = 908)
Age (years) [1]						
n	580	27	189	72	40	908
Mean (SD)	11.0 (4.42)	11.1 (6.13)	10.0 (3.61)	3.1 (0.91)	3.5 (0.90)	9.8 (4.75)
Median	10.0	10.0	10.0	3.0	4.0	9.0
Q1, Q3	8.0, 13.0	7.0, 12.0	7.0, 13.0	2.0, 4.0	3.0, 4.0	6.0, 13.0
Min, Max	4, 39	6, 36	4, 18	2, 5	2, 5	2, 39
Age Category						
1 – 3 years	0	0	0	47 (65.3%)	19 (47.5%)	66 (7.3%)
4 – 17 years	554 (95.5%)	26 (96.3%)	186 (98.4%)	25 (34.7%)	21 (52.5%)	812 (89.4%)
≥ 18 years	26 (4.5%)	1 (3.7%)	3 (1.6%)	0	0	30 (3.3%)
Sex						
Male	352 (60.7%)	15 (55.6%)	118 (62.4%)	43 (59.7%)	22 (55.0%)	550 (60.6%)
Female	228 (39.3%)	12 (44.4%)	71 (37.6%)	29 (40.3%)	18 (45.0%)	358 (39.4%)
Ethnicity						
Hispanic or Latino	27 (4.7%)	0	7 (3.7%)	2 (2.8%)	2 (5.0%)	38 (4.2%)

	Treatment Pathway 1 (N = 580)	Treatment Pathway 2 (N = 27)	Treatment Pathway 3 (N = 189)	Treatment Pathway 4 (N = 72)	Treatment Pathway 5 (N = 40)	Overall (N = 908)
Not Hispanic or Latino	546 (94.1%)	27 (100%)	177 (93.7%)	57 (79.2%)	32 (80.0%)	839 (92.4%)
Not collected	7 (1.2%)	0	5 (2.6%)	13 (18.1%)	6 (15.0%)	31 (3.4%)
Race [2]						
American Indian or Alaska Native	1 (0.2%)	0	0	0	0	1 (0.1%)
Asian	86 (14.8%)	0	35 (18.5%)	14 (19.4%)	8 (20.0%)	143 (15.7%)
Black or African American	16 (2.8%)	2 (7.4%)	7 (3.7%)	2 (2.8%)	2 (5.0%)	29 (3.2%)
Native Hawaiian or Other Pacific Islander	4 (0.7%)	0	2 (1.1%)	0	0	6 (0.7%)
White	474 (81.7%)	24 (88.9%)	142 (75.1%)	46 (63.9%)	26 (65.0%)	712 (78.4%)
Other	32 (5.5%)	2 (7.4%)	18 (9.5%)	11 (15.3%)	6 (15.0%)	69 (7.6%)
Not collected	0	0	0	1 (1.4%)	1 (2.5%)	2 (0.2%)
Country						
Canada	42 (7.2%)	2 (7.4%)	23 (12.2%)	0	0	67 (7.4%)
Germany	30 (5.2%)	0	7 (3.7%)	6 (8.3%)	5 (12.5%)	48 (5.3%)
Spain	24 (4.1%)	2 (7.4%)	5 (2.6%)	0	0	31 (3.4%)
France	7 (1.2%)	0	5 (2.6%)	4 (5.6%)	2 (5.0%)	18 (2.0%)
UK	46 (7.9%)	1 (3.7%)	13 (6.9%)	25 (34.7%)	10 (25.0%)	95 (10.5%)
Ireland	31 (5.3%)	1 (3.7%)	4 (2.1%)	0	0	36 (4.0%)
Italy	7 (1.2%)	0	3 (1.6%)	0	0	10 (1.1%)
Netherlands	3 (0.5%)	0	0	0	0	3 (0.3%)
Sweden	8 (1.4%)	0	2 (1.1%)	0	0	10 (1.1%)
US	382 (65.9%)	21 (77.8%)	127 (67.2%)	37 (51.4%)	23 (57.5%)	590 (65.0%)
History of Asthma [4]						
Yes	282 (48.6%)	11 (40.7%)	77 (40.7%)	13 (18.1%)	7 (17.5%)	390 (43.0%)
No	298 (51.4%)	16 (59.3%)	112 (59.3%)	59 (81.9%)	33 (82.5%)	518 (57.0%)

Source: Table 14.1.3
[1] Age was calculated relative to the date of informed consent.
[2] Subjects may be included in more than 1 category.
[3] BMI was calculated as [weight (kg)]/[height (cm)/100]^2.
[4] As indicated on the Allergy History CRF page.
Abbreviations: BMI, body mass index; CRF, case report form; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation; UK, United Kingdom; US, United States.

In terms of baseline immunoglobuline (Ig), for descriptive changes of respective biomarkers over time, the baseline data from the parent studies will be used as appropriate.

Medical History and Non-peanut Allergy History

Most subjects (60.4%) reported at least 1 non-allergy medical history condition. The most common (≥ 5% of subjects overall) SOC reported were infections and infestations (20.5%); skin and subcutaneous tissue disorders (18.2%); surgical and medical procedures (14.1%); respiratory, thoracic and mediastinal disorders (12.1%); gastrointestinal disorders (10.1%); psychiatric disorders (8.0%); nervous system disorders (7.4%); and injury, poisoning and procedural complications (6.4%).

A total of 613 (67.5%) subjects had a history of non-peanut food allergy and 830 (91.4%) subjects had other non-food allergy allergic disease history. The most common (occurring in ≥ 20% subjects overall) types of non-food allergy allergic histories were allergic rhinitis (628 [69.2%] subjects), atopic

dermatitis (599 [66.0%] subjects), asthma (406 [44.7%] subjects), category not specified (212 [23.3%] subjects), and other (190 [20.9%] subjects).

CHMP comment:

Baseline characteristics vary between subjects included in different pathways, which is caused by the design of this follow-up study. As such, Table 9 in the CSR depicts the baseline Ig data: pathway 2 and 5, for instance, include participants, which had been randomized to the placebo group of the parental study. Thus, it is obvious, that their "baseline" Ig data in ARC008 is different from those subjects, which received AR101 treatment for about 1 year beforehand. Similar in Table 2: "history of asthma" is less pronounced in children, aged 1-3, pathways 4 +5, due to their age. Therefore, only parts of correspondent data are depicted above.

Number analysed

Exposure:

A total of 107 (11.8%) subjects overall (including parent studies) had ≥ 5 years total AR101 exposure. A total of 164 (18.1%) subjects and 210 (23.1%) subjects overall (including parent studies) had 4 to< 5 years and 3 to < 4 years total AR101 exposure, respectively.

In ARC008 only, median exposure was 2.0 days during initial escalation, 159.0 days (range, 7 to 419 days) during up-dosing, and 750.0 days (range, 11 to 1744 days) during initial and extended maintenance.

In ARC008, the maximum dose of 300 mg/day was reached by 220 (90.2%) subjects during up-dosing and by 881 (100%) subjects during initial and extended maintenance.

Dose Modifications

The median total dose consumed was 139584.0 mg (ARC008 only) and the median average dose per day was 179.01 mg. The mean number of unsuccessful dose increases was 0. An unsuccessful dose increase was defined as a single dose given at the study site at a higher dose level followed by an immediate return to the previous dose level or a lower dose level. Overall, the maximum of unsuccessful dose increases was 3.

The mean number of dose reductions was 0.2 (ARC008 only). Overall, the maximum number of dose reductions was 6. A dose reduction was defined as any decrease in dose level that did not qualify as an unsuccessful dose increase.

Efficacy results

There were no primary efficacy endpoints in this study.

Secondary Efficacy Endpoints:

To assess the level of desensitization achievable through extended maintenance dosing of AR101:

Proportion of subjects tolerating each challenge dose in the open-label food challenge (OLFC) and the double-blind placebo-controlled food challenge (DBPCFC)

- Overall, in OLFC the treatment effect was sustained over time and clinical desensitization of tolerating at least 1000 mg of peanut protein was achieved by the majority of subjects at all exposure timepoints.
- Response rates in the DBPCFCs at End of Treatment by total AR101 exposure showed generally consistent and expected patterns for treatment duration, with the majority of subjects

tolerating at least 1000 mg of peanut protein after 1 or more years of treatment. Overall, a clinically relevant treatment effect (ie, clinical desensitization) was sustained over time up to > 5 years of exposure.

Table 3: Response Rates in OLFCs by Total Exposure (Safety Population)

	Total AR101 Exposure (N = 908)						
	< 1 Year	1 to < 2 Years	2 to < 3 Years	3 to < 4 Years	4 to < 5 Years	≥ 5 Years	Overall
Subjects who had an OLFC	**9**	**200**	**260**	**181**	**86**	**21**	**517**
MTD with no more than mild symptoms							
None	0	3 (1.5%)	6 (2.3%)	1 (0.6%)	0	0	6 (1.2%)
3 mg	0	0					
10 mg	0	0					
30 mg	0	0					
100 mg	1 (11.1%)	1 (0.5%)					1 (0.2%)
300 mg	0	7 (3.5%)	11 (4.2%)	10 (5.5%)	4 (4.7%)	1 (4.8%)	23 (4.4%)
600 mg	3 (33.3%)	23 (11.5%)	38 (14.6%)	27 (14.9%)	7 (8.1%)	4 (19.0%)	80 (15.5%)
1000 mg	2 (22.2%)	44 (22.0%)	53 (20.4%)	37 (20.4%)	18 (20.9%)	2 (9.5%)	118 (22.8%)
2000 mg	3 (33.3%)	122 (61.0%)	152 (58.5%)	106 (58.6%)	57 (66.3%)	14 (66.7%)	289 (55.9%)
Response rates [95% CI] [1]							
Tolerated a single highest dose of at least 300 mg	8 (88.9%) [51.8%, 99.7%]	196 (98.0%) [95.0%, 99.5%]	254 (97.7%) [95.0%, 99.1%]	180 (99.4%) [97.0%, 100.0%]	86 (100.0%) [95.8%, 100.0%]	21 (100.0%) [83.9%, 100.0%]	510 (98.6%) [97.2%, 99.5%]
Tolerated a single highest dose of at least 600 mg	8 (88.9%) [51.8%, 99.7%]	189 (94.5%) [90.4%, 97.2%]	243 (93.5%) [89.7%, 96.1%]	170 (93.9%) [89.4%, 96.9%]	82 (95.3%) [88.5%, 98.7%]	20 (95.2%) [76.2%, 99.9%]	487 (94.2%) [91.8%, 96.1%]
Tolerated a single highest dose of at least 1000 mg	5 (55.6%) [21.2%, 86.3%]	166 (83.0%) [77.1%, 87.9%]	205 (78.8%) [73.4%, 83.6%]	143 (79.0%) [72.3%, 84.7%]	75 (87.2%) [78.3%, 93.4%]	16 (76.2%) [52.8%, 91.8%]	407 (78.7%) [74.9%, 82.2%]
Tolerated a single highest dose of at least 2000 mg	3 (33.3%) [7.5%, 70.1%]	122 (61.0%) [53.9%, 67.8%]	152 (58.5%) [52.2%, 64.5%]	106 (58.6%) [51.0%, 65.8%]	57 (66.3%) [55.3%, 76.1%]	14 (66.7%) [43.0%, 85.4%]	289 (55.9%) [51.5%, 60.2%]

Source: Table 14.2.2
Total AR101 exposure was based on study drug exposure including parent studies. If a subject had multiple OLFCs within a given AR101 exposure window, the latest OLFC was summarized.
[1] The 95% CIs are based on exact Clopper Pearson intervals.
Abbreviations: CI, confidence interval; OLFC, open-label food challenge; MTD, maximum tolerated dose.

- Ad hoc analyses to group DBPCFC data by Treatment Pathways 1-3 (age at parent study baseline ≥ 4 years) and Treatment Pathways 4-5 (age at parent study baseline > 1 to 4 years) were performed. Treatment effects during the observed exposure time were clinically relevant and sustained in both age groups.

Table 4: Response Rates in DBPCFC at End of Treatment for Treatment Pathways 1-5 (Safety Population)

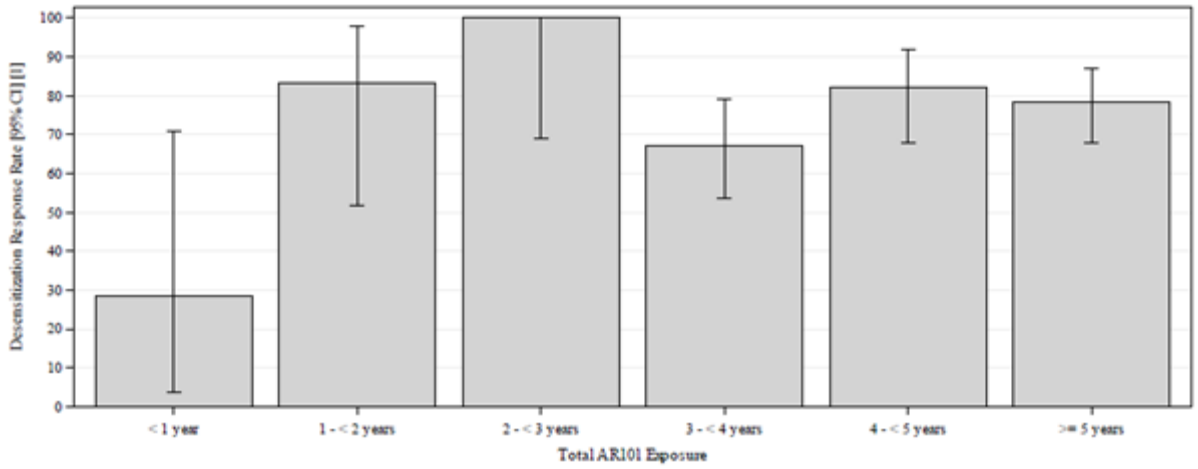
	Total AR101 Exposure						
	< 1 Year	1 to < 2 Years	2 to < 3 Years	3 to < 4 Years	4 to < 5 Years	≥ 5 Years	Overall
Subjects who had a DBPCFC	**7**	**12**	**10**	**58**	**45**	**79**	**211**
MTD with no more than mild symptoms							
None	0	0	0	0	0	0	0
3 mg	0	0	0	0	0	0	0
10 mg	0	0	0	0	1 (2.2%)	0	1 (0.5%)
30 mg	0	0	0	1 (1.7%)	0	0	1 (0.5%)
100 mg	2 (28.6%)	0	0	6 (10.3%)	1 (2.2%)	0	9 (4.3%)
300 mg	0	2 (16.7%)	0	6 (10.3%)	2 (4.4%)	4 (5.1%)	14 (6.6%)
600 mg	3 (42.9%)	0	0	6 (10.3%)	4 (8.9%)	13 (16.5%)	26 (12.3%)
1000 mg	0	1 (8.3%)	2 (20.0%)	12 (20.7%)	5 (11.1%)	13 (16.5%)	33 (15.6%)
2000 mg	2 (28.6%)	9 (75.0%)	8 (80.0%)	27 (46.6%)	32 (71.1%)	49 (62.0%)	127 (60.2%)
Desensitization response rates [95% CI] [1]							
Tolerated a single highest dose of at least 3 mg	7 (100.0%) [59.0%, 100.0%]	12 (100.0%) [73.5%, 100.0%]	10 (100.0%) [69.2%, 100.0%]	58 (100.0%) [93.8%, 100.0%]	45 (100.0%) [92.1%, 100.0%]	79 (100.0%) [95.4%, 100.0%]	211 (100.0%) [98.3%, 100.0%]
Tolerated a single highest dose of at least 10 mg	7 (100.0%) [59.0%, 100.0%]	12 (100.0%) [73.5%, 100.0%]	10 (100.0%) [69.2%, 100.0%]	58 (100.0%) [93.8%, 100.0%]	45 (100.0%) [92.1%, 100.0%]	79 (100.0%) [95.4%, 100.0%]	211 (100.0%) [98.3%, 100.0%]
Tolerated a single highest dose of at least 30 mg	7 (100.0%) [59.0%, 100.0%]	12 (100.0%) [73.5%, 100.0%]	10 (100.0%) [69.2%, 100.0%]	58 (100.0%) [93.8%, 100.0%]	44 (97.8%) [88.2%, 99.9%]	79 (100.0%) [95.4%, 100.0%]	210 (99.5%) [97.4%, 100.0%]
Tolerated a single highest dose of at least 100 mg	7 (100.0%) [59.0%, 100.0%]	12 (100.0%) [73.5%, 100.0%]	10 (100.0%) [69.2%, 100.0%]	57 (98.3%) [90.8%, 100.0%]	44 (97.8%) [88.2%, 99.9%]	79 (100.0%) [95.4%, 100.0%]	209 (99.1%) [96.6%, 99.9%]
Tolerated a single highest dose of at least 300 mg	5 (71.4%) [29.0%, 96.3%]	12 (100.0%) [73.5%, 100.0%]	10 (100.0%) [69.2%, 100.0%]	51 (87.9%) [76.7%, 95.0%]	43 (95.6%) [84.9%, 99.5%]	79 (100.0%) [95.4%, 100.0%]	200 (94.8%) [90.9%, 97.4%]
Tolerated a single highest dose of at least 600 mg	5 (71.4%) [29.0%, 96.3%]	10 (83.3%) [51.6%, 97.9%]	10 (100.0%) [69.2%, 100.0%]	45 (77.6%) [64.7%, 87.5%]	41 (91.1%) [78.8%, 97.5%]	75 (94.9%) [87.5%, 98.6%]	186 (88.2%) [83.0%, 92.2%]
Tolerated a single highest dose of at least 1000 mg	2 (28.6%) [3.7%, 71.0%]	10 (83.3%) [51.6%, 97.9%]	10 (100.0%) [69.2%, 100.0%]	39 (67.2%) [53.7%, 79.0%]	37 (82.2%) [67.9%, 92.0%]	62 (78.5%) [67.8%, 86.9%]	160 (75.8%) [69.5%, 81.4%]
Tolerated a single highest dose of at least 2000 mg	2 (28.6%) [3.7%, 71.0%]	9 (75.0%) [42.8%, 94.5%]	8 (80.0%) [44.4%, 97.5%]	27 (46.6%) [33.3%, 60.1%]	32 (71.1%) [55.7%, 83.6%]	49 (62.0%) [50.4%, 72.7%]	127 (60.2%) [53.2%, 66.8%]

Source: Table 14.2.3
Total AR101 exposure was based on study drug exposure including parent studies.
[1] The 95% CIs are based on exact Clopper-Pearson intervals.
Abbreviations: CI, confidence interval; DBPCFC, double-blind placebo-controlled food challenge; MTD, maximum tolerated dose.

- Response rates in the OLFCs by total AR101 exposure were overall consistent with the results obtained from the DBPCFCs.

Figure 2: Desensitization Response Rates in Double-Blind, Placebo-Controlled Food Challenge vs Total Exposure at End of Treatment – Bar Graph Safety Population

Part 3 of 4: Tolerated a Single Highest Dose of at least 1000 mg



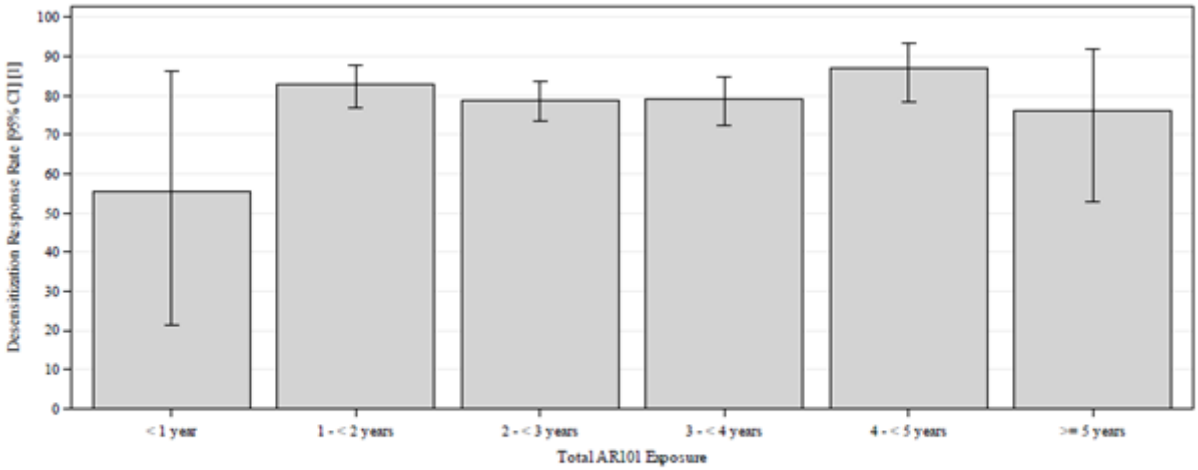
Total AR101 exposure is based on study drug exposure including parent studies.

[1] The 95% CIs are based on exact Clopper-Pearson intervals.

Abbreviation: DBPCFC, double-blind placebo-controlled food challenge.

Figure 3: Desensitization Response Rates in Open-Label Food Challenges vs Total Exposure – Bar Graph Safety Population

Part 3 of 4: Tolerated a Single Highest Dose of at Least 1000 mg



Total AR101 exposure is based on study drug exposure including parent studies. If a subject had multiple OLFCs within a given AR101 exposure window, the latest OLFC was summarized.

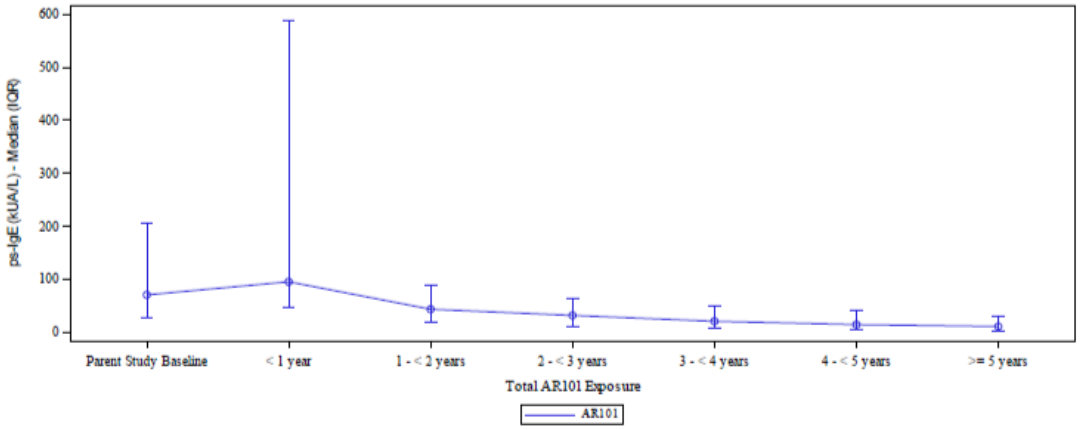
[1] The 95% CIs are based on exact Clopper-Pearson intervals.

Abbreviation: OLFC, open-label food challenge.

Exploratory Efficacy Endpoints (ad hoc analyses):

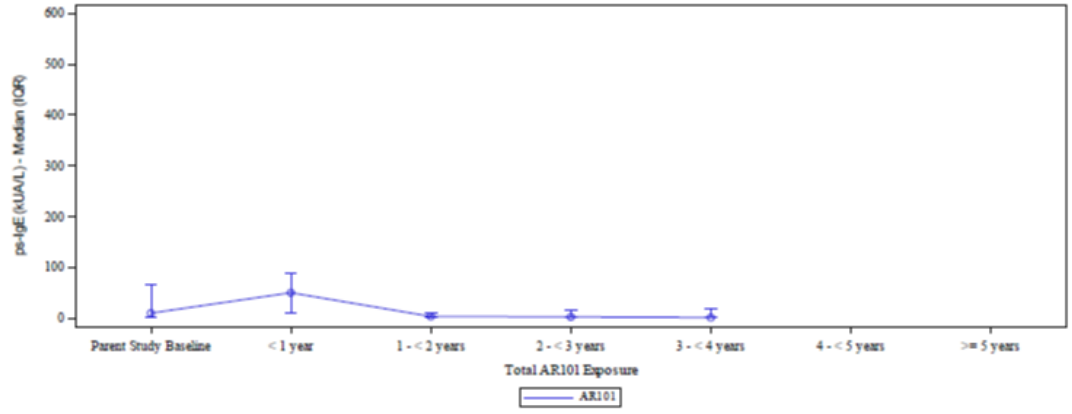
• Peanut-specific IgE decreased from 2 to ≥ 5 years of total AR101 exposure from parent study baseline. Because the baseline data collected during ARC008 were sparse, an ad hoc analysis was conducted to include the baseline data from the parent studies to use in change from baseline calculations. Results of the ad hoc analysis are summarized below.

Figure 4: Peanut-Specific IgE vs Time: Treatment Pathways 1-3 (Safety Population)



Source: Ad hoc Figure 4.1
Total AR101 exposure was based on study drug exposure including parent studies.
The figure includes baseline data from the parent study (including subjects who did not enter ARC008).
For cases where a subject had multiple visits within the same exposure window, the latest value was used in the summary.
Abbreviations: IgE, Immunoglobulin E; IQR, interquartile range; ps, peanut-specific.

Figure 5: Peanut-Specific IgE vs Time: Treatment Pathways 4-5 (Safety Population)



Source: Ad hoc Figure 4.4
Total AR101 exposure was based on study drug exposure including parent studies.
The figure includes baseline data from the parent study (including subjects who did not enter ARC008).
For cases where a subject had multiple visits within the same exposure window, the latest value was used in the summary.
Abbreviations: IgE, Immunoglobulin E; IQR, interquartile range; ps, peanut-specific.

• Peanut-specific IgG4 concentrations increased from the parent study baseline and remained elevated through to the last exposure window for AR101.

• The peanut-specific IgE/IgG4 ratio decreased from the parent study baseline and remained low through to the last exposure window for AR101.

• Peanut SPT mean wheal diameter decreased from parent study baseline to End of Treatment and

Study Exit. In general, mean wheal diameter decreased with increased total AR101 exposure. Peanut SPT mean wheal diameter decreased from parent study baseline to End of Treatment and Study Exit. The overall mean (SD) decrease in wheal diameter to End of Treatment was -5.23 (5.673) mm and the peak decrease in wheal diameter occurred at 3 to < 4 years total AR101 exposure and was -5.82

(5.773) mm. The overall mean (SD) decrease in wheal diameter to Study Exit was -6.83 (4.578) mm and the peak decrease in wheal diameter occurred at 4 to < 5 years total AR101 exposure and was -7.44 (4.237) mm.

Safety results

Primary Safety Endpoints:

• Treatment-emergent adverse events (TEAEs) occurred in 866/908 (95.4%) subjects overall. Overall, such events occurred in 100/229 (43.7%) subjects in initial escalation, 229/244 (93.9%) subjects in up-dosing, and 313/480 (65.2%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 608/749 (81.2%) subjects from 1 to < 2 years, 538/674 (79.8%) subjects from 2 to < 3 years, 313/481 (65.1%) subjects from 3 to < 4 years, 160/271 (59.0%) subjects from 4 to < 5 years, and 56/107 (52.3%) subjects from ≥ 5 years of AR101 exposure.

Table 5: Overall Summary of TEAEs (Safety Population) (extract)

			Total AR101 [1]						
	Initial Escalation (N = 229)	Up-Dosing (N = 244)	< 1 year [2] (N = 480)	1 to < 2 years (N = 749)	2 to < 3 years (N = 674)	3 to < 4 years (N = 481)	4 to < 5 years (N = 271)	≥ 5 years (N = 107)	Overall (N = 908)
Total number of TEAEs	201	5992	3346	7573	4723	2364	850	485	25433
Total number of TESAEs	1	5	4	23	11	5	2	2	53
Number (%) of subjects with at least 1:									
TEAE	100 (43.7%)	229 (93.9%)	313 (65.2%)	608 (81.2%)	538 (79.8%)	313 (65.1%)	160 (59.0%)	56 (52.3%)	866 (95.4%)
TEAE by severity [3]									
Grade 1: Mild	91 (39.7%)	154 (63.1%)	233 (48.5%)	417 (55.7%)	395 (58.6%)	234 (48.6%)	125 (46.1%)	42 (39.3%)	451 (49.7%)
Grade 2: Moderate	9 (3.9%)	72 (29.5%)	78 (16.3%)	177 (23.6%)	136 (20.2%)	74 (15.4%)	33 (12.2%)	13 (12.1%)	384 (42.0%)
Grade 3: Severe	0	3 (1.2%)	2 (0.4%)	14 (1.9%)	7 (1.0%)	5 (1.0%)	2 (0.7%)	0	33 (3.6%)
Grade 4: Life-Threatening	0	0	0	0	0	0	0	1 (0.9%)	1 (0.1%)
Grade 5: Death	0	0	0	0	0	0	0	0	0
TEAE by relationship to study product [4]									
Not related	22 (9.6%)	35 (14.3%)	161 (33.5%)	302 (40.3%)	339 (50.3%)	230 (47.8%)	119 (43.9%)	46 (43.0%)	320 (35.2%)
Related	78 (34.1%)	194 (79.5%)	152 (31.7%)	306 (40.9%)	199 (29.5%)	83 (17.3%)	41 (15.1%)	10 (9.3%)	546 (60.1%)
TEAE leading to early discontinuation of study product	1 (0.4%)	12 (4.9%)	7 (1.5%)	20 (2.7%)	8 (1.2%)	2 (0.4%)	2 (0.7%)	1 (0.9%)	53 (5.8%)
Treatment-emergent chronic/recurrent GI AEs/symptoms leading to early discontinuation of study product	1 (0.4%)	9 (3.7%)	2 (0.4%)	8 (1.1%)	1 (0.1%)	1 (0.2%)	2 (0.7%)	1 (0.9%)	25 (2.8%)
TEAE requiring dose interruption of study product	5 (2.2%)	131 (53.7%)	163 (34.0%)	393 (52.5%)	324 (48.1%)	177 (36.8%)	89 (32.8%)	34 (31.8%)	669 (73.7%)

	Initial Escalation (N = 229)	Up-Dosing (N = 244)	Total AR101 [1] < 1 year [2] (N = 480)	1 to < 2 years (N = 749)	2 to < 3 years (N = 674)	3 to < 4 years (N = 481)	4 to < 5 years (N = 271)	≥ 5 years (N = 107)	Overall (N = 908)
TEAE requiring dose reduction of study product	0	57 (23.4%)	32 (6.7%)	59 (7.9%)	26 (3.9%)	15 (3.1%)	9 (3.3%)	4 (3.7%)	167 (18.4%)
TEAE leading to early study withdrawal	1 (0.4%)	7 (2.9%)	4 (0.8%)	9 (1.2%)	3 (0.4%)	1 (0.2%)	2 (0.7%)	0	27 (3.0%)
Treatment-emergent GI AEI [5]	1 (0.4%)	12 (4.9%)	2 (0.4%)	8 (1.1%)	3 (0.4%)	1 (0.2%)	2 (0.7%)	1 (0.9%)	30 (3.3%)
TEAE that is an anaphylactic reaction	1 (0.4%)	30 (12.3%)	31 (6.5%)	82 (10.9%)	60 (8.9%)	22 (4.6%)	18 (6.6%)	5 (4.7%)	192 (21.1%)
TEAE that is associated with use of epinephrine as rescue medication	1 (0.4%)	21 (8.6%)	22 (4.6%)	50 (6.7%)	33 (4.9%)	18 (3.7%)	13 (4.8%)	2 (1.9%)	135 (14.9%)
TEAE that is associated with accidental/non-accidental non-study product food allergen exposure	2 (0.9%)	33 (13.5%)	30 (6.3%)	100 (13.4%)	71 (10.5%)	32 (6.7%)	17 (6.3%)	4 (3.7%)	227 (25.0%)
TEAE that is associated with eosinophilic esophagitis	0	0	0	0	0	0	0	1 (0.9%)	1 (0.1%)
TEAE that is a hypersensitivity event [6]	1 (0.4%)	30 (12.3%)	31 (6.5%)	82 (10.9%)	60 (8.9%)	22 (4.6%)	18 (6.6%)	5 (4.7%)	192 (21.1%)

Total AR101 exposure was based on study drug exposure including parent studies.
The 5-point CoFAR severity grading scale was used for coding allergic reactions. The 3-point Modified EAACI grading scale was used for grading the severity
of systemic allergic reactions (anaphylactic reactions). The 5-point CTCAE severity grading scale was used for coding all other AEs.
Treatment-emergent AEs include AEs or symptoms recorded on the AE CRFs that occur after first dose of AR101 in ARC008 through 30 days after last dose of
study product, but excluding AEs or symptoms that occur during or related to a food challenge.
[1] Subjects are counted towards the denominator for each Total AR101 Exposure window if they had AR101 exposure and were enrolled in the ARC008 study
during each exposure window.
[2] Only includes events during the Initial and Extended Maintenance period.
[3] Subjects with more than 1 AE were counted only once using the highest severity.
[4] Subjects with more than 1 AE were counted only once using the closest relationship to study product.
[5] Includes 3 categories of subjects: 1) Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level; 2) Any subject who develops chronic/recurrent GI AEs at or before reaching the 20 mg dose level and resumes dosing after a 30-day dosing hiatus; 3) Any subject who experienced GI AEs and discontinues early from the study.
[6] Hypersensitivity is defined as AEs that were an allergic reaction.
Abbreviations: AE, adverse event; AEI, AE of interest; CoFAR, Consortium of Food Allergy Research; CRF, case report form; CTCAE, Common Terminology Criteria for Adverse Events; EAACI, European Academy of Allergy and Clinical Immunology; GI, gastrointestinal; TEAE, treatment-emergent AE; TESAE, treatment-emergent serious AE.

The most common (occurring in ≥ 20% of subjects overall) TEAEs in descending order were cough (33.3%), vomiting and pyrexia (32.3%, each), abdominal pain (30.0%), urticaria (27.6%), headache (26.4%), nasopharyngitis (24.3%), upper respiratory tract infection (23.5%), systemic allergic reaction (anaphylactic reaction; 21.1%), pruritus (21.0%), and nausea (20.2%).

Table 6: Treatment-Emergent AEs in at Least 5% of Subjects Overall by SOC and PT (Safety Population)

SOC / PT [1]	Initial* Escalation (N = 229)	Up-Dosing (N = 244)	Initial and Extended Maintenance (N = 881)	Overall (N = 908)
Subjects with at least 1 AE	**100 (43.7%)**	**229 (93.9%)**	**827 (93.9%)**	**866 (95.4%)**
Infections and infestations	**7 (3.1%)**	**150 (61.5%)**	**657 (74.6%)**	**701 (77.2%)**
Nasopharyngitis	1 (0.4%)	41 (16.8%)	194 (22.0%)	221 (24.3%)
Upper respiratory tract infection	1 (0.4%)	52 (21.3%)	181 (20.5%)	213 (23.5%)
Viral infection	1 (0.4%)	19 (7.8%)	134 (15.2%)	143 (15.7%)
Influenza	0	5 (2.0%)	104 (11.8%)	109 (12.0%)
COVID-19	0	7 (2.9%)	95 (10.8%)	102 (11.2%)
Gastroenteritis viral	0	10 (4.1%)	83 (9.4%)	91 (10.0%)
Gastroenteritis	0	14 (5.7%)	80 (9.1%)	89 (9.8%)
Rhinitis	0	16 (6.6%)	63 (7.2%)	76 (8.4%)
Conjunctivitis	0	6 (2.5%)	50 (5.7%)	54 (5.9%)
Pharyngitis streptococcal	0	8 (3.3%)	46 (5.2%)	54 (5.9%)
Ear infection	0	3 (1.2%)	47 (5.3%)	50 (5.5%)
Sinusitis	1 (0.4%)	8 (3.3%)	41 (4.7%)	48 (5.3%)
Gastrointestinal disorders	**61 (26.6%)**	**197 (80.7%)**	**564 (64.0%)**	**636 (70.0%)**
Vomiting	5 (2.2%)	82 (33.6%)	239 (27.1%)	293 (32.3%)
Abdominal pain	30 (13.1%)	101 (41.4%)	205 (23.3%)	272 (30.0%)
Nausea	10 (4.4%)	52 (21.3%)	145 (16.5%)	183 (20.2%)
Abdominal pain upper	7 (3.1%)	34 (13.9%)	150 (17.0%)	173 (19.1%)
Abdominal discomfort	16 (7.0%)	69 (28.3%)	112 (12.7%)	166 (18.3%)
Diarrhoea	2 (0.9%)	34 (13.9%)	99 (11.2%)	127 (14.0%)
Oral pruritus	1 (0.4%)	29 (11.9%)	64 (7.3%)	88 (9.7%)
Lip swelling	0	8 (3.3%)	62 (7.0%)	68 (7.5%)
Paraesthesia oral	3 (1.3%)	16 (6.6%)	46 (5.2%)	59 (6.5%)
Lip pruritus	2 (0.9%)	16 (6.6%)	41 (4.7%)	53 (5.8%)
Dyspepsia	2 (0.9%)	22 (9.0%)	36 (4.1%)	51 (5.6%)
Respiratory, thoracic and mediastinal disorders	**30 (13.1%)**	**168 (68.9%)**	**538 (61.1%)**	**596 (65.6%)**
Cough	7 (3.1%)	69 (28.3%)	268 (30.4%)	302 (33.3%)
Throat irritation	6 (2.6%)	64 (26.2%)	131 (14.9%)	169 (18.6%)
Oropharyngeal pain	0	27 (11.1%)	141 (16.0%)	165 (18.2%)
Nasal congestion	3 (1.3%)	34 (13.9%)	118 (13.4%)	145 (16.0%)
Sneezing	9 (3.9%)	39 (16.0%)	84 (9.5%)	118 (13.0%)
Rhinorrhoea	2 (0.9%)	30 (12.3%)	96 (10.9%)	114 (12.6%)
Wheezing	1 (0.4%)	28 (11.5%)	91 (10.3%)	108 (11.9%)
Asthma	1 (0.4%)	18 (7.4%)	70 (7.9%)	87 (9.6%)

SOC / PT [1]	Initial Escalation (N = 229)	Up-Dosing (N = 244)	Initial and Extended Maintenance (N = 881)	Overall (N = 908)
Oropharyngeal discomfort	7 (3.1%)	35 (14.3%)	55 (6.2%)	85 (9.4%)
Rhinitis allergic	0	12 (4.9%)	50 (5.7%)	60 (6.6%)
Dyspnoea	0	15 (6.1%)	46 (5.2%)	59 (6.5%)
Throat tightness	0	11 (4.5%)	41 (4.7%)	50 (5.5%)
Skin and subcutaneous tissue disorders	**19 (8.3%)**	**121 (49.6%)**	**416 (47.2%)**	**479 (52.8%)**
Urticaria	7 (3.1%)	57 (23.4%)	218 (24.7%)	251 (27.6%)
Pruritus	7 (3.1%)	57 (23.4%)	151 (17.1%)	191 (21.0%)
Rash	1 (0.4%)	29 (11.9%)	97 (11.0%)	121 (13.3%)
Eczema	1 (0.4%)	14 (5.7%)	63 (7.2%)	74 (8.1%)
Erythema	4 (1.7%)	20 (8.2%)	47 (5.3%)	65 (7.2%)
General disorders and administration site conditions	**2 (0.9%)**	**75 (30.7%)**	**381 (43.2%)**	**424 (46.7%)**
Pyrexia	1 (0.4%)	41 (16.8%)	269 (30.5%)	293 (32.3%)
Illness	0	4 (1.6%)	57 (6.5%)	61 (6.7%)
Nervous system disorders	**2 (0.9%)**	**48 (19.7%)**	**247 (28.0%)**	**272 (30.0%)**
Headache	2 (0.9%)	43 (17.6%)	218 (24.7%)	240 (26.4%)
Immune system disorders	**1 (0.4%)**	**33 (13.5%)**	**224 (25.4%)**	**245 (27.0%)**
Anaphylactic reaction	1 (0.4%)	30 (12.3%)	172 (19.5%)	192 (21.1%)
Seasonal allergy	0	2 (0.8%)	49 (5.6%)	50 (5.5%)
Injury, poisoning and procedural complications	**4 (1.7%)**	**41 (16.8%)**	**185 (21.0%)**	**222 (24.4%)**
Eye disorders	**4 (1.7%)**	**28 (11.5%)**	**129 (14.6%)**	**154 (17.0%)**
Eye pruritus	2 (0.9%)	21 (8.6%)	63 (7.2%)	83 (9.1%)
Ear and labyrinth disorders	**2 (0.9%)**	**19 (7.8%)**	**88 (10.0%)**	**103 (11.3%)**
Ear pain	0	4 (1.6%)	44 (5.0%)	47 (5.2%)
Musculoskeletal and connective tissue disorders	**0**	**8 (3.3%)**	**85 (9.6%)**	**91 (10.0%)**
Psychiatric disorders	**2 (0.9%)**	**6 (2.5%)**	**53 (6.0%)**	**61 (6.7%)**

Source: Table 14.3.1.2
At each level of summarization (any event, SOC, and PT), subjects with more than 1 AE were counted only once within study period.
[1] AEs were coded to SOC and PT using MedDRA Version 26.0.
Abbreviations: AE, adverse event, MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.

TEAEs are listed by subject in Listing 16.2.6.2. Treatment-emergent allergic AEs (excluding food allergens) are listed by subject in Listing 16.2.6.6.

Non-treatment-emergent AEs are listed by subject in Listing 16.2.6.1.

Table 7: Treatment-Related AEs in at Least 5% of Subjects Overall by SOC and PT (Safety Population)

SOC / PT [1]	Initial Escalation (N = 229)	Up-Dosing (N = 244)	Initial and Extended Maintenance (N = 881)	Overall (N = 908)
Subjects with at least 1 AE	**78 (34.1%)**	**194 (79.5%)**	**467 (53.0%)**	**546 (60.1%)**
Gastrointestinal disorders	**56 (24.5%)**	**166 (68.0%)**	**321 (36.4%)**	**405 (44.6%)**
Abdominal pain	28 (12.2%)	93 (38.1%)	125 (14.2%)	196 (21.6%)
Vomiting	5 (2.2%)	51 (20.9%)	74 (8.4%)	113 (12.4%)
Abdominal discomfort	16 (7.0%)	60 (24.6%)	59 (6.7%)	108 (11.9%)
Nausea	9 (3.9%)	47 (19.3%)	63 (7.2%)	105 (11.6%)
Abdominal pain upper	6 (2.6%)	22 (9.0%)	46 (5.2%)	66 (7.3%)
Oral pruritus	1 (0.4%)	25 (10.2%)	36 (4.1%)	56 (6.2%)
Lip pruritus	2 (0.9%)	14 (5.7%)	36 (4.1%)	46 (5.1%)
Lip swelling	0	8 (3.3%)	39 (4.4%)	45 (5.0%)
Respiratory, thoracic and mediastinal disorders	**23 (10.0%)**	**121 (49.6%)**	**234 (26.6%)**	**303 (33.4%)**
Throat irritation	5 (2.2%)	57 (23.4%)	95 (10.8%)	130 (14.3%)
Cough	4 (1.7%)	40 (16.4%)	78 (8.9%)	107 (11.8%)
Oropharyngeal discomfort	7 (3.1%)	34 (13.9%)	43 (4.9%)	73 (8.0%)
Sneezing	9 (3.9%)	30 (12.3%)	41 (4.7%)	70 (7.7%)
Wheezing	0	15 (6.1%)	37 (4.2%)	48 (5.3%)
Skin and subcutaneous tissue disorders	**14 (6.1%)**	**79 (32.4%)**	**179 (20.3%)**	**232 (25.6%)**
Urticaria	6 (2.6%)	42 (17.2%)	111 (12.6%)	142 (15.6%)
Pruritus	6 (2.6%)	42 (17.2%)	90 (10.2%)	123 (13.5%)
Immune system disorders	**1 (0.4%)**	**24 (9.8%)**	**130 (14.8%)**	**147 (16.2%)**
Anaphylactic reaction	1 (0.4%)	24 (9.8%)	129 (14.6%)	146 (16.1%)
Eye disorders	**2 (0.9%)**	**15 (6.1%)**	**45 (5.1%)**	**59 (6.5%)**
General disorders and administration site conditions	**0**	**21 (8.6%)**	**38 (4.3%)**	**56 (6.2%)**

Source: Table 14.3.1.8
At each level of summarization (any event, SOC, and PT), subjects with more than 1 AE related to study product were counted only once within study period.
[1] AEs were coded to SOC and PT using MedDRA Version 26.0.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.

• Treatment-related TEAEs occurred in 546/908 (60.1%) subjects overall. Overall, such events occurred in 78/229 (34.1%) subjects in initial escalation, 194/244 (79.5%) subjects in up-dosing, and 152/480 (31.7%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 306/749 (40.9%) subjects from 1 to < 2 years, 199/674 (29.5%) subjects from 2 to < 3 years, 83/481 (17.3%) subjects from 3 to < 4 years, 41/271 (15.1%) subjects from 4 to <5 years, and 10/107 (9.3%) subjects from ≥ 5 years of AR101 exposure.

o The most common (occurring in > 10% of subjects overall) treatment-related AEs were abdominal pain (21.6%), systemic allergic reaction (anaphylactic reaction; 16.1%), urticaria (15.6%), throat irritation (14.3%), pruritus (13.5%), vomiting (12.4%), abdominal discomfort (11.9%), cough (11.8%), and nausea (11.6%).

o Treatment-related AEs occurred in 500/796 (62.8%) subjects in Treatment Pathways 1-3 and in 46/112 (41.1%) subjects in Treatment Pathways 4-5.

Adverse Events by Severity

• Overall, most subjects had AEs of grade 1 (mild) (451/908 [49.7%] subjects) and grade 2 (moderate) (384/908 [42.0%] subjects) maximum severity. Thirty-three/908 (3.6%) subjects had at least one grade 3 (severe) TEAE.

  o In Treatment Pathways 1-3, TEAEs were grade 1 (mild) in 386/796 (48.5%) subjects, grade 2 (moderate) in 342/796 (43.0%) subjects, grade 3 in 31/796 (3.9%) subjects, and there was 1 subject who experienced a grade 4 (life-threatening) TEAE of appendicitis; the event occurred in Treatment Pathway 1 during extended maintenance on Day 1192. The event of appendicitis was considered by the investigator to be not related to either study product or procedure.

  o In Treatment Pathways 4-5, TEAEs were grade 1 (mild) in 65/112 (58.0%) subjects, grade 2 (moderate) in 39/112 (38.4%) subjects, and grade 3 in 2/112 (1.8%) subjects.

• No subject had a TEAE that led to death.

• Treatment-emergent SAEs occurred in 42/908 (4.6%) subjects overall. Overall, such events occurred in 1/229 (0.4%) subject in initial escalation, 4/244 (1.6%) subjects in up-dosing, and 4/480 (0.8%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 18/749 (2.4%) subjects from 1 to < 2 years, 8/674 (1.2%) subjects from 2 to < 3 years, 5/481 (1.0%) subjects from 3 to < 4 years, 2/271 (0.7%) subjects from 4 to < 5 years, and 2/107 (1.9%) subjects from ≥ 5 years of AR101 exposure.

  o Treatment-emergent SAEs occurred in 36/796 (4.5%) subjects in Treatment Pathways 1-3 and in 6/112 (5.4%) subjects in Treatment Pathways 4-5. A grade 4 (life-threatening) treatment-emergent SAE occurred in 1 (0.1%) subject in Treatment Pathways 1-3 only.

• Treatment-emergent SAEs considered related to study product occurred in 5/908 (0.6%) subjects overall. Overall, such events occurred in no subjects in the initial escalation or during up-dosing. One out of 480 (0.2%) subjects experienced a treatment-related SAE during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence remained low across the exposure time points (1/749 [0.1%] subject from 1 to < 2 years; 2/674 [0.3%] subjects from 2 to < 3 years; no subjects from 3 to <4 years; 1/271 [0.4%] subject from 4 to < 5 years and no subjects with ≥ 5 years of AR101 exposure).

  o Treatment-emergent SAEs considered related to study product occurred in 5/796 (0.6%) subjects in Treatment Pathways 1-3 only.

• TEAEs leading to discontinuation of study product occurred in 53/908 (5.8%) subjects overall. Overall, such events occurred in 1/229 (0.4%) subject in initial escalation, 12/244 (4.9%) subjects in up-dosing, and 7/480 (1.5%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 20/749 (2.7%) subjects from 1 to <2 years, 8/674 (1.2%) subjects from 2 to <3 years, 2/481 (0.4%) subjects from 3 to <4 years, 2/271 (0.7%) subjects from 4 to <5 years, and 1/107 (0.9%) subjects from ≥ 5 years of AR101 exposure.

  o TEAEs leading to discontinuation of study product occurred in 51/796 (6.4%) subjects in Treatment Pathways 1-3 and in 2 /112 (1.8%) subjects in Treatment Pathways 4-5.

  o The most common TEAE leading to discontinuation of study product was systemic allergic reaction (anaphylactic reaction; 1.9%). All other TEAEs leading to discontinuation of study product occurred in < 1% of subjects overall.

o Treatment-related TEAEs leading to discontinuation of study product occurred in 45/908 (5.0%) subjects.

Table 8: Overall Summary of Treatment-Related Adverse Events Safety Population

	Initial Escalation (N=229)	Up-Dosing (N=244)	Initial and Extended Maintenance (N=881)	Overall (N=908)
Total number of TEAEs	150	4373	9148	13671
Total number of TESAEs	0	0	5	5
Number (%) of subjects with at least 1:				
TEAE	78 (34.1%)	194 (79.5%)	467 (53.0%)	546 (60.1%)
TEAE by severity [1]				
Grade 1: Mild	73 (31.9%)	151 (61.9%)	357 (40.5%)	401 (44.2%)
Grade 2: Moderate	5 (2.2%)	43 (17.6%)	103 (11.7%)	138 (15.2%)
Grade 3: Severe	0	0	7 (0.8%)	7 (0.8%)
Grade 4: Life-Threatening	0	0	0	0
Grade 5: Death	0	0	0	0
TEAE by relationship to study product [2]				
Not related	0	0	0	0
Related	78 (34.1%)	194 (79.5%)	467 (53.0%)	546 (60.1%)
TEAE leading to early discontinuation of study product	1 (0.4%)	12 (4.9%)	32 (3.6%)	45 (5.0%)
Treatment-emergent chronic/recurrent GI AEs/symptoms leading to early discontinuation of study product	1 (0.4%)	9 (3.7%)	12 (1.4%)	22 (2.4%)
TEAE requiring dose interruption of study product	1 (0.4%)	37 (15.2%)	112 (12.7%)	140 (15.4%)
TEAE requiring dose reduction of study product	0	46 (18.9%)	56 (6.4%)	93 (10.2%)
TEAE leading to early study withdrawal	1 (0.4%)	7 (2.9%)	13 (1.5%)	21 (2.3%)

The 5-point CoFAR severity grading scale was used for coding allergic reactions. The 3-point Modified EAACI grading scale was used for grading the severity of anaphylactic reactions. The 5-point CTCAE severity grading scale was used for coding all other adverse events.
Treatment-emergent AEs include AEs or symptoms recorded on the AE CRFs that occur after first dose of AR101 in ARC008 through 30 days after last dose of study product, but excluding AEs or symptoms that occur during or related to a food challenge.

• Treatment-emergent systemic allergic reaction (anaphylactic reaction) occurred in 192/908 (21.1%) subjects overall. Overall, treatment-emergent systemic allergic reaction (anaphylactic reaction) occurred in 1/229 (0.4%) subject in initial escalation, 30/244 (12.3%) subjects in up-dosing, 31/480 (6.5%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 82/749 (10.9%) subjects from 1 to < 2 years, 60/674 (8.9%) subjects from 2 to <3 years, 22/481 (4.6%) subjects from 3 to < 4 years, 18/271 (6.6%) subjects from 4 to < 5 years, and 5/107 (4.7%) subjects from ≥ 5 years of AR101 exposure.

o Treatment-emergent systemic allergic reaction (anaphylactic reaction) was reported in 175/796 (22.0%) subjects in Treatment Pathways 1-3 and in 17/112 (15.2%) subjects in Treatment Pathways 4-5.

o Overall, treatment-emergent systemic allergic reaction (anaphylactic reaction) with a maximum severity of mild and moderate was reported for 97/908 (10.7%) and 89/908 (9.8%) subjects, respectively. Severe treatment-emergent systemic allergic reaction (anaphylactic reaction) occurred in 6/908 (0.7%) subjects overall.

o Treatment-related systemic allergic reaction (anaphylactic reaction) occurred in 146/908 (16.1%) subjects overall.

• Treatment-emergent systemic allergic reaction (anaphylactic reaction) led to discontinuation of study product in 17/908 (1.9%) subjects overall. Overall, such events occurred in no subjects in initial escalation, 1/244 (0.4%) subject in up-dosing, 2/480 (0.4%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 8/749 (1.1%) subjects from 1 to < 2 years, 5/674 (0.7%) subjects from 2 to < 3 years, 1/481 (0.2%) subjects from 3 to < 4 years, and no subjects from 4 to < 5 years or from ≥ 5 years of AR101 exposure.

• Treatment-emergent GI AEs of interest occurred in 30/908 (3.3%) subjects overall. Such events occurred in 1/229 (0.4%) subject in initial escalation, 12/244 (4.9%) subjects in up-dosing, and 2/480 (0.4%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 8/749 (1.1%) subjects from 1 to <2 years, 3/674 (0.4%)

subjects from 2 to <3 years, 1/481 (0.2%) subjects from 3 to <4 years, 2/271 (0.7%) subjects from 4 to <5 years, and 1/107 (0.9%) subjects from ≥ 5 years of AR101 exposure.

  - o Treatment-emergent GI AEs of interest occurred in 28/796 (3.5%) subjects in Treatment Pathways 1-3 and in 2/112 (1.8%) subjects in Treatment Pathways 4-5.
  - o Treatment-related GI AEs of interest occurred in 26/908 (2.9%) subjects overall.

• Treatment-emergent chronic/recurrent GI AEs/symptoms leading to early discontinuation of study product occurred in 25/908 (2.8%) subjects overall. Overall, treatment-emergent chronic/recurrent GI AEs/symptoms leading to early discontinuation of study product occurred in 1/229 (0.4%) subject in initial escalation, 9/244 (3.7%) subjects in up-dosing, and 2/480 (0.4%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 8/749 (1.1%) subjects from 1 to < 2 years, 1/674 (0.1%) subjects from 2 to < 3 years, 1/481 (0.2%) subjects from 3 to < 4 years, 2/271 (0.7%) subjects from 4 to < 5 years, and 1/107 (0.9%) subjects from ≥ 5 years of AR101 exposure.

  - o Treatment-related treatment-emergent chronic/recurrent GI AEs/symptoms leading to early discontinuation of study product occurred in 22/908 (2.4%) subjects.

• TEAEs leading to study discontinuation occurred in 27/908 (3.0%) subjects overall. Overall, such events occurred in 1/229 (0.4%) subject in initial escalation, 7/244 (2.9%) subjects in up-dosing, and 4/480 (0.8%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 9/749 (1.2%) subjects from 1 to < 2 years, 3/674 (0.4%) subjects from 2 to < 3 years, 1/481 (0.2%) subjects from 3 to < 4 years, and 2/271 (0.7%) subjects from 4 to < 5 years. No TEAEs leading to study discontinuation were reported from ≥ 5 years of AR101 exposure.

  - o TEAEs leading to study discontinuation occurred in 26/796 (3.3%) subjects in Treatment Pathways 1-3 and in 1/112 (0.9%) subject in Treatment Pathways 4-5.
  - o Treatment-related TEAEs leading to study discontinuation occurred in 21/908 (2.3%) subjects.

• TEAEs associated with use of epinephrine as rescue medication (excluding use during food challenges) occurred in 135/908 (14.9%) subjects overall. Overall, such events occurred in 1/229 (0.4%) subject in initial escalation, 21/244 (8.6%) subjects in up-dosing, and 22/480 (4.6%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 50/749 (6.7%) subjects from 1 to <2 years, 33/674 (4.9%) subjects from 2 to < 3 years, 18/481 (3.7%) subjects from 3 to < 4 years, 13/271 (4.8%) subjects from 4 to < 5 years, and 2/107 (1.9%) subjects from ≥ 5 years of AR101 exposure.

Table 9: Treatment-Emergent and Treatment-Related Adverse Events Associated with Use of Epinephrine by Treatment Pathways and Geographic Region Safety Population

	Geographic Region	Treatment Pathway	Number of Subjects with Event	N (All Subjects)	Percent of Subjects with Event (All Subjects)	N (In Subgroup)	Percent of Subjects with Event (In Subgroup)
Treatment Emergent Adverse Events Associated with use of Epinephrine	Europe	1-3	24	908	2.64	199	12.06
		4-5	3	908	0.33	52	5.77
	North America	1-3	101	908	11.12	597	16.92
		4-5	7	908	0.77	60	11.67
Treatment Emergent and Treatment Related Adverse Events Associated with use of Epinephrine	Europe	1-3	18	908	1.98	199	9.05
		4-5	1	908	0.11	52	1.92
	North America	1-3	73	908	8.04	597	12.23
		4-5	3	908	0.33	60	5.00

Subjects with more than 1 adverse event associated with use of epinephrine were counted only once within each region and treatment pathway grouping.

Reference: Listing 16.2.6.2

o TEAEs associated with use of epinephrine as rescue medication (excluding use during food challenges) occurred in 125/796 (15.7%) subjects in Treatment Pathways 1-3 and in 10/112 (8.9%) subjects in Treatment Pathways 4-5.

o Treatment-related TEAEs associated with use of epinephrine as a rescue medication (excluding use during food challenges) occurred in 95/908 (10.5%) subjects overall.

Accidental and Non-accidental Food-> Peanut Allergen Exposure

• Fifty-nine (6.5%) subjects had 65 non-AR101 peanut-related exposure episodes, the majority had 1 episode of peanut-related exposure, with only 5 subjects reporting more than 1 episode. No subjects reported peanut-related exposure episodes during the initial escalation period and a similar proportion of subjects experienced these events during the up-dosing and initial and extended dosing periods (11/244 [4.5%] and 50/881 [5.7%] subjects, respectively).

• Nineteen/908 (2.1%) subjects had 20 systemic allergic reaction (anaphylactic reaction) events triggered by 'exposure to peanut or peanut-containing food' (18 subjects) or 'possible peanut exposure, unable to verify food' (1 subject).

• TEAEs associated with accidental/non-accidental non-study product food allergen exposure occurred in 227/908 (25.0%) subjects overall. Overall, such events occurred in 2/229 (0.9%) subjects in initial escalation, 33/244 (13.5%) subjects in up-dosing, and 30/408 (6.3%) subjects during the first year while on maintenance dosing (excluding events during initial escalation and up-dosing); the incidence was 100/749 (13.4%) subjects from 1 to <2 years, 71/674 (10.5%) subjects from 2 to < 3 years, 32/481 (6.7%) subjects from 3 to < 4 years, 17/271 (6.3%) subjects from 4 to < 5 years, and 4/107 (3.7%) subjects from ≥ 5 years of AR101 exposure.

o TEAEs associated with accidental/non-accidental non-study product food allergen exposure occurred in 185/796 (23.2%) subjects in Treatment Pathways 1-3 and in 42/112 (37.5%) subjects in Treatment Pathways 4-5.

Table 10: Treatment-Emergent Food Allergy Episodes (Safety Population)

	Initial Escalation (N = 229)	Up-Dosing (N = 244)	Initial and Extended Maintenance (N = 881)	Overall (N = 908)
Total number of food allergy episodes	**2**	**46**	**339**	**387**
Total number of peanut allergy episodes	**0**	**11**	**54**	**65**
Total number of non-peanut allergy episodes	**2**	**35**	**286**	**323**
Total number of accidental food allergy episodes	**2**	**41**	**292**	**335**
Total number of non-accidental food allergy episodes	**0**	**5**	**47**	**52**
Subjects experiencing any food allergy episodes	**2 (0.9%)**	**33 (13.5%)**	**204 (23.2%)**	**227 (25.0%)**
1 episode	2 (0.9%)	26 (10.7%)	142 (16.1%)	153 (16.9%)
2 episodes	0	6 (2.5%)	32 (3.6%)	40 (4.4%)
3 episodes	0	0	11 (1.2%)	13 (1.4%)
> 3 episodes	0	1 (0.4%)	19 (2.2%)	21 (2.3%)
Subjects experiencing a peanut-related food allergy episode	**0**	**11 (4.5%)**	**50 (5.7%)**	**59 (6.5%)**
1 episode	0	11 (4.5%)	47 (5.3%)	54 (5.9%)
2 episodes	0	0	2 (0.2%)	4 (0.4%)
3 episodes	0	0	1 (0.1%)	1 (0.1%)
> 3 episodes	0	0	0	0
Subjects experiencing a non-peanut-related food allergy episode	**2 (0.9%)**	**23 (9.4%)**	**169 (19.2%)**	**184 (20.3%)**
1 episode	2 (0.9%)	17 (7.0%)	117 (13.3%)	122 (13.4%)
2 episodes	0	5 (2.0%)	26 (3.0%)	32 (3.5%)
3 episodes	0	0	9 (1.0%)	11 (1.2%)
> 3 episodes	0	1 (0.4%)	17 (1.9%)	19 (2.1%)
Subjects experiencing an accidental food allergy episode	**2 (0.9%)**	**32 (13.1%)**	**184 (20.9%)**	**208 (22.9%)**
1 episode	2 (0.9%)	28 (11.5%)	130 (14.8%)	145 (16.0%)
2 episodes	0	3 (1.2%)	29 (3.3%)	36 (4.0%)
3 episodes	0	0	12 (1.4%)	12 (1.3%)
> 3 episodes	0	1 (0.4%)	13 (1.5%)	15 (1.7%)
Subjects experiencing a non-accidental food allergy episode	**0**	**4 (1.6%)**	**31 (3.5%)**	**35 (3.9%)**
1 episode	0	3 (1.2%)	22 (2.5%)	25 (2.8%)
2 episodes	0	1 (0.4%)	4 (0.5%)	5 (0.6%)
3 episodes	0	0	4 (0.5%)	4 (0.4%)
> 3 episodes	0	0	1 (0.1%)	1 (0.1%)
Subjects experiencing any food allergy episodes that was an SAE	**0**	**0**	**4 (0.5%)**	**4 (0.4%)**
Subjects experiencing any food allergy episodes that required treatment	**1 (0.4%)**	**22 (9.0%)**	**159 (18.0%)**	**179 (19.7%)**
Subjects experiencing any food allergy episodes that required epinephrine use	**0**	**5 (2.0%)**	**39 (4.4%)**	**43 (4.7%)**

Source: Table 14.3.1.14

Denominators for percentages were based on the number of subjects who were at risk during the corresponding study period. Treatment-emergent food allergy episodes included food allergy episodes that occurred after first dose of AR101 in ARC008 through 30 days after last dose of study product, but excluding food allergy episodes that occurred during or were related to a food challenge.

Abbreviation: SAE, serious adverse event.

EoE

EoE (all in Treatment Pathways 1 and 3), diagnosed by biopsy/endoscopy, occurred in 7 (0.8%) subjects overall during the treatment period; these events led to discontinuation of study product in all 7 subjects. EoE was grade 1 in 2 (0.2%) subjects, grade 2 in 4 (0.4%) subjects, and grade 3 in 1 (0.1%) subject.

Additional EoE events, including those during follow-up, are listed by subject in Listing 16.2.8.10.

CHMP comment:

The description of EoE events in ARC008 CSR seems incomplete and is not comprehensible. The MAH refers to 7 events which occurred during AR101 treatment period. However, section 14.3.3. lists 11 EoE events, which based on information provided in AR101 IB Edition 10 also occurred during AR101 treatment. In fact, IB Edition 10 lists 13 EoE events for ARC008. 2 of these events are recorded as non-related, which might explain the discrepancy of 11 versus 13 events.

Upon request, the MAH provided a clarification on number of EoEs during ARC008 and presented information (see response to question 6). It is understood that the discrepancy is caused by events diagnosed under current treatment and events diagnosed during safety follow-up. Nevertheless, even if diagnosed after actual AR101 exposure, also most events detected during safety follow-up were considered related. Therefore, the presentation of numbers in ARC008 CSR is misleading. However, the discrepancies have been clarified. The three cases listed as not related raise doubts about their classification (related/non-related), but will not be discussed further at this point as EoE is already an identified adverse reaction and the frequency described so far will not be any different.

Besides, it seems that also only those events that were diagnosed under current treatment are reflected in the PI. The MAH is requested to update this information in the PI based on all treatment-related EoE cases occurring in AR101 clinical trials (see section 3.).

2.3.3. Discussion on clinical aspects

Introduction/Study Aim

AR008 is an open-label, longer-term follow-on study of AR101 in subjects who participated in a previous AR101 clinical study. The overarching aim of this study was to (1) determine the safety and tolerability during longer-term administration and (2) to perform follow-up observation after the last dose of Palforzia. The pre-formulated rationale for conducting ARC008 was as follows:

- To allow subjects who received placebo in MAH clinical studies with AR101 to receive AR101 drug product.
- To allow subjects who received AR101 in MAH clinical studies to continue treatment.
- To assess safety and tolerability during longer-term administration of AR101 and follow up observation after the last dose of AR101.
- To explore whether the level of desensitization to peanut protein was maintained or continued to increase after longer-term administration of AR101 and follow up observation after the last dose of AR101.

The MAH currently presented data on safety and tolerability during longer-term administration of AR101 and the level of desensitization achievable through extended maintenance dosing of AR101. This is acknowledged, correspondent data will be discussed below.

However, in reflection of the pre-specified objectives and endpoints, no to limited data is presented on the follow-up observation period after the last dose of AR101. This aspect was included to assess "sustained clinical effect of AR101 treatment". Likewise, limited data / in parts only raw data is presented for the interaction of AR101 on asthma control or nasal allergy symptoms in correspondent subjects, and more importantly no data on QoL of patients and families during AR101 treatment has been submitted (see discussion below).

Baseline Data

As per CSR, in this phase 3, international, open-label, longer-term study of an AR101 regimen in children and adults with peanut allergy, included subjects entering ARC008 were prior participating in one of the MAH AR101 clinical studies. However, the dosing regimens and procedures in the parent studies were not uniform. Correspondingly, baseline characteristics of included subjects varied not only in terms of age, but also in terms of Ig parameters (due to subjects being randomized to placebo or AR101 in the parent study), or for instance history of concomitant diseases, including asthma. Furthermore, presented results regarding efficacy or safety outcomes need to be assessed in reflection of dosing, dosing regimen (frequency), or duration etc.

Of 911 subjects, which were screened and enrolled, 582 (63.9%) were assigned to Treatment Pathway 1, 27 (3.0%) to Treatment Pathway 2, 190 (20.9%) to Treatment Pathway 3, 72 (7.9%) to Treatment Pathway 4, and 40 (4.4%) to Treatment Pathway 5.

881 (96.7%) subjects entered the initial or extended maintenance period. As the study progresses, it becomes apparent that the number of participants is thinning out considerably. Only 134 (14.7%) entered the follow-up observation period.

Study discontinuation

During the MAA process the relatively high treatment effort in daily life has been discussed in detail. As such for example, reflection on co-factors is outlined in the SmPC Table 5: Management of co-factors. During the current proceedings it was adequately explained that within ARC008, AR101 treatment discontinuations were mainly due to withdrawal of consent and sponsor's decision to terminate the study early. For study discontinuation, the main reason was sponsor's decision.

The main reasons for withdrawal of consent include dislike of the study drug, transitioning to other forms of treatment and practical reasons.

Efficacy

A total of 107 (11.8%) subjects overall (including parent studies) had ≥ 5 years total AR101 exposure. A total of 164 (18.1%) subjects and 210 (23.1%) subjects overall (including parent studies) had 4 to< 5 years and 3 to < 4 years total AR101 exposure, respectively.

In principle, response rates in the DBPCFCs at End of Treatment by total AR101 exposure showed generally consistent and expected patterns for treatment duration. As per CSR, a DBPCFC was performed as End of Treatment by total AR101 exposure. Overall n= 211 subjects received a DBPCFC. Evaluation of efficacy endpoints reveals that response rates in the DBPCFCs at End of Treatment by total AR101 exposure showed with the majority of subjects tolerating at least 1000 mg of peanut protein after 1 or more years of treatment. This treatment effect was rather constant over time up to > 5 years of exposure and observed in both age groups. Response rates obtained from the OLFCs (required in pathways 4 + 5 after 12 months of AR101, and optional in all pathways every 12 months) and obtained from the DBPCFCs (End of treatment) by total AR101 exposure were overall consistent.

In terms of OLFC, it is noted that constantly a few subjects did not tolerate even the lowest step of the (4 steps: 300, 600, 1000, 2000mg) provocation regimen, e.g. Extended maintenance: Month 12 – n=9

(2%), Month 24 – n=1 (0.5%), respectively overall n=6 (1.2%) did not tolerate 3 mg, as shown in Table 3 OLFC by total exposure (ARC008 - Report Body). In this context, the MAH emphasized that in general, OLFC is inferior to the double-blind, placebo-controlled food challenge (DBPCFC), and that there are occasional false positive results stemming from symptoms and objective findings that are not due to an IgE-mediated reaction (e.g. anxiety on the test day with associated flaring of eczema, urticaria, and/or subjective throat tightness could be interpreted as evidence of a positive challenge). The MAH further explained that the OLFC during the extended maintenance phase started with the lowest dose of 300 mg. A patient not tolerating this dose was documented with a MTD of 0 mg. The definite reasons why patients did not tolerate at least the dose of 300 mg (AR 101 maintenance dose) can only be speculated and could be both, false positive or false negative results.

In general, mean wheal diameter (SPT), and Peanut-specific IgE (after initial increase) decreased over time of total AR101 exposure from parent study baseline. This is acknowledged.

Safety

908 (99.7%) subjects received AR101 during ARC008 and thus corresponded to the definition of the Safety Population.

Generally spoken, the results of this study were consistent with the established safety profile of AR101 from previous pivotal clinical studies, with a predominance of AEs being allergic in etiology. It may be agreed that overall, no new safety concerns for AR101 were identified during longer-term follow-up. However, some aspects should be evaluated further:

Table 5 depicts the (known) observed high rates of subjects with at least 1 TEAEs during up-doing (93.9%). Presented rates in Table 5 **newly suggests a certain peak of TEAEs** in the time period of 1 to 2 (81.2%), respectively 2 to 3 years (79.8%), whereas presented rates are lower for treatment periods < 1 year (65.2%), 3 to 4 yrs (65.1%), 4 to 5 yrs (59%) or >5 yrs (52.3%). Likewise, treatment related TEAEs are most pronounced (as already described) during the up-dosing phase (79.5%), followed by 40.9% between 1 to 2 yrs treatment and a bit less with 31.7% <1 year of AR101 treatment. In opposite, starting with around 2 to 3 - 3 to 4 years of AR101 treatment, non-treatment related TEAES seem to be levelling off at 43-45% without having the above discussed peak.

TEAEs requiring dose reduction, leading to study withdrawal, emergent GI AEIs, anaphylactic reactions, epinephrine, non-study-product food allergen exposure, hypersensitivity related event **all seem to be slightly more pronounced in the time frame 1-2yrs, respectively 2-3 years of AR101 treatment**. Thus, especially, the pronounced occurrence of TEAEs that is associated with accidental/non-accidental non-study product food allergen exposure, respectively TEAEs that is an anaphylactic reaction, is striking. These are almost 1.5 to 2 times as often if you compare the number of treatments under one year with those of 1 to 2 years, or 2 to 3 years of treatment.

The MAH provided some explanation regarding changes in number of occurrence of TEAEs that are associated with accidental/non-accidental non-study product food allergen exposure and TEAEs that are anaphylactic reactions. It is highlighted that direct comparison across treatment years might be biased by the different treatment pathways (e.g. duration of AR101 exposure in parent study).

It is further discussed that patients (and their caregivers) received continuous training regarding peanut avoidance and allergy training. This might over time have reduced occurrence of peanut-related but also other food-related TEAEs. It is therefore regarded as important that during these trainings the consequent treatment adherence including the daily intake are mandatory to maintain the gained efficacy. This is also reflected in the PI. Management of co-factors need to be trained consequently likewise. Information on co-factors is available in the PI.

As already known from previous studies, GI disorders remain a constant problem. Here too, **GI disorders** (including vomiting, abdominal pain, nausea, abdominal pain upper, abdominal discomfort etc.) were observed in 187 cases (80.7%) during up-dosing and 564 (64%) during maintenance (Treatment-Emergent AEs, Table 6). In terms of Treatment-Related AEs, GI disorders are depicted with overall 44.6%, during up-dosing 68% and during maintenance with 36.4% (Table 7). Upon request of supplementary information, the MAH emphasized again that treatment related GI AEs across exposure time indicate that patients are at a higher risk of a GI event during up-dosing. After this, the risk of a GI event is lower and appears to lessen with long-term AR101 exposure (> 3 years).

An interplay of GI disorders with ARFID (Avoidant/Restrictive Food Intake Disorder (ARFID) or likely ARFID (L-ARFID/GI)) has been described in literature (Int J Eat Disord. 2021 Jun;54(6):995-1008). However, it was stressed by the MAH that the clinical program was not designed for the collection of adequate endpoints to draw meaningful conclusions on this topic. Still, the MAH provided an additional detailed discussing regarding potential risk of ARFID in relation to AR101 treatment and concludes that there is no clear evidence of ARFID or events potentially consistent with this eating disorder in the ARC008 study - even if eating disorder cases were observed in the study collective. Based on the information provided, this conclusion can be agreed.

Treatment-emergent GI AEs of interest occurred in 30/908 (3.3%) subjects. The latter includes 3 categories of subjects: 1) Any subject whose dose is withheld for > 7 days due to GI AEs and resumes dosing at a reduced dose level; 2) Any subject who develops chronic/recurrent GI AEs at or before reaching the 20 mg dose level and resumes dosing after a 30-day dosing hiatus; 3) Any subject who experienced GI AEs and discontinues early from the study. Following the presentation in Table 5, theses treatment-emergent GI AEIs remain constant over the observed time period of up to 5 years with levelling around 1% between 1 to 2 years and > 5 years. In addition, it should be noted, that cases of EoE (all in Treatment Pathways 1 and 3), diagnosed by biopsy/endoscopy, had been stated to occur in 7 (0.8%) subjects overall during the treatment period. This observation may be interpreted that, despite prior longer-term treatment, **the risk for developing EoE seems to remain**.

Treatment-emergent systemic allergic reaction (**anaphylactic reaction**) occurred in 192/908 (21.1%) subjects overall, of which in **146/908 (16.1%)** subjects the reaction was classified as Treatment-related. Most cases of Treatment-emergent systemic allergic reaction (anaphylactic reaction) occurred again during up-dosing with 30/244 (12.3%) subjects, followed by the time period from 1 to < 2 years with 82/749 (10.9%) subjects, from 2 to <3 years with 60/674 (8.9%) subjects, from 4 to < 5 years 18/271 (6.6%) subjects and from 4 to < 5 years. 31/480 (6.5%) subjects had a reaction during the first year of AR101 exposure. Thus, again a certain peak / increase of reaction is observed in the time period from 1 to < 2 years and from 2 to <3 years. The same observation is seen, when focusing on anaphylactic reactions which led to discontinuation: Overall anaphylactic reaction led to discontinuation of study product in 17/908 (1.9%) subjects. Interestingly, most cases had been observed from 1 to < 2 years with 8/749 (1.1%) subjects and from 2 to < 3 years with 5/674 (0.7%) subjects.

Non-daily regimen

N = 64 subjects had been disposed to a non-daily dosing regimen. According to the MAH, these 64 subjects had been disposed to a twice weekly (BIW) dosing regimen with a median treatment exposure of 959.0 days (range, 42-1762 days) in ARC008. It is described that one subject switched back to daily dosing. Overall the treatment-related adverse events were reported of being consistent with the safety profile of AR101 for all subjects in ARC008. The PI currently reflects the following: "*Strict daily, long-term dosing in conjunction with a peanut-avoidant diet is required to achieve desensitisation and maintain the treatment effect of PALFORZIA. Treatment interruptions, including non-daily dosing, may potentially lead to an increased risk of allergic reactions or even anaphylaxis*." Based on the low numbers of subject's who experienced this non-daily dosing, this statement should remain.

Follow-up observation period

As per ARC008-Report Body, this follow-up observation period after the last dose of AR101 was included to assess **sustained clinical effect** of AR101 treatment.

According to the CSR, this follow-up observation period was planned for all treatment pathways. During this 12-month observation period, which followed the End of Treatment visit, several phone calls were scheduled. As such, it was enquired about the current treatment plan of the subject (eg commercially available product, use of food equivalents or else), and event(s) of systemic allergic reactions, EoE, accidental/nonaccidental exposures to food allergens and their outcomes, use of epinephrine, hospitalizations etc. It is noticed in Table 11, that (only) n=134 (14.7%) entered the follow-up observation period.

The MAH describes that of these 134 subjects who entered this period, 122 subjects reported their peanut allergy treatment plan during follow-up guided by the subjects' physician. Peanut allergy treatment during follow-up were as follows: food equivalent for peanut oral immunotherapy (83.6%), commercially available product (Palforzia) (13.9%), and complete peanut avoidance or other (6.6% each). The MAH further declares that however, a sustained efficacy of the effects of AR101 treatment after the end of treatment (i.e., subjects who had 1 year of complete peanut avoidance) could not be assessed.

Quality of Life

The evaluation of subjects' and caregivers Quality of Life, including treatment satisfaction during AR101 treatment on daily and non-daily treatment regimens was predefined as secondary objective.

Provided data on QoL aspects describes that treatment resulted in improved subject-reported FAQLQ scores for subjects and parental burden. Improvements in parent-reported FAQLQ scores were noted, though not clinically significant. Treatment with AR101 resulted in improved subject-reported and parent-reported Food Allergy Independent Measure (FAIM) scores.

3. CHMP overall conclusion and recommendation

Study ARC008 was a multicenter, open-label, longer-term investigation of AR101, an oral desensitization immunotherapy, focusing on participants from prior AR101 studies. This specific study serves as a long-term assessment of AR101 safety and tolerability during extended administration, along with post-treatment follow-up. As the parent studies were not completely uniform, certain baseline characteristics of included subjects varied, and results regarding efficacy or safety outcomes need also to be assessed in reflection of dosing, dosing regimen (frequency), or duration of treatment accordingly.

Response rates in the Double-blind Placebo-Controlled Food Challenge (DBPCFC) at the "End of Treatment" visit, and in the open-label food challenge (OLFC) by total exposure (meaning AR101 exposure during ARC008 and parent studies), respectively, showed generally consistent and expected patterns for treatment duration. As such, the majority of subjects tolerated at least 1000 mg of peanut protein after 1 or more years of treatment.

The established safety profile of AR101 was in principle confirmed, with a predominance of AEs being allergic in etiology. New safety concerns for AR101 were not identified. When looking at the presentation of the TEAEs over the entire study period (from dose escalation up to ≥ 5 years of total AR101 exposure), most TEAEs occurred during up-dosing. In addition, the impression is given that, after a decrease within the first year of treatment, some TEAEs seem to be slightly more pronounced in the time frame 1-2 years, respectively 2-3 years of AR101 treatment. But here, too, it is important to remember that direct comparison across treatment years might be biased by the different treatment pathways (e.g. duration of AR101 exposure in parent study). Nevertheless, the importance of ongoing allergy education including management of co-factors for patients (and their caregivers) was confirmed.

Generally, a higher risk of GI events (like vomiting, abdominal pain, nausea, etc.) was observed during up-dosing, and it appears to be lessened with long-term AR101 exposure (> 3 years). It should be emphasized, that in ARC008 in total 13 cases of eosinophilic oesophagitis (EoE) had been observed. This observation may be interpreted that, despite prior longer-term treatment, the risk for developing EoE seems to remain. Currently, there were a total of 22 cases of EoE reported in the global safety database. As, it seems that only the events of EoE that were diagnosed under the current treatment are reflected in the product information, the MAH is requested to update this information based on all treatment-related EoE cases occurring in AR101 clinical trials, as appropriate. In addition, the RMP should be updated at the next regulatory opportunity, i.e. as part of the next application or as a stand-alone variation.

Of those subjects who entered the (post-treatment) follow-up observation period after the last dose of AR101 was given, peanut allergy treatment was presented as follows: 83.6% switched to food equivalent for peanut oral immunotherapy, 13.9% to the commercially available product (Palforzia), and complete peanut avoidance or "other" was practiced by 6.6% each. It was further declared that a sustained efficacy of the effects of AR101 treatment after the end of treatment (i.e., subjects who had 1 year of complete peanut avoidance) could not be assessed.

☒ **Fulfilled:**

In view of the available data regarding all treatments-related eosinophilic oesophagitis (EoE) cases occurring in Palforzia clinical trials, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and no later than 60 days after the receipt of these conclusions. (Please see question 6 for further details below).

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. **Subject disposition**: Please clarify

    1.1. Nearly 80% (n=710) did not complete all dosings as defined in the protocol and more than 50% (n=478) did not complete the study per protocol. (ARC008 Report Body, Tabl. 6). Please comment and summarize/describe reasons for these high percentages.

    1.2. In terms of "Withdrew consent (unrelated to AE)" with n= 352 (38.6%), please give more information on reasons behind these withdrawals.

Efficacy

2. It is noted that in the OLFCs constantly a few subjects did not tolerate even the lowest step of the open provocation regimen, e.g. as shown in Table 3 OLFC by total exposure (ARC008 - Report Body). Please explain.

Safety

3. There seems to be a pronounced occurrence of TEAEs that are associated with accidental/non-accidental non-study product food allergen exposure, respectively TEAEs that are anaphylactic reactions. Regarding the first year of treatment, the number of these TEAEs are almost 1.5 to 2 times higher than between 1 to 2 years, or 2 to 3 years of treatment. Please comment and describe possible reasons for this observation (including based on QoL data).

4. GI disorders (including vomiting, abdominal pain, nausea, abdominal pain upper, abdominal discomfort etc.) were observed in 197 subjects (80.7%) during up-dosing and 564 (64%) during Maintenance (Table 6, ARC008 - Report Body). In terms of Treatment-Related AEs, GI disorders are depicted with overall 44.6% (Table 7). In order to determine whether these symptoms change in frequency over a period of up to 5 years or more, the MAH is asked to depict occurrence of symptoms over time (<1 year, after 1 to <2 years, 2 to < 3 years, 3 to < 4 years, 4 to < 5 years, or ≥ 5 years of AR101 exposure).

5. An interplay of GI disorders with ARFID (Avoidant/Restrictive Food Intake Disorder (ARFID) or likely ARFID (L-ARFID/GI)) has been described in literature (Int J Eat Disord. 2021 Jun;54(6):995-1008). Therefore, the MAH should discuss if Palforzia (in a susceptible population) reinforce or induce eating behaviour in such a way that it is pathological (towards L-ARFID/GI) and may require improved therapy (e.g. psychotherapy, nutritional counselling) to optimize care. In this discussion, the described 6.7% of subjects who suffered from TEAE in the SOC 'psychiatric disorders' should be included**.**

6. The description of EoE events in ARC008 CSR seems incomplete and is not comprehensible:

    6.1. The MAH refers to 7 events which occurred during AR101 treatment period. However, section 14.3.3. lists 11 EoE events, which should have occurred during AR101 treatment based on information provided in AR101 IB Edition 10. However, IB Edition 10 lists in total 13 EoE events for ARC008. 2 of these events are recorded as non-related, which might explain the discrepancy of 11 versus 13 events. However, the discrepancy to the 7 events referred to in section 12.2.4.2.1 of the CSR is not plausible and should be explained and/or corrected accordingly.

    6.2. In addition, section 12.2.4.2.1 of the CSR refers to EoE events during follow-up. Respective Listing 16.2.8.10 is not available in the dossier. Considering that EoE events are of special

interest, the MAH is asked to provide information on EoE events including those events that might have occurred during follow-up.

7. In terms of non-AR101 peanut-related exposure episodes, the MAH is asked to present a description of when exactly these episodes were observed >1 year, after 1 to < 2 years, 2 to < 3 years, 3 to < 4 years, 4 to < 5 years, or ≥ 5 years of AR101 exposure. The same should be done with regard to systemic allergic reactions (anaphylactic reactions), events triggered by 'exposure to peanut or peanut-containing food', or food allergy episodes that required epinephrine.

8. Please submit data on non-daily treatment experience, experience of subjects after end of study (follow-up observation) and Quality of Life during treatment/influenced by AR101

   8.1. 64 subjects had been disposed to a **non-daily dosing** regimen. It is assumed that all these subjects derived from ARC004 where they tolerated the non-daily regimen. The MAH is asked to give more detail about this population in terms of: frequency of intake (e.g. every other day), duration (in total) of exposition non-daily or daily (in case of change). How many ARC004 subjects who tolerated the non-daily regimen in ARC004 but who subsequently did not tolerate the non-daily regimen after entering ARC008 switched to Treatment Pathway 1, or discontinued treatment? Please also present information on occurrence of treatment-related AEs.

   8.2. Please precise why only 134 subjects entered the **follow-up observation** period. Please also explain the reason(s) for the high numbers of missing 'End of Treatment', 'Disposition – Study Exit' and 'End of follow-up' forms. The footnotes (Tab. 6 Subject Disposition, ARC008-Report Body) do not appear meaningful enough, as they do not clarify whether "missing" is actually based on the fact that the study was terminated and thus no FU took place or if they are missing according to other reasons. Accordingly, some of the "missing" may then have to be renamed "Sponsor decision". Please clarify.

      8.2.1. The MAH stated in the ARC008-Report Body, Section 9.2 Discussion of Study Design, that data on sustained efficacy was assessed ("A follow-up observation period after the last dose of AR101 was included to assess sustained clinical effect of AR101 treatment"). However, the corresponding analysis has not been found. Please precise what is meant with "sustained effect" and submit corresponding data.

   8.3. The evaluation of subjects' and caregivers **QoL**, including treatment satisfaction during AR101 treatment on daily and non-daily treatment regimens was predefined as secondary objective. According data is missing and needs to be submitted as of relevance for the benefit/risk assessment.

The timetable is a 30-day response timetable with clock stop.

5. MAH responses to Request for supplementary information

1. **Subject disposition**: Please clarify

   1.1. Nearly 80% (n=710) did not complete all dosings as defined in the protocol and more than 50% (n=478) did not complete the study per protocol. (ARC008 Report Body, Tabl. 6). Please comment and summarize/describe reasons for these high percentages.

   1.2. In terms of "Withdrew consent (unrelated to AE)" with n= 352 (38.6%), please give more information on reasons behind these withdrawals.

Applicant Response to Question 1

Response to 1.1

Subject disposition was discussed and summarized in ARC008 CSR Section 10.1 (Table 11 from the CSR is also provided below).

Of the subjects enrolled into the parent studies, 99.7% (908/911) subjects were dosed with AR101 in ARC008. Of the enrolled subjects, 25.2% (230/911) subjects entered ARC008 from Treatment Pathways 3 and 5, i.e. these subjects received placebo in the parent study and were exposed to AR101 for the first time in ARC008.

Discontinuation of AR101

AR101 treatment was discontinued early during ARC008 in 77.9% (710/911) subjects, completed in 21.3% (194/911) subjects and treatment disposition was missing for 0.8% (7/911) subjects; the latter subjects did not have 'End of Treatment' forms. The main reasons for treatment discontinuation were withdrawal of consent (unrelated to adverse event [AE]) in 38.6% (352/911) subjects and sponsor decision in 22.9% (209/911) subjects. Further information on withdrawals of consent are discussed in part 2 of this response. As explained in the CSR, the reason for early treatment discontinuation due to

"sponsor decision" was due to the sponsor's decision to close the study as study objectives to assess the longer-term safety and efficacy of AR101 were fulfilled.

Therefore, withdrawal of consent and sponsor decision account for 79.0% (561/710) of the early treatment discontinuations. The remaining reasons for early treatment discontinuation that occurred in >2% of the enrolled population include "other" in 4.2% (38/911) subjects and chronic/recurrent gastrointestinal (GI) AEs/symptoms in 2.6% (24/911) subjects. Further details on "other" reasons are provided in part 2 of this response.

Study Discontinuation

The ARC008 study was discontinued early in 52.5% (478/911) subjects, completed in 2.0% (18/911) subjects and study completion data were missing for 45.6% (415/911) subjects; the latter subjects did not have Disposition – Study Exit forms (see explanation below). The main reason for study discontinuation where data were available was sponsor decision in 38.3% (349/911) subjects and withdrawal of consent (unrelated to AE) in 9.4% (86/911) subjects. The remaining reason for early study discontinuation that occurred in >2% of the enrolled population include "other" in 2.2% (20/911), Detailed reasons for withdrawal of consent (unrelated to AE) and other reasons for early study discontinuation are provided in Listing 16.2.1.

Disposition – Study Exit forms

In the ARC008 study, Disposition - Study Exit forms were introduced in Protocol Amendment 6.0 (22 December 2020) and did not exist prior to this amendment.

Disposition - Study Exit forms were not completed in 45.6% (415/911) subjects. Of these 415 subjects, 412 had not given informed consent/assent to Protocol Amendment 6.0 and thus did not complete the Disposition – Study Exit form. Last study visit date for 312/415 subject occurred before the introduction of Protocol Amendment 6.0 (22 December 2020). It is also likely that additional subjects reached last study last visit prior to IRB approval of Protocol Amendment 6.0.

The remaining 3 subjects (subjects 009-80178, 079-80546 and 109-80801) who were missing a Disposition - Study Exit form, did provide informed consent for Protocol Amendment 6.0.

Table 11: Subject Disposition (All Subjects)

	AR101
Number of subjects screened	911
Number of screen failures	0
Number of subjects enrolled	911
Safety population [1]	908 (99.7%)
Treatment Pathway	
1	582 (63.9%)
2	27 (3.0%)
3	190 (20.9%)
4	72 (7.9%)
5	40 (4.4%)
Initial ARC008 Dosing Regimen	
Daily	844 (92.6%)
Non-daily	64 (7.0%)
Unknown	3 (0.3%)
Entered initial escalation period [2]	229 (25.1%)
Entered up-dosing [3]	244 (26.8%)
Entered initial or extended maintenance period [4]	881 (96.7%)

Entered follow-up observation period [4]	134 (14.7%)
Did subject require follow-up due to chronic/recurrent GI symptoms?	
Yes	28 (3.1%)
No	883 (96.9%)
Completed all dosing as defined in the protocol	
Yes	194 (21.3%)
No	710 (77.9%)
Missing [5]	7 (0.8%)
Reason for early treatment discontinuation	
AE	26 (2.9%)
Allergen exposure	0
In clinic dosing symptom	1 (0.1%)
At home dosing event	8 (0.9%)
Chronic/recurrent GI AEs/symptoms	24 (2.6%)
Withdrew consent (unrelated to AE)	352 (38.6%)
Protocol violation	18 (2.0%)
Investigator decision (unrelated to AE)	13 (1.4%)
Sponsor decision	209 (22.9%)
Death	0
Lost to follow-up	18 (2.0%)
Pregnancy	0
COVID-19	3 (0.3%)
Other	38 (4.2%)
Completed study per protocol	
Yes	18 (2.0%)
No	478 (52.5%)
Missing [6]	415 (45.6%)
Reason for early study discontinuation	
AE	0
Allergen exposure	0
Chronic/recurrent GI AEs/symptoms	0
Withdrew consent (unrelated to AE)	86 (9.4%)
Protocol violation	2 (0.2%)
Investigator decision (unrelated to AE)	13 (1.4%)
Sponsor decision	349 (38.3%)
Death	0
Lost to follow-up	7 (0.8%)
Pregnancy	0
COVID-19	1 (0.1%)
Other	20 (2.2%)

Completed safety follow-up per protocol	
Yes	9 (1.0%)
No	514 (56.4%)
Missing [7]	388 (42.6%)
Reason for premature discontinuation from follow-up	
AE	0
Allergic AE	0
Dosing symptom	0
Chronic/recurrent GI AEs/symptoms	0
Withdrew consent (unrelated to AE)	3 (0.3%)
Protocol violation	1 (0.1%)
Investigator decision (unrelated to AE)	2 (0.2%)
Sponsor decision	0
Death	0
Lost to follow-up	5 (0.5%)
Pregnancy	0
COVID-19	0
Other	10 (1.1%)
Missing	493 (54.1%)

Source: Table 14.1.1
Denominators for percentages were based on total subjects screened for screen failure and based on number of enrolled subjects for all other percentages.
[1] Safety population included all subjects who received AR101 during ARC008.
[2] Treatment Pathways 3 and 5.
[3] Treatment Pathways 2, 3, and 5.
[4] All Treatment Pathways.
[5] Subjects in the 'Missing' category did not have 'End of Treatment' forms.
[6] Subjects in the 'Missing' category did not have Disposition - Study Exit forms.
[7] Subjects in the 'Missing' category did not have 'End of Follow-Up' forms.
Abbreviations: AE, adverse event; COVID-19, Coronavirus Disease 2019; GI, gastrointestinal.

Response to 1.2

Listing 16.2.1 has been revised to include the detailed comments on early treatment discontinuation for reasons of "withdrew consent (unrelated to AE)". This listing also provides detailed comments on "other" reasons for early treatment discontinuation. These verbatim fields are not categorized further, however from visual inspection of the listing, examples of frequent reasons given include the following:

- Dislike of the AR101 taste and / or texture
- Subject's schedule / schooling no longer allows for study visits
- Withdrew to start clinical oral immunotherapy
- Withdrew to transition to food product / real-world peanut / peanut candy
- Study fatigue / too many food challenges
- Family / subject decision
- Moved and did not wish to transfer site / Transition to college and finding it difficult
- At one site: "Subject has been on 300 mg for at least 12 months, completed OLFC (open-label food challenge), and completed RWFC (real-world food challenge)"

Assessment of response:

The MAH provided a thorough explanation regarding the reasons for discontinuation of AR101 of study discontinuations. AR101 treatment discontinuations were mainly due to withdrawal of consent and sponsor's decision to terminate the study early. For study discontinuation, the main reason was sponsor's decision. It was further clarified that the high number of missing 'Disposition – Study Exit Form' was partly due to late introduction of this form with protocol amendment 6 (22 December 2020).

In part 2 of the response, the sponsor provided some further insight into reasons for withdrawal of consent. The reasons include dislike of the study drug, transitioning to other forms of treatment and practical reasons.

The provided information is acknowledged.

The issue is solved.

Efficacy

2. It is noted that in the OLFCs constantly a few subjects did not tolerate even the lowest step of the open provocation regimen, e.g. as shown in Table 3 OLFC by total exposure (ARC008 - Report Body). Please explain.

Applicant Response to Question 2

In the ARC008 study, the open-label food challenge (OLFC) at the end of Initial Maintenance (for subjects in Treatment Pathway 5 only) started at 3 mg peanut protein (with challenge doses of 3, 10, 30, 100, 300, 600, 1000, and up to 2000 mg peanut protein). The OLFC during Extended Maintenance (all treatment pathways, approximately every 12 months) started at 300 mg peanut protein (challenge doses of 300, 600, 1000, and 2000 mg peanut protein). Subjects who did not tolerate this first challenge dose of 300 mg were assigned a dose of 0 mg as their tolerated dose.

Of the 517 subjects who had an OLFC, 7 (1.4%) subjects were included in the statistical summary with a maximum tolerated dose (MTD) below 300 mg of peanut protein during the last available OLFC: 1 subject with an MTD of 100 mg and 6 subjects with an MTD of 0 mg (ARC008 CSR Table 3).

A summary of individuals with MTD < 300 mg at any OLFC timepoint is provided in Table 12. Subjects who comprise the 7 subjects identified in ARC008 CSR Table 3. are highlighted in bold text. The listing below also includes subjects with MTD < 300 mg at earlier OLFC timepoints. All subjects with an MTD recorded as 0 mg were exposed to a starting dose of 300 mg in the OLFC which was not tolerated. Two subjects with an MTD of 100 mg had started the challenge at the lowest dose of 3 mg.

Table 12: Listing of Subjects with MTD <300 mg During an OLFC

Case no.	Years Of Total AR101 Exposure	Time Point	MTD (mg peanut protein)	Symptoms at 300 mg Challenge Dose
CN01	**2.6**	**Ext Maint: Month 12**	**0**	**Mild abdominal pain**
CN02	**2.7**	**Ext Maint: Month 12**	**0**	**Mild abdominal pain, throat irritation**
CN03	2.6	Ext Maint: Month 12	0	Mild lip swelling, urticaria, pruritus
	3.8	Ext Maint: Month 24	1000	-
CN04	1.9	Ext Maint: Month 12	2000	-
	2.9	**Ext Maint: Month 24**	**0**	**Mild cough, rash**
CN05	2.0	Ext Maint: Month 12	0	Moderate nasal congestion
	3.0	Ext Maint: Month 24	2000	-
	4.0	Ext Maint: Month 36	1000	-
CN06	3.3	Ext Maint: Month 12	0	Mild lip oedema, pruritus, rash, throat irritation, abdominal pain, eye pruritus, cough
	4.3	Ext Maint: Month 24	1000	-
CN07	2.2	Ext Maint: Month 12	0	Mild abdominal discomfort, conjunctivitis, asthenia
	3.3	Ext Maint: Month 24	300	-
CN08	**1.6**	**Ext Maint: Month 12**	**0**	**Mild oral pruritus**
CN09	**2.2**	**Ext Maine Month 12**	**0**	**Mild urticaria, sneezing, pruritus**
CN10	**1.0**	**End of Initial Maint**	**100**	**Mild urticaria, rhinitis, nasal congestion**
CN11	1.0	End of Initial Maint	100	Mild urticaria, rhinorrhoea. sneezing
	1.9	Ext Maint: Month 12		-
CN12	**2.0**	**Ext Maint: Month 12**	**0**	**Mild cough, abdominal discomfort, urticaria**

Source: ARC008 Listing 16.2.5.1. Listing 16.2.5.4
Bolded subjects had a MTD < 300 mg of peanut protein during the last available OLFC
Ext Main, Extended Maintenance; Initial Maint, Initial Maintenance; MTD, maximum tolerated dose.

It is not known precisely why a few subjects in ARC008 did not tolerate doses of ≤300mg of peanut protein during the OLFC, although the applicant believes that false positive OLFC results contributed in at least some of the cases. In general, OLFC is inferior to the double-blind, placebo-controlled food challenge (DBPCFC) for diagnosing allergy to a specific food, and while the DBPCFC is considered the gold standard, there are occasional false positive results stemming from symptoms and objective findings that are not due to an IgE-mediated reaction. For example, anxiety on the test day with associated flaring of eczema, urticaria, and/or subjective throat tightness could be interpreted as evidence of a positive challenge. This was reported in a retrospective study by an experienced food allergy center in Germany where 21 of 740 (2.8%) placebo oral challenges were assessed as positive, and the rate of placebo reactors among young children ≤1.5 years was 4% (Ahrens et al., 2014).

It is also possible that these OLFC results were true positives, reflecting an unexpected change in reaction threshold. Potential explanations for this include poor adherence to study medication doses in the days/weeks prior to the OLFC or the presence of co-factors on the challenge day (eg, viral upper respiratory infection, poor sleep). As the OLFC during Extended Maintenance was conducted with 300 mg peanut protein as the first challenge dose, it is unknown if subjects would have tolerated lower challenge doses on food challenge days. However, since all subjects successfully tolerated 300 mg of AR101 prior to the challenge, it is unlikely that this would dramatically reverse with short term poor adherence or in the presence of co-factors.

Assessment of response:

The MAH provided some additional information regarding patient's not tolerating even the lowest step during the OLFC. It is highlighted that the OLFC during the extended maintenance phase started with the lowest dose of 300 mg. A patient not tolerating this dose was documented with a MTD of 0 mg.

The definite reasons why patients did not tolerate at least the dose of 300 mg (AR 101 maintenance dose) can only be speculated and could be both, false positive or false negative results.

The additional information provided by the MAH is acknowledged.

The issue is solved.

Safety

3. There seems to be a pronounced occurrence of TEAEs that are associated with accidental/non-accidental non-study product food allergen exposure, respectively TEAEs that are anaphylactic reactions. Regarding the first year of treatment, the number of these TEAEs are almost 1.5 to 2 times higher than between 1 to 2 years, or 2 to 3 years of treatment. Please comment and describe possible reasons for this observation (including based on QoL data).

Applicant Response to Question 3

ARC008 is an open-label, follow-on study for all prior AR101 studies, with subjects starting or continuing AR101 in ARC008 at different time points of treatment as follows:

Treatment Pathway	Prior Study	Duration of Treatment from Prior Study [1]
1	ARC002 (ARC001 follow-on)	22 weeks
	ARC004 (ARC003 follow-on)	17.8 months (former ARC003 placebo-treated) 19.4 months (former ARC003 AR101-treated): 6.4-13 months daily dosing in ARC004 6.8-13.4 months non-daily dosing in ARC004
	ARC010	8.52 months
	ARC011 (ARC007 follow-on)	11.2 months (5.6 months maintenance only in ARC011 plus 5.6 months up-dosing in ARC007)
2	ARC004 (ARC003 follow-on) ARC007 ARC010	Variable. Subjects had up-dosing/repeat up-dosing or initial maintenance if they had any of the following: - Did not complete their dosing regimen - Received a non-daily dosing regimen and did not tolerate it (ARC004 only) - Missed or withheld their non-daily dose for > 3 days, or who received non-daily dosing regimen and tolerated < 300 mg peanut protein at the exit DBPCFC (ARC004 only)
3	ARC007	0 (former placebo-treated subjects)
	ARC010	0 (former placebo-treated subjects)
4	ARC005	12.24 months
5	ARC005	0 (former placebo-treated subjects)

Source: Module 5.2.

[1] Duration of treatment for the primary study population (4-26 years for ARC001, ARC002; 4-17 years for ARC003, ARC004, ARC007, ARC010, ARC011; and 1 to < 4 years for ARC005) is provided as median exposure to AR101.

For the ARC008 CSR by exposure analyses, total AR101 exposure was calculated based on all AR101 exposure including parent studies; whereas, adverse events were included that occurred during participation in ARC008 maintenance only.

Of the 908 subjects in the safety population, 654 (72.0%) subjects continued their extended maintenance regimen from their parent study in ARC008 (582 subjects in Treatment Pathway 1 and 72 subjects in Treatment Pathway 4). If a subject reported adverse events during maintenance in a parent

study prior to ARC008 enrollment, these adverse events were not counted in the ARC008 analyses within the exposure period that corresponded to the time in the parent study. Therefore, adverse events during all exposure periods are those reported in ARC008 only and do not include all events subjects experienced during the entire course of their AR101 treatment, such that direct comparisons of event incidence across years of exposure cannot be made.

Treatment-emergent food allergen episodes are summarized by total AR101 exposure period in Table 13.

Table 13: Treatment-Emergent Food Allergen Episodes by Total AR101 Exposure (Safety Population)

Table 2: Treatment-Emergent Food Allergen Episodes by Total AR101 Exposure (Safety Population)

	Total AR101 Exposure [1]								
	IDE (N=229)	Up-Dosing (N=244)	<1 yr [2] (N=480)	1 to <2 yr (N=749)	2 to <3 yr (N=674)	3 to <4 yr (N=481)	4 to <5 yr (N=271)	≥5 yr (N=107)	Overall (N=908)
Subjects experiencing any food allergy episodes	2 (0.9%)	33 (13.5%)	30 (6.3%)	100 (13.4%)	71 (10.5%)	32 (6.7%)	17 (6.3%)	4 (3.7%)	227 (25.0%)
1 episode	2 (0.9%)	26 (10.7%)	23 (4.8%)	76 (10.1%)	58 (8.6%)	29 (6.0%)	13 (4.8%)	3 (2.8%)	153 (16.9%)
2 episodes	0	6 (2.5%)	5 (1.0%)	12 (1.6%)	9 (1.3%)	3 (0.6%)	2 (0.7%)	0	40 (4.4%)
3 episodes	0	0	1 (0.2%)	8 (1.1%)	2 (0.3%)	0	0	1 (0.9%)	13 (1.4%)
> 3 episodes	0	1 (0.4%)	1 (0.2%)	4 (0.5%)	2 (0.3%)	0	2 (0.7%)	0	21 (2.3%)
Subjects experiencing a peanut-related food allergy episode	0	11 (4.5%)	7 (1.5%)	21 (2.8%)	11 (1.6%)	9 (1.9%)	4 (1.5%)	0	59 (6.5%)
1 episode	0	11 (4.5%)	7 (1.5%)	21 (2.8%)	10 (1.5%)	9 (1.9%)	4 (1.5%)	0	54 (5.9%)
2 episodes	0	0	0	0	0	0	0	0	4 (0.4%)
3 episodes	0	0	0	0	1 (0.1%)	0	0	0	1 (0.1%)
> 3 episodes	0	0	0	0	0	0	0	0	0
Subjects experiencing a non-peanut-related food allergy episode	2 (0.9%)	23 (9.4%)	25 (5.2%)	85 (11.3%)	61 (9.1%)	23 (4.8%)	15 (5.5%)	4 (3.7%)	184 (20.3%)
1 episode	2 (0.9%)	17 (7.0%)	20 (4.2%)	66 (8.8%)	49 (7.3%)	20 (4.2%)	12 (4.4%)	3 (2.8%)	122 (13.4%)
2 episodes	0	5 (2.0%)	3 (0.6%)	8 (1.1%)	9 (1.3%)	3 (0.6%)	1 (0.4%)	0	32 (3.5%)
3 episodes	0	0	1 (0.2%)	7 (0.9%)	2 (0.3%)	0	0	1 (0.9%)	11 (1.2%)
> 3 episodes	0	1 (0.4%)	1 (0.2%)	4 (0.5%)	1 (0.1%)	0	2 (0.7%)	0	19 (2.1%)
Subjects experiencing any food allergy episodes that was an SAE	0	0	0	3 (0.4%)	0	1 (0.2%)	0	0	4 (0.4%)
Subjects experiencing any food allergy episodes that required treatment	1 (0.4%)	22 (9.0%)	21 (4.4%)	77 (10.3%)	48 (7.1%)	26 (5.4%)	14 (5.2%)	4 (3.7%)	179 (19.7%)
Subjects experiencing any food allergy episodes that required epinephrine use	0	5 (2.0%)	5 (1.0%)	16 (2.1%)	11 (1.6%)	7 (1.5%)	4 (1.5%)	0	43 (4.7%)

Source: Table 34, Table 14.3.1.14

Denominators for percentages were based on the number of subjects who were at risk during the corresponding study period and exposure period.
Treatment-emergent food allergy episodes include food allergy episodes that occur after first dose of AR101 in ARC008 through 30 days after last dose of study product, but excluding food allergy episodes that occur during or related to a food challenge.

[1] Total AR101 exposure is based on study drug exposure including parent studies. Subjects are counted towards the denominator for each Total AR101 Exposure window if they had AR101 exposure and were enrolled in the ARC008 study during each exposure window.

[2] Only includes events during the Initial and Extended Maintenance period.

IDE, initial dose escalation; SAE, serious adverse event; yr, year(s).

For the analysis of ARC008 data by exposure period, 480 subjects were exposed to AR101 and received ARC008 maintenance at any time during the first year of total exposure to AR101 (including exposure during parent studies). Of the 911 subjects screened for ARC008, 229 subjects (from Treatment Pathways 3 and 5) had received placebo in the parent study and were exposed to AR101 for the first time in ARC008.

These 229 subjects started initial dose escalation (2 days) and up-dosing (approximately 22-52 weeks in Treatment Pathway 3 and up to 40 weeks in Treatment Pathway 5) in the first year of total exposure to AR101. These previously placebo-treated subjects are likely to comprise approximately half of the 480 subjects included in the < 1 year total exposure period in the analyses in Table 13.

During the < 1 year total AR101 exposure period, in the subjects also receiving ARC008 maintenance at any time, 30/480 (6.3%) subjects had at least 1 treatment-emergent food allergen episode that occurred during maintenance in ARC008 only. The incidence in this analysis does not include adverse events which occurred in parent studies prior to ARC008 enrollment or any events during initial dose escalation or up-dosing in ARC008 within the < 1 year total exposure period. By comparison, during the ARC008 up-dosing period (which also occurred within the first year of exposure to AR101), 33/244 (13.5%) subjects had at least 1 treatment-emergent food allergen episode Table 13.

The second and third year of total AR101 exposure comprised more subjects from the overall safety population who were also receiving ARC008 maintenance at any time in each exposure period (1 to <2 years, N=749; 2 to <3 years, N=679). At least 1 treatment-emergent food allergen episode that occurred during maintenance in ARC008 was reported in 100/749 [13.4%] subjects in the 1 to < 2

years total AR101 exposure period and 71/674 [10.5%] subjects in the 2 to < 3 years total AR101 exposure period.

The denominators for the later exposure periods are more likely to be impacted by study withdrawals rather than the time of transition from parent study to ARC008 maintenance.

The proportions of subjects with at least 1 treatment-emergent food allergen episode appear to be lower during the later exposure periods than during second and third years of total AR101 exposure: 3 to < 4 years [6.7%], 4 to < 5 years [6.3%], ≥ 5 years [3.7%].

Although comparisons across exposure periods are clearly confounded and biased by the rules for selection of "at risk" subjects who receive ARC008 maintenance and the varying periods of exposure to maintenance in ARC008 within each exposure period, the impact of these confounding issues is likely reduced in the later exposure periods.

In ARC008, subjects are provided peanut allergy training at each study visit (every 3 months during extended maintenance), including instructions to continue to follow a peanut-avoidant diet, recognition of an allergic reaction and of the symptoms of anaphylactic reaction, and ways to minimize the risk of accidental exposure to peanut in and outside of the home. This continued reinforcement of allergen avoidance and patient education may have contributed to a low incidence (< 3%) of peanut-related food allergy episodes over time during ARC008 maintenance.

Most food allergy episodes reported during ARC008 maintenance were associated with non-peanut food allergies (Table 13). A total of 613 (67.5%) subjects had a history of a non-peanut food allergy. Unlike peanut allergies, which are typically life long, non-peanut allergies such as those to milk and hen eggs resolve over time. During ARC008 maintenance, the incidence of non-peanut food allergies appeared to be lower during the later years of total AR101 exposure than compared to the second and third years. Some subjects' non-peanut food allergy may have resolved as they age. It may also be possible that the continued reinforcement of allergen avoidance and patient education for peanut allergy affected the subjects' management of their other food allergens. As additional details of non-peanut exposures and reactions (eg, prior testing or oral challenge to non-peanut food allergens, reaction details) were not collected in the AR101 clinical development program, meaningful conclusions on changes in non-peanut food allergen exposure and events over time cannot be made.

Treatment-emergent systemic allergic reactions (anaphylactic reactions) by total AR101 exposure period are summarized in Table 14.

Table 14: Treatment-Emergent Systemic Allergic Reactions (Anaphylactic Reactions) by Total AR101 Exposure (Safety Population)

	IDE (N=229)	Up-Dosing (N=244)	Total AR101 Exposure [1]						Overall (N=908)
			<1 yr [2] (N=480)	1 to <2 yr (N=749)	2 to <3 yr (N=674)	3 to <4 yr (N=481)	4 to <5 yr (N=271)	≥5 yr (N=107)	
Number of anaphylactic reactions	1	47	43	117	77	29	20	8	342
Number of anaphylactic reactions by trigger									
Study product/IP	1	40	36	90	62	21	15	5	270
Peanut or peanut containing food	0	3	4	3	1	1	2	0	14
Other food allergen	0	4	2	21	12	7	3	3	52
Unknown	0	0	1	1	2	0	0	0	4
Other	0	0	0	2	0	0	0	0	2
Number of subjects experiencing an anaphylactic reaction									
1 episode	1 (0.4%)	19 (7.8%)	24 (5.0%)	61 (8.1%)	40 (7.3%)	17 (3.5%)	16 (5.9%)	3 (2.8%)	120 (13.2%)
2 episodes	0	6 (2.5%)	4 (0.8%)	12 (1.6%)	8 (1.2%)	3 (0.6%)	2 (0.7%)	1 (0.9%)	42 (4.6%)
3 episodes	0	4 (1.6%)	2 (0.4%)	5 (0.7%)	2 (0.3%)	2 (0.4%)	0	1 (0.9%)	14 (1.5%)
> 3 episodes	0	1 (0.4%)	1 (0.2%)	4 (0.5%)	1 (0.1%)	0	0	0	16 (1.8%)

Source: Table 8, Table 14.3.1.13.1

Denominators for percentages were based on the number of subjects who were at risk during the corresponding study period or exposure period.

Anaphylactic reaction is defined as adverse event or group of adverse events from the same trigger that were marked as an anaphylactic reaction on the adverse event of interest case report form page. Treatment-emergent anaphylactic reactions include anaphylactic reactions that occur after first dose of AR101 in ARC008 through 30 days after last dose of study product, but excluding anaphylactic reactions that occur during or related to a food challenge.

[1] Total AR101 exposure is based on study drug exposure including parent studies. Subjects are counted towards the denominator for each Total AR101 Exposure window if they had AR101 exposure and were enrolled in the ARC008 study during each exposure window.

[2] Only includes events during the Initial and Extended Maintenance period.

IDE, initial dose escalation; IP, investigational product; yr, year(s).

The analysis of treatment-emergent systemic allergic reactions by total AR101 exposure period is confounded by the selection of subjects and duration of ARC008 maintenance within each exposure period in the same way as described for food allergy episodes above. During the < 1 year total AR101 exposure period, in the subjects also receiving ARC008 maintenance at any time, 31/480 (6.5%) subjects had at least 1 treatment-emergent systemic allergic reaction (anaphylactic reaction) that occurred during maintenance in ARC008 only. At least 1 treatment-emergent systemic allergic reaction

(anaphylactic reaction) that occurred during maintenance in ARC008 was reported in 82/749 (10.9%) subjects in the 1 to < 2 years total AR101 exposure period and 60/674 8.9% subjects in the 2 to < 3 years total AR101 exposure period. The incidence of subjects with events appeared to be lower during later exposure periods than during the second and third years of AR101 total exposure: 3 to < 4 years [4.6%], 4 to < 5 years [6.6%], ≥ 5 years [4.7%] (Table 14).

The number of systemic allergic reactions (anaphylactic reactions) due to peanut or peanut containing foods was low across the exposure periods (ranging from 0 to 4 within each period) compared with systemic allergic reactions due to other food allergens (ranging from 2 to 21 reactions within each period) (Table 14). These differences may be attributed to the peanut allergy training at each study visit, as well as clinical desensitization sustained over time from AR101 treatment.

The changes in systemic allergic reactions (anaphylactic reactions) due to other food allergens during ARC008 maintenance were consistent with the changes in incidences of accidental/non-accidental non-peanut food allergen episodes over each total AR101 exposure period. As described above, a lower number of systemic allergic reactions (anaphylactic reactions) due to other food allergens in later exposure years compared to the second and third years total AR101 exposure, may be due to natural resolution with increasing age or better management of non-peanut food allergies.

As discussed later in the Response to Question 8.3, the change in quality of life measurement scores at the end of study/end of treatment compared to baseline show improved subject-reported and parent-reported scores, some of which are clinically significant. Taken together, the quality of life and food allergen episode observations indicated a sustained long-term effect with continued AR101 treatment in subjects with peanut allergy.

In summary, due to the different total AR101 exposure time points at which subjects enrolled in ARC008 to continue AR101 maintenance treatment from parent studies or to start AR101 treatment, direct comparisons of event incidence across years of exposure are confounded. The lower incidences of events during ARC008 maintenance observed during the first year of total AR101 exposure compared with the second year, can in part be explained by the selection of at risk subjects. For the <1 year total AR101 exposure period, approximately half of these subjects were de novo subjects who would not have entered maintenance in ARC008 until after 22 to 52 weeks of AR101 exposure (initial dose escalation and up-dosing). Similarly, subjects who transitioned from parent studies into ARC008 maintenance would not have started maintenance in ARC008 until later in the first year of AR101 exposure. This reduced time on ARC008 maintenance within the first year of AR101 exposure would have affected the potential for occurrence of events in the first year compared with the second year of total AR101 exposure. The at risk population in the second and third years of total AR101 exposure were more similar to the overall safety population, although counts of events may to some extent have been affected by the timing of transition from parent studies to ARC008. The later years of AR101 exposure would have been less impacted by these issues, but exposure and event reporting would have been impacted by study discontinuations. Despite this, the incidence of events generally appeared to be lower across the later years of exposure (from 3 years total AR101 exposure) possibly due to training and clinical desensitization over time.

Assessment of response:

The MAH provided some explanation regarding changes in number of occurrence of TEAEs that are associated with accidental/non-accidental non-study product food allergen exposure and TEAEs that are anaphylactic reactions.

It is highlighted that direct comparison across treatment years might be biased by the different treatment pathways (e.g. duration of AR101 exposure in parent study).

It is further discussed that patients (and their caregivers) received continuous training regarding peanut avoidance and allergy training. This might over time have reduced occurrence of peanut-related but also other food-related TEAEs. It is therefore regarded as important that during these trainings the consequent treatment adherence including the daily intake is mandatory to maintain the gained efficacy. This is also reflected in the PI. Management of co-factors need to be trained consequently likewise. Information on co-factors is available in the PI.

The information provided is acknowledged.

The issue is solved.

4. GI disorders (including vomiting, abdominal pain, nausea, abdominal pain upper, abdominal discomfort etc.) were observed in 197 subjects (80.7%) during up-dosing and 564 (64%) during Maintenance (Table 6, ARC008 - Report Body). In terms of Treatment-Related AEs, GI disorders are depicted with overall 44.6% (Table 7). In order to determine whether these symptoms change in frequency over a period of up to 5 years or more, the MAH is asked to depict occurrence of symptoms over time (<1 year, after 1 to <2 years, 2 to < 3 years, 3 to < 4 years, 4 to < 5 years, or ≥ 5 years of AR101 exposure).

Applicant Response to Question 4

The overall number of subjects with at least 1 treatment-related GI disorder event reported during ARC008 was 405/908 (44.6%); the most common treatment-related AEs in this system organ class (SOC) were abdominal pain (21.6%), vomiting (12.4%), abdominal discomfort (11.9%), and nausea (11.6%).

The proportion of subjects who had at least 1 treatment-related GI disorders adverse event by study treatment period in ARC008 was 68.0% during up-dosing (subjects from Treatment Pathways 2, 3, and 5), 36.4% during initial and extended maintenance (all treatment pathways), and 34.1% during initial dose escalation (Treatment Pathways 3 and 5).

As described in Response to Question 3, comparisons across exposure periods are confounded by the analyses where exposure periods of total AR101 treatment includes parent studies but subjects (and therefore events) are only included within an exposure period when receiving maintenance in ARC008 at any time in that period.

The proportions of subjects who had at least 1 treatment-related GI event during ARC008 maintenance were 21.9% in the < 1 year total AR101 exposure period, 25.9% in the 1 to <2 years total AR101 exposure period, and 17.5% in the 2 to <3 years total AR101 exposure period. The denominators for the later exposure periods are likely to be impacted by study withdrawals and are limited by time on study. Therefore, these later exposure periods are less likely to include subjects from Treatment Pathway 3 and Treatment Pathway 5. The proportions of subjects who had at least 1 treatment-related GI event during ARC008 maintenance appears to be lower during the later exposure periods than during the second and third years of total AR101 exposure: 3 to < 4 years [9.4%], 4 to < 5 years [6.3%], and ≥ 5 years [3.7%].

The incidence of treatment-emergent GI disorders by exposure follows a similar pattern to the treatment-related events.

Overall, subjects are at a greater risk of a GI event during up-dosing for treatment-related (68.0%) and non-treatment related events (80.7%). After this, the risk of a GI event is markedly lower and appears to diminish with long-term AR101 exposure (> 3 years).

Table 15: Treatment-Related Adverse Events in Gastrointestinal Disorder System Organ Class by Preferred Term and Total AR101 Exposure in ≥10 Patients (Safety Population)

System Organ Class / Preferred Term [2]	IDE (N=229)	Up-Dosing (N=244)	Total AR101 Exposure [1] <1 yr [3] (N=480)	1 to <2 yr (N=769)	2 to <3 yr (N=674)	3 to <4 yr (N=481)	4 to <5 yr (N=271)	≥5 yr (N=107)	Overall (N=908)
Gastrointestinal disorders	56 (24.5%)	166 (68.0%)	105 (21.9%)	194 (25.9%)	118 (17.5%)	45 (9.4%)	17 (6.3%)	4 (3.7%)	405 (44.6%)
Abdominal pain	28 (12.2%)	93 (38.1%)	36 (7.5%)	74 (9.9%)	39 (5.8%)	12 (2.5%)	2 (0.7%)	3 (2.8%)	196 (21.6%)
Vomiting	5 (2.2%)	51 (20.9%)	19 (4.0%)	41 (5.5%)	19 (2.8%)	6 (1.2%)	1 (0.4%)	1 (0.9%)	113 (12.4%)
Abdominal discomfort	16 (7.0%)	60 (24.6%)	16 (3.3%)	36 (4.8%)	14 (2.1%)	2 (0.4%)	4 (1.5%)	1 (0.9%)	108 (11.9%)
Nausea	9 (3.9%)	47 (19.3%)	16 (3.3%)	30 (4.0%)	26 (3.9%)	10 (2.1%)	2 (0.7%)	0	105 (11.6%)
Abdominal pain upper	6 (2.6%)	22 (9.0%)	9 (1.9%)	24 (3.2%)	18 (2.7%)	5 (1.0%)	0	0	66 (7.3%)
Oral pruritus	1 (0.4%)	25 (10.2%)	12 (2.5%)	24 (3.2%)	13 (1.9%)	6 (1.2%)	4 (1.5%)	0	56 (6.2%)
Lip pruritus	2 (0.9%)	14 (5.7%)	7 (1.5%)	20 (2.7%)	12 (1.8%)	6 (1.2%)	1 (0.4%)	0	46 (5.1%)
Lip swelling	0	8 (3.3%)	8 (1.7%)	18 (2.4%)	11 (1.6%)	5 (1.0%)	2 (0.7%)	1 (0.9%)	45 (5.0%)
Paraesthesia oral	3 (1.3%)	15 (6.1%)	15 (3.1%)	10 (1.3%)	8 (1.2%)	6 (1.2%)	1 (0.4%)	1 (0.9%)	42 (4.6%)
Dyspepsia	2 (0.9%)	20 (8.2%)	8 (1.7%)	15 (2.0%)	3 (0.4%)	3 (0.6%)	0	1 (0.9%)	30 (4.0%)
Diarrhoea	0	22 (9.0%)	3 (0.6%)	11 (1.5%)	2 (0.3%)	1 (0.2%)	0	0	35 (3.9%)
Tongue pruritus	1 (0.4%)	9 (3.7%)	7 (1.5%)	8 (1.1%)	2 (0.3%)	2 (0.4%)	1 (0.4%)	0	25 (2.8%)
Gastrooesophageal reflux disease	0	11 (4.5%)	3 (0.6%)	5 (0.7%)	6 (0.9%)	1 (0.2%)	1 (0.4%)	0	20 (2.2%)

Source: Table 33, Table 14.3.1.8

Total AR101 exposure is based on study drug exposure including parent studies. At each level of summarization (system organ class and preferred term), subjects with more than 1 related adverse event were counted only once within each exposure window.

[1] Subjects are counted towards the denominator for each Total AR101 Exposure window if they had AR101 exposure and were enrolled in the ARC008 study during each exposure window.

[2] Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 26.0.

[3] Only includes events during the Initial and Extended Maintenance period.

IDE, initial dose escalation; yr, year(s).

Assessment of response:

The MAH provided information regarding treatment related GI AEs across exposure time. In summary, patients are at a higher risk of a GI event during up-dosing. After this, the risk of a GI event is lower and appears to lessen with long-term AR101 exposure (> 3 years).

The issue is solved.

5. An interplay of GI disorders with ARFID (Avoidant/Restrictive Food Intake Disorder (ARFID) or likely ARFID (L-ARFID/GI)) has been described in literature (Int J Eat Disord. 2021 Jun;54(6):995-1008). Therefore, the MAH should discuss if Palforzia (in a susceptible population) reinforce or induce eating behaviour in such a way that it is pathological (towards L-ARFID/GI) and may require improved therapy (e.g. psychotherapy, nutritional counselling) to optimize care. In this discussion, the described 6.7% of subjects who suffered from TEAE in the SOC 'psychiatric disorders' should be included**.**

Applicant Response to Question 5

When the AR101 clinical development program was designed, the emphasis from regulators and the MAH was on a priori determination of endpoints related to the immunologic effects of treatment. No measures assessing avoidant/restrictive food intake disorder (ARFID) was pre-specified and as such, the clinical program was not designed for the collection of adequate endpoints to draw meaningful conclusions on this topic.

The applicant reviewed available data for behavioral changes, nutrition-related events, and weight changes for possible unreported ARFID, including adverse events reported in the psychiatric SOC and the adverse events associated with metabolism and nutrition SOC, as well as standard growth curves from subjects' weight measurements during the study.

Of the 908 subjects in the safety population, 61 (6.7%) subjects had treatment-emergent adverse events of psychiatric disorders. Reported events in more than 1 subject were anxiety (2.4%), attention deficit hyperactivity disorder (ADHD) (1.9%), depression and insomnia (0.7% each), obsessive-

compulsive disorder (0.3%), and tic (0.2%). One subject (13-year-old female) had moderate anorexia nervosa considered not related by the investigator. No ARFID was reported in study ARC008.

Six (0.7%) subjects experienced related adverse events under the psychiatric disorders SOC; 5 subjects had related adverse events of anxiety and 1 subject had a related adverse event of restlessness.

Subjects who reported recurrent GI adverse events resulting in prolonged interruption of dosing (withholding AR101 for > 7 days) which also preceded a psychiatric adverse event were reviewed for potential unreported ARFID. Most psychiatric events were anxiety, ADHD, depression, and insomnia; there were no events that are likely ARFID (Listing 1, Listing 2).

In addition, the applicant reviewed events reported by subjects who had adverse events in the metabolism and nutritional disorders SOC. Nine (1.0%) subjects had decreased appetite (8 mild in severity, 1 moderate) and 1 subject had abnormal loss of weight (moderate); all events were reported as not related to AR101 by the investigator. None of these events were chronic/recurrent, associated with recurrent GI adverse events that may contribute to the decreased appetite or loss of weight, or GI adverse events resulting in prolonged interruption of dosing. None of these subjects reported psychiatric events that are likely ARFID or events potentially consistent with this eating disorder. All subjects continued AR101 treatment.

The applicant additionally conducted analysis of weight measurements in ARC008. Nutritional status was assessed by subjects' height and weight measurements at study site visits at several time points during the study, and changes in weight during ARC008 were reviewed. The weight percentile rank for each subject was determined using standard weight-for-age growth charts ranging from 3rd to 97th percentile (United States National Center for Health Statistics). Changes in subjects' weight percentile rank were evaluated throughout their participation in the study.

Analysis of subjects' change in weight percentile rank (increases or decreases) at their last study visit compared to study entry (baseline) are as follows:

- Of the 908 subjects in the safety population, 795 (87.6%) subjects either had no change in percentile rank (439 [48.4%] subjects) or had a one percentile rank change increase (189 [20.8%] subjects) or decrease (167 [18.4%] subjects). Two percentile rank changes were observed in 68 (7.5%) subjects (increase in 47 [5.2%], decrease in 21 [2.3%]). Greater than two percentile rank changes were observed in 44 (4.8%) subjects (increase in 33 [3.6%], decrease in 11 [1.2%]).

- In the 61 subjects who reported treatment-emergent adverse event of psychiatric disorders, 48 (78.7%) had no change in percentile rank (29 [47.5%] subjects) or one percentile rank change (increase in 12 [19.7%], decrease in 7 [11.5%]). Two percentile rank changes were observed in 6 (9.8%) subjects (increase in 1 [1.6%], decrease in 5 [8.2%]). Greater than two percentile rank changes were observed in 7 (11.5%) subjects (increase in 4 [6.6%], decrease in 3 [4.9%]). Three subjects who reported an adverse event of psychiatric disorders had a weight decrease of greater than two percentile ranks at the last study visit compared to baseline. Their reported relevant medical history were ADHD, autism, insomnia, and tics; adverse events in the psychiatric disorders SOC were anorexia nervosa, anxiety, depression, and insomnia.

- All of the 10 subjects who reported treatment-emergent adverse events in the metabolism and nutritional disorders of decreased appetite or loss of weight had no change in percentile rank or had a one percentile rank change.

Analysis of subjects' change in weight percentile rank for weight decreases at any study visit compared to study entry (baseline) are as follows:

- Of the 908 subjects in the safety population, 835 (92.0%) subjects either had no change in percentile rank during the study or a worst weight decrease of one percentile rank at any visit compared to baseline.

- Of the 61 subjects who reported adverse event of psychiatric disorders, 12 had a worst weight decrease of two or greater percentile rank at any visit compared to baseline, and 6 had a worst weight decrease of greater than two percentile rank at any visit compared to baseline (Listing 5). For these 6 subjects, the reported relevant medical history were autism, ADHD, insomnia, obsessive-compulsive disorder, tics, and Tourette's disorder. Adverse events in the psychiatric disorders SOC were ADHD, anorexia nervosa, anxiety (2 subjects), depression, insomnia, and irritability. Of these 6 subjects, 3 had a weight decrease of greater than two percentile rank at the last study visit compared to baseline as described above.

- All of the 9 subjects who reported adverse events of decreased appetite had no change in percentile rank during the study or a worst weight decrease of one percentile rank at any visit compared to baseline. The one subject who reported abnormal loss of weight considered not related to AR101 had a worst weight decrease of two percentile rank at any visit and a decrease of one percentile rank at the last visit compared to baseline.

In summary, the analysis of weight-for-age percentile rank changes did not identify any potential trends of decreasing weight due to AR101 treatment in ARC008. More than 90% of subjects had no change in percentile rank, an increase in weight, or a decrease in weight of one percentile rank, a change that is not clinically significant.

Taken together, there is no clear evidence of ARFID or events potentially consistent with this eating disorder in the ARC008 study, and the applicant believes that there is no weight deficit-related safety concern associated with AR101.

The reported incidence of depression and anxiety in subjects in ARC008 was lower than those reported in the literature of patients with peanut allergy under peanut avoidance and dietary restrictions only. In a study of healthcare resource utilization in more than 14,000 patients with peanut allergy under allergen avoidance, depression and anxiety were reported in 12.2% and 10.0% of patients (Meadows et al, 2021). A study evaluating the quality of life in adults and adolescents with peanut allergy under allergen avoidance, together with their caregivers, indicate that mental/psychosocial health was more problematic than physical health, with worse general health-related quality of life in all domains in comparison to healthy controls, corroborating results from previous studies that children and families appear to experience high levels of caregiver stress and child anxiety, similar to children with chronic health conditions, such as asthma or diabetes (Nowak-Wegrzyn et al, 2021).

Assessment of response:

The MAH emphasized that the clinical program was not designed for the collection of adequate endpoints to draw meaningful conclusions on this topic. This is correct and agreed. All the more, the detailed workup is acknowledged. The MAH provided a detailed discussing regarding potential risk of ARFID in relation to AR101 treatment and concludes that there is no clear evidence of ARFID or events potentially consistent with this eating disorder in the ARC008 study - even if eating disorder cases were observed in the study collective.

Based on the information provided, this conclusion is agreed.

The issue is solved.

6. The description of EoE events in ARC008 CSR seems incomplete and is not comprehensible:

   6.1. The MAH refers to 7 events which occurred during AR101 treatment period. However, section 14.3.3. lists 11 EoE events, which should have occurred during AR101 treatment based on information provided in AR101 IB Edition 10. However, IB Edition 10 lists in total 13 EoE events for ARC008. 2 of these events are recorded as non-related, which might explain the discrepancy of 11 versus 13 events. However, the discrepancy to the 7 events referred to in section 12.2.4.2.1 of the CSR is not plausible and should be explained and/or corrected accordingly.

   6.2. In addition, section 12.2.4.2.1 of the CSR refers to EoE events during follow-up. Respective Listing 16.2.8.10 is not available in the dossier. Considering that EoE events are of special interest, the MAH is asked to provide information on EoE events including those events that might have occurred during follow-up.

Applicant Response to Question 6

In study ARC008, the total number of reported events of eosinophilic esophagitis (EoE) was 13, of which 7 were treatment-emergent and 6 were during safety follow-up. Some subjects completed the Additional EoE form which includes additional details on endoscopy results, symptoms, and treatment of EoE.

Subject narratives in Section 14.3.3 include 12 cases of EoE, 1 of which was reported as an adverse event of moderate vomiting leading to discontinuation (the diagnosis of EoE was included in the details of the event). One event has no narrative, as the case report was invalidated as it was considered by the investigator as not fitting the criteria of nonserious adverse event of interest. The event occurred during safety follow-up after the subject withdrawal from study treatment (due to study fatigue) and was considered not related to AR101 treatment.

To provide a full description of EoE across all clinical studies in the AR101 development program the applicant has summarized the EOE reports in Table 16. There were a total of 22 cases of EoE reported in the global safety database, which include non-treatment-emergent cases that were reported during safety follow-up. Links are provided to subject narratives in the respective clinical study reports and remarks from any additional safety follow-up reports are included in the table.

Table 16: Summary of Subjects With Eosinophilic Esophagitis (All Studies) as of 07 Jun 2024

Study Case no.	Study Period/ Day Onset to Resolved	Event Dose (mg)	Severity	Related	Treatment [1]	Biopsy Proven	Outcome	Disc Day Trt / Study	Total Days AR101	Case Number/ CSR Narrative / Safety Follow-Up & Comments
ARC001 CN01	Up-dosing 16-Ongoing [2]	12	Mild	Yes	Esomeprazole, swallowed fluticasone, elimination diet	Yes	Ongoing [2] Resolved [6]	20 / 141	20	Case no. 01 / Biopsy confirmation ~1 mo later showed peptic-type duodenopathy with gastric foveolar metaplasia and an eosinophilic pattern of injury. Symptoms improved ~6 days after study product discontinuation and resolved on an unknown date. Follow-up EGD performed (date and results unknown).
ARC002 CN02	Maintenance 428-Ongoing [2]	950	Moderate	Yes	Ranitidine, omeprazole, lansoprazole	Yes	Ongoing [2] Resolved [6]	1059 / 1074	1059	Case no. 02 / Symptoms still present after ~5 mo but showed improvement with use of omeprazole. ~2 mo later EoE was considered resolved on repeat biopsy. History of gastric reflux.
ARC003 CN03	Up-dosing 176-Ongoing [2]	200	Mild	Yes	Omeprazole, elimination diet	Yes	Ongoing [2] Ongoing [6]	186 / 211	186	Case no. 03 / Symptoms improved 2 mo after study product discontinuation. Follow-up EGD after ~6 mo showed improvement, but not complete resolution. Follow-up endoscopy ~8 mo later showed EoE was ongoing. Investigator: Possible EoE was present before study entry that worsened with study treatment.
ARC004 CN04	Up-dosing 50-129	12	Severe	No	Lansoprazole	Yes	Resolved [2]	50 / 64	49	Case no. 04 / Follow-up EGD after ~2.5 mo showed no evidence of eosinophil infiltration; considered recovered; subject reported no symptoms ~4 mo later. Investigator: EoE was most likely intercurrent pre-existing disease.
ARC004 CN05	Maintenance 225-710 [7]	200 [3]	Severe	Yes	Budesonide, prednisone, fluticasone, ranitidine	Yes	Resolved [2]	220 / 709	543	Case no. 05 / Symptoms were still present after ~7 mo but showed improvement with use of budesonide. Subject was seen by a gastroenterologist ~3 mo later. ~2 mo later EoE was considered resolved on repeat biopsy. No symptoms at 1 year follow-up.
ARC004 CN06	Maintenance 293-Ongoing [2]	300	Moderate	Yes	Calcium carbonate, omeprazole	Yes	Ongoing [2] Resolved [6]	399 / 441	399	Case no. 06 / Biopsy confirmation ~2.5 mo later showed proximal esophagus squamous mucosa with mild chronic inflammation, eosinophilic infiltrate, and minimal chronic inflammation of the gastric mucosa. ~9.5 mo later the subject was asymptomatic and the EoE was considered resolved. Investigator: Possible causal factors included eosinophilic GI disease and progression of a previous condition of constipation.

Study Case no.	Study Period/ Day Onset to Resolved	Event Dose (mg)	Severity	Related	Treatment [1]	Biopsy Proven	Outcome	Disc Day Trt / Study	Total Days AR101	Case Number/ CSR Narrative / Safety Follow-Up & Comments
ARC007 CN07	Up-dosing 138- Ongoing [2]	40	Moderate	Yes	Omeprazole	Yes	Resolv-ing [2] Resolv-ing [6]	138 / 372	138	Case no. 07 / Follow-up upper GI endoscopy after ~2 mo showed gross esophageal mucosal changes consistent with EoE; ~3 mo later, occasional abdominal pain present but no dysphagia or esophageal globus symptoms. ~7 mo after study treatment discontinuation, repeated endoscopy showed resolving/stable EoE; subject was asymptomatic on continued omeprazole. No follow-up endoscopy was planned. Investigator thought the disease presentation was possibly already in progress before study start based on the subject's other atopic history in absence of baseline pathology or endoscopy data.
ARC007 CN08	Up-dosing 79- Ongoing [2]	80	Mild	No	Lansoprazole, budesonide	Yes [4]	Resolv-ing [2] Resolved [6]	141 / 432	141	Case no. 08 / Subject was seen by a pediatric GI specialist ~2 mo afterward, topical budesonide started, and referred to an adult GI specialist. By ~4 mo later, subject had not seen an adult GI specialist. Symptoms improving but not resolved ~2 mo later. Symptoms resolved ~8 mo later. Investigator: Other possible causal factors indicated symptoms were present before study start and part of the medical history (i.e., postprandial abdominal pain).

Study Case no.	Study Period/ Day Onset to Resolved	Event Dose (mg)	Severity	Related	Treatment [1]	Biopsy Proven	Outcome	Disc Day Trt / Study	Total Days AR101	Case Number/ CSR Narrative / Safety Follow-Up & Comments
ARC007 CN09	Up-dosing 475 [8] - Ongoing	4	Moderate	Yes	Pepcid Omeprazole	Yes	Recover-ing [6]	28/29	28	Case no. 09 / No CSR narrative as subject was diagnosed with EoE > 1 year after study discontinuation, which was past the study reporting period for safety follow-up and the ARC007 database was already closed (CSR published 26Nov2018). The GI symptoms began during ARC007, causing the subject to drop out after a few weeks. The symptoms resolved within 3 weeks, then reappeared following the exit of the study. After the trial, the GI symptoms persisted, especially abdominal pain and intermittent emesis. GI evaluated, and treatment was tried. At clinic visit 28Jan2019 (PI is also patient's allergist), reported that EGD 19Oct2018 diagnosed EoE. As of 20May2019, no new biopsy or endoscopy had been completed. The subject still complained of frequent abdominal pain/stomachache that affects daily activities.

Study Case no.	Study Period/ Day Onset to Resolved	Event Dose (mg)	Severity	Related	Treatment [1]	Biopsy Proven	Outcome	Disc Day Trt / Study	Total Days AR101	Case Number/ CSR Narrative / Safety Follow-Up & Comments
ARC008 CN10	Maintenance 682-Ongoing [2]	300	Moderate	Yes	Swallowed fluticasone propionate	Yes	Resolved [2]	790/ 1110	1515	Case no. 10 / Subject reported no GI symptoms or other adverse events ~3 weeks after AR101 discontinuation and remained on study for follow-up.
ARC008 CN11	Maintenance 144-482	160	Moderate	No	Esomeprazole, budesonide	Yes	Resolved [2]	155 / 162	798	Case no. 11 / Symptoms improved after ~2 mo with use of esomeprazole. Follow-up endoscopy after ~3 mo showed no improvement. Repeat endoscopy ~2 mo later showed marked improvement and no active signs of EoE. ~5 mo later the subject was asymptomatic and the EoE was considered resolved. Sponsor Assessment Comment: Expected, related and does not meet SAE criteria.
ARC008 CN12	Maintenance 577-589	160	Severe	Yes	None	Yes	Resolved [2]	579 / 589	579	Case no. 12 / Investigator instructed subject to start budesonide and lansoprazole. Treatment was not started as the subject reported symptoms resolved ~2 weeks after AR101 discontinuation.
ARC008 CN13	Maintenance 380-Ongoing [2]	160	Moderate	Yes	Budesonide	Yes	Ongoing [2]	385 / 412	385	Case no. 13 / Subject reported symptoms of abdominal discomfort and dysphagia after AR101 dosing. No follow-up information is available.
ARC008 CN14	Maintenance 48-441	240	Moderate	Yes	Pantoprazole, (rabeprazole, fluticasone per mother), budesonide sinus rinse	Yes	Resolved [2]	70 / 84	662	Case no. 14 / Symptoms were improved but not fully recovered as of ~2 mo afterward; symptoms were much better ~3 mo later and a repeat endoscopy revealed endoscopic improvement. ~8 mo later a repeat endoscopy was negative for increased eosinophils with a mostly negative eosinophil count and the EoE was considered resolved.
ARC008 CN15	Maintenance 967-Ongoing [2]	300	Moderate	Yes	Fluticasone propionate	Yes	Ongoing [2]	949/ 1049	949	Case no. 15 / Reported symptoms of GERD before start of AR101. Discontinued AR101 to receive dupilumab, and GERD symptoms improved after discontinuation. EGD showed increased eosinophils consistent with EoE. No follow-up information is available.
ARC008 CN16	Up-dosing 231-452	160	Moderate	Yes	Swallowed fluticasone propionate	Yes	Resolved [2]	231 / 239	231	Case no. 16 / Subject reported no symptoms after ~2 mo. ~1 mo later a repeat EGD with biopsy showed reactive squamous cells with acute inflammation and frequent eosinophils considered compatible with the subject's history of EoE. Subject reported no symptoms ~1 mo later. ~3 mo later a repeat EGD showed normal esophagus and stomach biopsies and the EoE was considered resolved.
ARC008 CN17	Up-dosing 188-Ongoing [2]	40	Moderate	Yes	Omeprazole	Yes	Resolv-ing [2]	136 / 324	136	Case no. 17 / The EoE was considered resolving at the time of diagnosis. No follow-up information is available.

Study Case no.	Study Period/ Day Onset to Resolved	Event Dose (mg)	Severity	Related	Treatment [1]	Biopsy Proven	Outcome	Disc Day Trt / Study	Total Days AR101	Case Number/ CSR Narrative / Safety Follow-Up & Comments
ARC008 CN18	Maintenance 805-967	300	Moderate	Yes	Budesonide	Yes	Resolved [2]	818 / 994	1189	Case no. 18 / The EoE was considered serious due to overnight stay in the hospital after the endoscopy for monitoring after anesthesia. Budesonide after AR101 discontinuation was considered effective.
ARC008 CN19	Maintenance 1594-Ongoing [2]	300	Mild	Yes	Fluticasone propionate	Yes	Ongoing [2] Ongoing [6]	1857	1856	Case no. 19 / EoE confirmed by oesophageal biopsy. *Helicobacter pylori* also colonized but not considered associated with EoE and no further action needed. Still ongoing at last follow-up on 02Nov2022.
ARC008 CN20	Maintenance 959-Ongoing [2]	300	Mild	Yes	Fluticasone propionate	Yes	Ongoing [2] Ongoing [6]	958 / 1143	1215	Case no. 20 / The study site was notified of diagnosis of EoE ~1.5 weeks after subject had an endoscopy. AR101 treatment was discontinued. Still ongoing at last follow-up on 17May2021.
ARC008 CN21	Maintenance 408 Ongoing [2]	300	Severe [9]	No	Budesonide	Yes	Ongoing [2] Ongoing [6]	368 / 719	1216	Case no. 21 / No CSR narrative Subject withdrew from the study and 13 days later had an endoscopy. The study site was not aware of the procedure until notified 25 days later during a study site visit. Endoscopy ~6 mo later showed EoE. Budesonide was started ~3 mo later with apparently good result. Investigator: Symptoms of abdominal pain, dysphagia, and diarrhea were present for many years before study start. Sponsor Assessment Comment: Expected, related and does not meet SAE criteria. Follow-up information received on 20-Jun-2023: Per PI decision, the event did not fit the criteria of NS-AEI, therefore the case was invalidated.
ARC008 CN22	Maintenance 252-Ongoing [2]	200	Mild	Yes	Omeprazole, fluticasone propionate	Yes	Ongoing [2] Recover-ing [6]	252 / 576	252	Case no. 22 / Biopsy confirmation ~7.5 mo later showed 16 to 17 eosinophils per high power field and sclerosis was noted. Subject continued to have mild dysphagia and was under the care of a gastroenterologist at the time of the 6-month follow-up.

[1] Includes follow-up treatment.
[2] At the time of the early discontinuation visit or the end of follow-up.
[3] Dose reduced to 200 mg 2 weeks before event.
[4] Endoscopy performed on onset day showed 2× gastric inlet patches in the proximal esophagus with evidence of esophageal eosinophilia and some basal cell hyperplasia more distally. In the proximal esophagus, 1 of 2 fragments showed intraepithelial eosinophils with maximal count of approximately 25 per high power field. Pathology notes possibility of focal to patchy EoE.
[5] Study discontinuation day not yet available.
[6] At time of last known safety follow-up.
[7] Severity reduced from severe to mild on Day 604 before event resolved on Day 710.
[8] Start date reported as the date of diagnosis, however, intermittent vomiting started during the study from Day 22 until Day 40.
[9] Reported as severe in the clinical database and moderate in the safety database.
CSR, clinical study report; Disc, discontinuation; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; F, female; GI, gastrointestinal; M, male; mo, months; trt, treatment.

Assessment of response:

The MAH provides a more detailed explanation on number of EoEs during ARC008 and presented numbers. It is now understood that the discrepancy is caused by events diagnosed under current treatment and events diagnosed during safety follow-up. Nevertheless, even if diagnosed after actual AR101 exposure, also most events detected during safety follow-up were considered related. Therefore, the presentation of numbers in ARC008 CSR is misleading. However, the question has been clarified. The three cases listed as not related raise doubts about their classification (related/non-related), but will not be discussed further at this point as EoE is already an identified adverse reaction and the frequency described so far will not be any different.

Besides, it seems that also only those events that were diagnosed under current treatment are reflected in the PI. The MAH is requested to update this information in the PI based on all treatment-related EoE cases occurring in AR101 clinical trials **(see section 3.)**.

The issue is not solved.

7. In terms of non-AR101 peanut-related exposure episodes, the MAH is asked to present a description of when exactly these episodes were observed >1 year, after 1 to < 2 years, 2 to < 3 years, 3 to < 4 years, 4 to < 5 years, or ≥ 5 years of AR101 exposure. The same should be done with regard to systemic allergic reactions (anaphylactic reactions), events triggered by 'exposure to peanut or peanut-containing food', or food allergy episodes that required epinephrine.

Applicant Response to Question 7

Non-AR101 peanut-related exposure episodes, events triggered by 'exposure to peanut or peanut-containing food', and food allergy episodes that required epinephrine are summarized by exposure period in Table 13 of response to Question 3. Systemic allergic reactions (anaphylactic reactions) by exposure periods are discussed in Response to Question 3.

During the ARC008 study overall, 59/908 subjects (6.5%) reported peanut-related food allergen episodes, 184/908 subjects (20.3%) reported a non-peanut-related food allergen episode, and 227/908 (25.0%) subjects reported any food allergen episodes.

During ARC008 initial and extended maintenance, 50/881 (5.7%) subjects had at least 1 peanut-related allergen episode. From the analyses by exposure period (including total AR101 exposure in parent studies), the proportion of subjects who had at least one peanut-related allergen episode during ARC008 maintenance was below 3% for all total AR101 exposure periods: < 1 year (maintenance only) (7/480 [1.5%]), 1 to < 2 years (21/749 [2.8%]), 2 to < 3 years (11/674 [1.6%]), 3 to < 4 years (8/481 [1.9%]), 4 to < 5 years (4/271 [1.5%]), and ≥ 5 years (none).

During ARC008 initial and extended maintenance, 39/881 (4.4%) subjects with at least 1 food allergen episode associated with epinephrine use. From the analyses by total AR101 exposure, the proportions of subjects with any food allergen episode associated with epinephrine use during ARC008 maintenance was below 2.5% for all total AR101 exposure periods: < 1 year (maintenance only) (5/480 [1.0%]), 1 to < 2 years (16/749 [2.1%]), 2 to < 3 years (11/674 [1.6%]), 3 to < 4 years (7/481 [1.5%]), 4 to < 5 years (4/271 [1.5%]), and ≥ 5 years (none).

In addition to the continued reinforcement of allergen avoidance and patient education at study visits, the low incidence of peanut-related food allergen episodes and food allergy episodes that required epinephrine use across exposure periods may reflect the desensitization response of AR101 treatment.

As ARC008 is an open-label follow-on study, the assessment of accidental exposure reaction patterns can only be descriptive within the constraints of the study design.

Additional possible contributing factors to the low incidences of peanut allergen episodes and food allergen episodes associated with epinephrine use include continued desensitization to peanut from AR101 treatment, improved avoidance of peanut and other food allergens due to repeated peanut allergy training during study visits over the duration of the study, and natural history of non-peanut food allergy resolution over time (eg, milk, egg) as discussed in Response to Question 3.

Assessment of response:

The MAH provided data of events triggered by 'exposure to peanut or peanut-containing food', or food allergy episodes that required epinephrine over time, in which the MAH explains

- that the proportion of subjects who had at least one peanut-related allergen episode during ARC008 maintenance was below 3% for all total AR101 exposure periods.

- and the proportions of subjects with any food allergen episode associated with epinephrine use during ARC008 maintenance was below 2.5% for all total AR101 exposure periods.

It is discussed that these rather low rates are connected to the constant training the study participants receive or/and also the natural history of non-peanut food allergy resolution over time.

It is further emphasized that the assessment of accidental exposure reaction patterns is only descriptive as ARC008 is an open-label follow-on study. Furthermore the MAH refers to Q3 for the detailed discussion on systemic allergic reactions (anaphylactic reactions) by exposure periods.

The information provided is acknowledged.

The issue is solved.

8. Please submit data on non-daily treatment experience, experience of subjects after end of study (follow-up observation) and Quality of Life during treatment/influenced by AR101

   8.1. 64 subjects had been disposed to a **non-daily dosing** regimen. It is assumed that all these subjects derived from ARC004 where they tolerated the non-daily regimen. The MAH is asked to give more detail about this population in terms of: frequency of intake (e.g. every other day), duration (in total) of exposition non-daily or daily (in case of change). How many ARC004 subjects who tolerated the non-daily regimen in ARC004 but who subsequently did not tolerate the non-daily regimen after entering ARC008 switched to Treatment Pathway 1, or discontinued treatment? Please also present information on occurrence of treatment-related AEs.

   8.2. Please precise why only 134 subjects entered the **follow-up observation** period. Please also explain the reason(s) for the high numbers of missing 'End of Treatment', 'Disposition – Study Exit' and 'End of follow-up' forms. The footnotes (Tab. 6 Subject Disposition, ARC008-Report Body) do not appear meaningful enough, as they do not clarify whether "missing" is actually based on the fact that the study was terminated and thus no FU took place or if they are missing according to other reasons. Accordingly, some of the "missing" may then have to be renamed "Sponsor decision". Please clarify.

      8.2.1. The MAH stated in the ARC008-Report Body, Section 9.2 Discussion of Study Design, that data on sustained efficacy was assessed ("A follow-up observation period after the last dose of AR101 was included to assess sustained clinical effect of AR101 treatment"). However, the corresponding analysis has not been found. Please precise what is meant with "sustained effect" and submit corresponding data.

   8.3. The evaluation of subjects' and caregivers **QoL**, including treatment satisfaction during AR101 treatment on daily and non-daily treatment regimens was predefined as secondary objective.

According data is missing and needs to be submitted as of relevance for the benefit/risk assessment.

Applicant Response to Question 8

Response to 8.1

A total of 64 subjects continued their non-daily dosing regimen (all twice weekly [BIW]) from parent study ARC004 in Treatment Pathway 1 in study ARC008 (Listing 16.2.1). The median exposure was 2.63 years (ARC008 only) and 4.51 years (including parent studies [ARC003 and ARC004]). For these subjects in ARC008, the median exposure was 959.0 days (range, 42-1762 days).

One subject who received non-daily dosing (BIW) in Treatment Pathway 1 switched to daily dosing in Treatment Pathway 2 .

Treatment-related adverse events were reported by 43.8% of subjects who continued nondaily dosing. The most common (occurring in ≥ 10% of subjects overall) preferred terms of treatment-related adverse events were systemic allergic reaction (anaphylactic reaction; 15.6%), urticaria (14.1%), and abdominal pain and nausea (10.9% each). This is consistent with the safety profile of AR101 for all subjects in ARC008.

Response rates in the 37 subjects who had an open-label food challenge (OLFC) are in Table 17.

Table 17: Response Rates in OLFCs for Non-daily Dosing Regimen

Time Point	Ext Maint Month 12	Ext Maint Month 24	Ext Maint Month 36	Ext Maint Month 48
Subjects who had an OLFC	37	25	13	2
MTD with no more than mild symptoms				
None	1 (2.7%)	0	0	0
300 mg	2 (5.4%)	1 (4.0%)	0	1 (50.0%)
600 mg	7 (18.9%)	4 (16.0%)	1 (7.7%)	0
1000 mg	6 (16.2%)	8 (32.0%)	3 (23.1%)	0
2000 mg	21 (56.8%)	12 (48.0%)	9 (69.2%)	1 (50.0%)
Desensitization response rates [95% CI] [1]				
Tolerated a single highest dose of at least 300 mg	36 (97.3%) [85.8%, 99.9%]	25 (100.0%) [86.3%, 100.0%]	13 (100.0%) [75.3%, 100.0%]	2 (100.0%) [15.8%, 100.0%]
Tolerated a single highest dose of at least 600 mg	34 (91.9%) [78.1%, 98.3%]	24 (96.0%) [79.6%, 99.9%]	13 (100.0%) [75.3%, 100.0%]	1 (50.0%) [1.3%, 98.7%]
Tolerated a single highest dose of at least 1000 mg	27 (73.0%) [55.9%, 86.2%]	20 (80.0%) [59.3%, 93.2%]	12 (92.3%) [64.0%, 99.8%]	1 (50.0%) [1.3%, 98.7%]
Tolerated a single highest dose of at least 2000 mg	21 (56.8%) [39.5%, 72.9%]	12 (48.0%) [27.8%, 68.7%]	9 (69.2%) [38.6%, 90.9%]	1 (50.0%) [1.3%, 98.7%]

Source: Table 35
[1] The 95% CIs are based on exact Clopper-Pearson intervals.
DBPCFC, double-blind, placebo-controlled food challenge; MTD, maximum tolerated dose.

The response rate in the 21 subjects who had an end of treatment DBPCFC are summarized in Table 18. A majority of subjects who received non-daily dosing regimen tolerated at least 1000 mg of peanut protein. Overall, a clinically relevant treatment effect (ie, clinical desensitization) was sustained over time up to > 5 years of exposure.

Table 18: Response Rate in End of Treatment DBPCFC for Non-daily Dosing Regimen

	Total AR101 Exposure		
	4 to < 5 Years	≥ 5 Years	Overall
Subjects who had a DPBCFC	1	20	21
MTD with no more than mild symptoms			
300 mg	0	1 (5.0%)	1 (4.8%)
600 mg	0	4 (20.0%)	4 (19.0%)
1000 mg	0	3 (15.0%)	3 (14.3%)
2000 mg	1 (100.0%)	12 (60.0%)	13 (61.9%)
Desensitization response rates [95% CI] [1]			
Tolerated a single highest dose of at least 300 mg	1 (100.0%) [2.5%, 100.0%]	20 (100.0%) [83.2%, 100.0%]	21 (100.0%) [83.9%, 100.0%]
Tolerated a single highest dose of at least 600 mg	1 (100.0%) [2.5%, 100.0%]	19 (95.0%) [75.1%, 99.9%]	20 (95.2%) [76.2%, 99.9%]
Tolerated a single highest dose of at least 1000 mg	1 (100.0%) [2.5%, 100.0%]	15 (75.0%) [50.9%, 91.3%]	16 (76.2%) [52.8%, 91.8%]
Tolerated a single highest dose of at least 2000 mg	1 (100.0%) [2.5%, 100.0%]	12 (60.0%) [36.1%, 80.9%]	13 (61.9%) [38.4%, 81.9%]

Source: Table 36
Total AR101 exposure is based on study drug exposure including parent studies.
[1] The 95% CIs are based on exact Clopper-Pearson intervals.
DBPCFC, double-blind, placebo-controlled food challenge; MTD, maximum tolerated dose.

Response to 8.2

The 1- year follow-up observation period was introduced in Protocol Amendment 6.0 (22 December 2020). As discussed in the Response to Question 1.1, AR101 treatment was discontinued early during ARC008 in 77.9% (710/911) subjects, the study was discontinued early in 52.5% (478/911) of subjects, and most subjects who did not complete the Disposition – Study Exit form did not do so because that form was introduced in Protocol Amendment 6.0.

Response to 8.2.1

Of the 134 subjects who entered the 1-year follow-up observation period, 122 subjects reported their peanut allergy treatment plan during follow-up guided by the subjects' physician. Peanut allergy treatment during follow-up were as follows: food equivalent for peanut oral immunotherapy (83.6%), commercially available product (Palforzia) (13.9%), and complete peanut avoidance or other (6.6% each).

No subjects had the optional DBPCFC at the end of the 1-year follow-up observation.

Sustained efficacy on AR101 treatment was assessed over time in ARC008 with the OLFC and the end of treatment DBPCFC. Sustained efficacy of the effects of AR101 treatment after the end of treatment (ie, subjects who had 1 year of complete peanut avoidance) could not be assessed.

Response to 8.3

Changes from baseline in subject-reported and parent-reported Food Allergy Quality of Life Questionnaire (FAQLQ) total scores are summarized across all treatment pathways in Table 19 and by treatment pathway and domains in the response tables document: Table 40 (FAQLQ for subjects, 8-12 years), Table 41 (FAQLQ for subjects, 13 to 17 years), Table 42 (FAQLQ for subjects, adults), Table 43 (FAQLQ for parents, 0-12 years), Table 44 (FAQLQ for parents, 13 to 17 years), and Table 45 (FAQLQ for parents, parental burden).

Treatment with AR101 resulted in improved subject-reported FAQLQ scores for subjects and parental burden with a decrease change greater than 0.5. Improvements in parent-reported FAQLQ scores were noted, though the change is not clinically significant.

Table 19: Change from Baseline in FAQLQ (Safety Population)

	Baseline	End of Treat/Study [1]	Change from Baseline
FAQLQ for Subjects – 8 to 12 Years			
n	299	362	201
Mean (SD)	2.64 (1.425)	1.83 (1.229)	-0.95 (1.231)
Median	2.50	1.60	-0.70
Q1, Q3	1.50, 3.80	0.90, 2.60	-1.80, -0.10
Min, Max	0.0, 6.0	0.0, 5.9	-4.5, 2.4
FAQLQ for Subjects – 13 to 17 Years			
n	178	191	106
Mean (SD)	2.87 (1.297)	2.20 (1.196)	-0.65 (1.123)
Median	2.85	2.10	-0.65
Q1, Q3	2.00, 3.80	1.20, 3.10	-1.40, 0.10
Min, Max	0.2, 5.9	0.0, 5.1	-3.8, 2.6
FAQLQ for Subjects – Adults			
n	22	42	19
Mean (SD)	2.69 (1.400)	2.04 (1.085)	-0.83 (0.870)
Median	2.80	1.90	-0.90
Q1, Q3	1.60, 4.00	1.20, 2.70	-1.70, 0.00
Min, Max	0.6, 5.3	0.0, 4.5	-2.4, 0.5
FAQLQ for Parents – 0 to 12 Years			
n	525	458	375
Mean (SD)	2.36 (1.355)	1.91 (1.352)	-0.42 (1.199)
Median	2.30	1.60	-0.30
Q1, Q3	1.20, 3.30	0.80, 2.90	-1.00, 0.30
Min, Max	0.0, 5.7	0.0, 6.0	-4.5, 3.6
FAQLQ for Parents – 13 to 17 Years			
n	172	171	83
Mean (SD)	2.96 (1.042)	2.58 (1.163)	-0.28 (0.904)
Median	2.90	2.60	-0.20
Q1, Q3	2.25, 3.50	1.80, 3.40	-0.90, 0.40
Min, Max	0.7, 5.6	0.1, 5.8	-2.7, 1.9

	Baseline	End of Treat/Study [1]	Change from Baseline
FAQLQ for Parental Burden (FAQL-PB)			
n	524	452	296
Mean (SD)	2.35 (1.366)	1.80 (1.347)	-0.52 (1.171)
Median	2.20	1.50	-0.60
Q1, Q3	1.20, 3.30	0.75, 2.60	-1.30, 0.20
Min, Max	0.0, 6.0	0.0, 6.0	-4.2, 4.0

Source: Table 40, Table 41, Table 42, Table 43, Table 44, Table 45

[1] Earliest visit from End of Treatment / Early Discontinuation, End of Study (Legacy Only), and Study Exit Visits.

End of Treat/Study, End of Treatment/Study; FAQLQ, Food Allergy Quality of Life Questionnaire.

Changes from baseline in subject-reported Food Allergy Independent Measure (FAIM) total scores for subjects and parents are summarized across all treatment pathways in Table 20 and by treatment pathway in the response tables document: Table 46 (FAIM for subjects, 8 to 12 years), Table 47 (FAIM for subjects, 13 to 17 years), Table 48 (FAIM for subjects, adults), Table 49 (FAIM for parents, 0 to 12 years), and Table 50 (FAIM for parents, 13-17 years).

Treatment with AR101 resulted in improved subject-reported and parent-reported FAIM scores.

Table 20: Change from Baseline in FAIM (Safety Population)

	Baseline	End of Treat/Study [1]	Change from Baseline
FAIM for Subjects – 8 to 12 Years			
n	288	349	189
Mean (SD)	2.19 (0.986)	1.65 (0.895)	-0.62 (0.842)
Median	2.00	1.50	-0.60
Q1, Q3	1.50, 2.80	1.00, 2.20	-1.20, 0.00
Min, Max	0.3, 5.3	0.0, 5.7	-2.7, 1.3
FAIM for Subjects – 13 to 17 Years			
n	170	189	102
Mean (SD)	2.19 (0.905)	1.78 (0.857)	-0.39 (0.876)
Median	2.10	1.70	-0.40
Q1, Q3	1.50, 2.70	1.20, 2.20	-0.90, 0.00
Min, Max	0.3, 5.5	0.0, 5.3	-2.5, 3.0
FAIM for Subjects – Adults			
n	22	40	17
Mean (SD)	2.08 (0.830)	1.69 (0.756)	-0.56 (0.953)
Median	1.90	1.70	-0.50
Q1, Q3	1.50, 2.80	1.25, 2.20	-0.80, -0.20
Min, Max	0.7, 4.0	0.5, 4.0	-2.7, 1.8
FAIM for Parents – 0 to 12 Years			
n	488	438	337
Mean (SD)	2.93 (0.976)	2.50 (0.976)	-0.44 (1.020)
Median	2.90	2.35	-0.40
Q1, Q3	2.30, 3.50	1.90, 3.00	-1.10, 0.30
Min, Max	0.4, 6.0	0.0, 6.0	-4.0, 2.4

	Baseline	End of Treat/Study [1]	Change from Baseline
FAIM for Parents – 13 to 17 Years			
n	165	165	77
Mean (SD)	3.19 (1.064)	2.85 (0.857)	-0.15 (0.868)
Median	3.00	2.80	-0.20
Q1, Q3	2.50, 3.80	2.30, 3.30	-0.50, 0.30
Min, Max	0.5, 6.0	1.0, 5.3	-3.3, 1.8

Source: Table 46, Table 47, Table 48, Table 49, Table 50

[1] Earliest visit from End of Treatment / Early Discontinuation, End of Study (Legacy Only), and Study Exit Visits.

End of Treat/Study, End of Treatment/Study; FAIM, Food Allergy Independent Measure.

Assessment of response:

The MAH answers the question as follows:

8.1. The MAH explains that 64 subjects had been disposed to a twice weekly (BIW) dosing regimen with a median treatment exposure of 959.0 days (range, 42-1762 days) in ARC008. It is described that one subject switched back to daily dosing. Overall the treatment-related adverse events were reported of being consistent with the safety profile of AR101 for all subjects in ARC008. The information provided now gives more insight in the non-daily dosing regimen as requested.

8.2. In terms of the *only* 134 subjects entered the follow-up observation period, the MAH explains that this is linked to the Protocol Amendment 6.0 in 22 December 2020. Due to this Amendment, the high numbers of missing 'End of Treatment', 'Disposition – Study Exit' and 'End of follow-up' forms are explainable. As such, treatment was discontinued early during ARC008 in 77.9% (710/911) subjects, the study was discontinued early in 52.5% (478/911) of subjects, and most subjects who did not complete the Disposition – Study Exit form did not do so because that form was introduced in Protocol Amendment 6.0. The answer provided clarifies sufficiently.

8.2.1. In terms of the mentioned "sustained effect" ("A follow-up observation period after the last dose of AR101 was included to assess sustained clinical effect of AR101 treatment"), the MAH describes that of the 134 subjects who entered this period, 122 subjects reported their peanut allergy treatment plan during follow-up guided by the subjects' physician. Peanut allergy treatment during follow-up were as follows: food equivalent for peanut oral immunotherapy (**83.6%),** commercially available product

(Palforzia) (13.9%), and complete peanut avoidance or other (6.6% each). Unfortunately, no subjects had the optional DBPCFC at the end of the 1-year follow-up observation.

However, sustained efficacy of the effects of AR101 treatment after the end of treatment (ie, subjects who had 1 year of complete peanut avoidance) could not be assessed.

8.3. The MAH firstly presented data on the evaluation of subjects' and caregivers QoL. It is described that treatment resulted in improved subject-reported FAQLQ scores for subjects and parental burden. Improvements in parent-reported FAQLQ scores were noted, though not clinically significant. Treatment with AR101 resulted in improved subject-reported and parent-reported Food Allergy Independent Measure (FAIM) scores.

The information provided is acknowledged.

The issue is solved.