IQWiG Reports – Commission No. A21-135

AR101 (peanut allergy) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *AR101 (Erdnussallergie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 January). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
AR101 (peanut allergy) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
15 October 2021

Internal Commission No.
A21-135

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

No feedback of persons concerned or patient organizations was received within the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Sascha Abbas
- Reza Fathollah-Nejad
- Lisa Junge
- Marco Knelangen
- Petra Kohlepp
- Daniela Preukschat
- Christoph Schürmann
- Carolin Weigel

Keywords: AR101, Peanut Hypersensitivity, Child, Adolescent, Benefit Assessment, NCT02635776, NCT03201003

Table of contents

List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CoFAR	Consortium for Food Allergy Research
CTCAE	Common Terminology Criteria for Adverse Events
DBPCFC	double-blind placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
FAIM	Food Allergy Independent Measure
FAQLQ	Food Allergy Quality of Life Questionnaire
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IgE	immunoglobulin E
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PRACTALL	Practical Allergy
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug AR101. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 October 2021.

Research question

The aim of the present report is the assessment of the added benefit of AR101 in comparison with watchful waiting as appropriate comparator therapy (ACT) in patients aged 4 to 17 years with confirmed diagnosis of peanut allergy.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of AR101

Therapeutic indication	ACT[a]
Patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy[b]	Watchful waiting[c]
a. Presentation of the ACT specified by the G-BA. b. The use can be continued in patients who are 18 years and older. Use of the drug has to be accompanied by a peanut-free diet. c. A peanut-avoiding diet was assumed in both study arms. It is assumed that in the event of accidental exposure, the use of a rescue medication is possible in both arms in case of clinical necessity. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit. In the present benefit assessment, it is assumed that RCTs in which all treatment phases of AR101 (initial dose escalation, dose increase and maintenance phase) are completed and whose study duration exceeds 6 months allow statements on short-term effects. However, in the present therapeutic indication, a study duration of 2 to 3 years is required for long-term statements, also on the sustainability of effects.

Study pool and study design

The study pool for the benefit assessment of AR101 consists of the studies ARC003 and ARC010. ARC003 and ARC010 are randomized, double-blind studies on the comparison of AR101 with placebo. Patients aged 4 to 55 years (ARC003) or patients aged 4 to 17 years (ARC010) were included. In addition to a serum concentration ≥ 0.35 kU_A/L of

immunoglobulin E (IgE) antibodies against peanut within the last 12 months and/or a mean hive diameter ≥ 3 mm larger after a peanut skin prick test compared with the negative control, the diagnosis was confirmed in a double-blind placebo-controlled food challenge (DBPCFC) at screening. Inclusion criteria were dose-limiting symptoms at ≤ 100 mg peanut protein in study ARC003 or at ≤ 300 mg in study ARC010. The severity of reactions was graded with minor deviations from the Practical Allergy (PRACTALL) guidelines.

In the ARC003 study, 555 patients were randomly assigned either to treatment with AR101 (N = 416) or placebo (N = 139) in a 3:1 ratio. The relevant subpopulation of children and adolescents aged 4 to 17 years included 374 children in the AR101 arm and 125 children in the placebo arm. In the ARC010 study, 175 patients were randomly assigned either to treatment with AR101 (N = 132) or placebo (N = 43) in a 3:1 ratio.

The dosing regimen of AR101 is divided into an initial dose escalation of 1 day (on day 2, the 3 mg dose was administered again to decide about the transition to the next treatment phase based on the severity of symptoms encountered), a dose increase phase (between 20 and a maximum of 40 weeks), in which the medication was dosed up daily at 2-week intervals starting with 3 mg up to a maintenance dose of 300 mg, and a maintenance phase with a daily dose of 300 mg (24 to 28 weeks in ARC003 and 12-16 weeks in ARC010).

In both studies, dosage of AR101 was in compliance with the Summary of Product Characteristics (SPC). Patients had to adhere to a peanut-avoiding diet during the entire study duration. Allergic reactions were recorded within the framework of the dose escalation in the study centre according to specified criteria and rated by the degree of severity. For the treatment of acute allergic reactions, antihistamines and/or adrenaline could be administered as rescue medication, and, if indicated, also together with IV infusions, beta-adrenoceptor agonists, oxygen and/or steroids. The ACT was adequately implemented in the studies ARC003 and ARC010.

After reaching the maximum duration of the maintenance phase, treatment with the study medication was terminated and a DBPCFC (exit DBPCFC) was performed. Primary outcome in both studies was tolerating 1000 mg of peanut protein (in study ARC003, 600 mg of peanut protein only in North America) with no more than mild symptoms during the exit DBPCFC. Further patient-relevant outcomes on morbidity and side effects were additionally recorded.

The successful passing of a medically supervised food provocation is described as a surrogate for the effectiveness of desensitization. However, the DBPCFC does not represent an everyday situation, so that its outcome does not allow predictions to be made regarding the future risk and frequency of allergic reactions after peanut exposure. Thus, the outcome “absence of symptoms” defined posthoc by the company (defined as no symptoms up to a maximum tested dose of 1000 mg peanut protein in the exit DBPCFC) is not considered per se as a valid surrogate for the occurrence of allergic reactions after accidental exposure to peanuts in the course of out-of-hospital setting.

Comparability of the studies ARC003 and ARC010 for the quantitative interpretation of the results

The studies ARC003 and ARC010 are largely comparable with regard to the study design, the inclusion and exclusion criteria and the characteristics of the patients included. Differences exist in the maximum tolerated dose of peanut protein at study inclusion as defined by the protocol, the duration of treatment and the location of the study. However, the differences are not serious, so that the two studies, ARC003 and ARC010 can be pooled in a meta-analysis.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for the studies ARC003 and ARC010. At outcome level, the risk of bias of the results was rated as high for all outcomes except for "all-cause mortality" and "discontinuation due to adverse events (AEs)".

Based on the available information, no more than proof, e.g. of an added benefit, can be determined for all outcomes with the exception of the outcome “allergic reactions due to accidental exposure to peanuts” despite a partially high risk of bias due to sensitivity analyses calculated by the Institute. For the outcome "allergic reactions due to accidental exposure to peanuts", there is a reduced certainty of conclusions, so that at most indications can be determined for this outcome.

Results

Mortality

All-cause mortality

No deaths occurred in the studies ARC003 and ARC010. This resulted in no hint of an added benefit of AR101 in comparison with watchful waiting for the outcome “all-cause mortality”; an added benefit is therefore not proven.

Morbidity

Allergic reactions due to accidental exposure to peanuts

There was no statistically significant difference between the treatment groups for the outcome "allergic reactions due to accidental exposure to peanuts”. This resulted in no hint of an added benefit of AR101 in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

There were no usable data on health-related quality of life. The company presented analyses on the Food Allergy Independent Measure (FAIM) and Food Allergy Quality of Life Questionnaire (FAQLQ) instruments and assigned them to health-related quality of life. Regardless of the examination of the instruments’ validity, the recording of the FAQLQ and FAIM instruments planned in the studies is not suitable to adequately capture patient-reported morbidity/health-related quality of life in the present indication. This resulted in no hint of an

added benefit of AR101 in comparison with watchful waiting for the outcome "health-related quality of life"; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from AR101 in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs

There was no statistically significant difference between the treatment groups for the outcome "severe AEs". This resulted in no hint of greater or lesser harm from AR101 in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", there is a statistically significant difference to the disadvantage of AR101. This resulted in proof of greater harm from AR101 in comparison with watchful waiting.

Systemic allergic reactions

For the outcome "systemic allergic reactions", there is a statistically significant difference to the disadvantage of AR101. This resulted in proof of greater harm from AR101 in comparison with watchful waiting.

Severe systemic allergic reactions

There was no statistically significant difference between the treatment groups for the outcome "severe systemic allergic reactions". This resulted in no hint of greater or lesser harm from AR101 in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Abdominal pain, pain in the upper abdomen, itching in the oral cavity, paraesthesia oral, tightness in the throat (preferred term [PT], AE each) and ear and labyrinth disorders (System Organ Class [SOC], AE)

There is a statistically significant difference to the disadvantage of AR101 for each of the outcomes "abdominal pain", "pain in the upper abdomen", "itching in the oral cavity", "paraesthesia oral", "tightness in the throat" (PT, AE each) and "ear and labyrinth disorders" (SOC, AE). This results in a proof of greater harm from AR101 compared to watchful waiting for these outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug AR101 in comparison with the ACT are assessed as follows:

The available data only allow statements on short-term effects.

The overall consideration showed only negative effects for AR101 versus the ACT watchful waiting in the outcome category of non-serious/non-severe side effects, each with the extent "considerable".

Treatment with AR101 is a permanent therapy in which patients must still maintain a peanut-free diet throughout and follow recommended measures to mitigate the risks associated with co-factors during treatment. This means that patients continue to be restricted in terms of their diet and lifestyle even during treatment with AR101. Moreover, the observed disadvantages of AR101 - with the exception of discontinuations due to AEs - were not exclusively limited to the initial phase of the dose increase, but still occurred in the maintenance phase. Particularly in the case of systemic allergic reactions, no decrease in the risk, which was significantly increased compared to the control arm, could be seen in the course of the study.

Although an advantage of AR101 over placebo was observed with respect to the outcome "absence of symptoms in the exit DBPCFC", this was not reflected in the patient-relevant outcome "allergic reactions due to accidental exposure to peanuts". It is unclear whether this is due to the study duration being too short. Whether the advantages in provocation testing are reflected in a reduction of the allergic reactions (both reactions due to accidental exposure as well as in general) in the further course can only be answered by a longer study duration/follow-up observation. Moreover, there were no usable data on health-related quality of life. These data would be important to assess the impact of permanent treatment with AR101 o patients while at the same time maintaining a peanut-avoiding diet.

In summary, there is proof of lesser benefit of AR101 compared to the ACT "observational waiting" for patients aged 4-17 years with a confirmed diagnosis of peanut allergy.

Table 3 shows a summary of probability and extent of the added benefit of AR101.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: AR101 – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy[b]	Watchful waiting[c]	Proof of lesser benefit[d]

a. Presentation of the ACT specified by the G-BA.
b. The use can be continued in patients who are 18 years and older. Use of the drug has to be accompanied by a peanut-free diet.
c. A peanut-avoiding diet was assumed in both study arms. It is assumed that in the event of accidental exposure, the use of a rescue medication is possible in both arms in case of clinical necessity.
d. The available data only allow statements on short-term effects. In the studies relevant for the present assessment, the diagnosis of peanut allergy was confirmed within the framework of a DBPCFC at screening (inclusion criteria were dose-limiting symptoms at ≤ 100 mg peanut protein in the ARC003 study or at ≤ 300 mg in the ARC010 study). It is unclear whether the observed effects are transferable to patients with peanut allergy who did not undergo DBPCFC to confirm the diagnosis and/or who are less severely affected (i.e. who only show dose-limiting symptoms in DBPCFC at > 300 mg). According to the SPC, no DBPCFC is required.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; DBPCFC: double-blind placebo-controlled food challenge

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of AR101 in comparison with watchful waiting as ACT in patients aged 4 to 17 years with confirmed diagnosis of peanut allergy.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of AR101

Therapeutic indication	ACT[a]
Patients aged 4 to 17 years with a confirmed diagnosis of peanut allergyb	Watchful waiting[c]

a. Presentation of the ACT specified by the G-BA.
b. The use can be continued in patients who are 18 years and older. Use of the drug has to be accompanied by a peanut-free diet.
c. A peanut-avoiding diet was assumed in both study arms. It is assumed that in the event of accidental exposure, the use of a rescue medication is possible in both arms in case of clinical necessity.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

In the present benefit assessment, it is assumed that RCTs in which all treatment phases of AR101 (initial dose escalation, dose increase and maintenance phase) are completed and whose study duration exceeds 6 months allow statements on short-term effects. However, in the present therapeutic indication, a study duration of 2 to 3 years is required for long-term statements, also on the sustainability of effects [3].

The assessment deviates from that of the company, which imposed no restrictions regarding the minimum study duration and additionally included “follow-up studies of RCTs”.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on AR101 (status: 6 October 2021)
- bibliographical literature search on AR101 (last search on 20 September 2021)
- search in trial registries/trial results databases for studies on AR101 (last search on 6 October 2021)
- search on the G-BA website for AR101 (last search on 6 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on AR101 (last search on 3 November 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: AR101 vs. watchful waiting

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
PALISADE (ARC003[c])	Yes	Yes	No	Yes [4]	Yes [5,6]	Yes [7]
ARTEMIS (ARC010[c])	Yes	Yes	No	Yes [8]	Yes [9,10]	Yes [11]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment of AR101 consisted of the studies ARC003 and ARC010.

This deviates from the company, which additionally included the studies ARC004 [12-14] and ARC007 [15]. However, both studies were unsuitable to derive conclusions on the added benefit of AR101 in comparison with the ACT. This is justified below.

Study ARC004: no comparison against the ACT

ARC004 is an open-label extension study to study ARC003 (see Section 2.3.2) investigating alternative dosing intervals (i.e. including non-daily) for the maintenance phase of treatment with AR101. Patients who successfully completed the double-blind, placebo-controlled food provocation at the end of treatment (exit DBPCFC) in study ARC003 could be included in study ARC004 (see Section 2.3.2 for a description of the implementation of the DBPCFC). A successful completion of the ARC003 study was defined as the occurrence of no or mild symptoms after the 300 mg dose peanut protein (cumulative 443 mg) in the exit DBPCFC. Patients in the placebo arm of ARC003 were allocated to group 1, and patients in the intervention arm of the ARC003 study were assigned to group 2. Group 2 was again divided into several cohorts (1, 2, 3A, 3B, 3C) in which AR101 was administered at different dosing intervals (including non-daily). Primary outcome of the study was the frequency of AEs during the course of the study.

For the derivation of the added benefit, the company used cohorts 1 and 3A, in which the patients received AR101 daily in doses specified in the SPC [16]. Patients from cohort 1 and cohort 3A received further treatment with AR101 for 28 or 56 weeks after termination of study ARC003. Thus, from the view of the company, data are available in combination with the

ARC003 study that allow statements on the long-term treatment effects of AR101. Cohort 1 and cohort 3A included 112 and 31 patients, respectively.

The company's assessment was not shared. In the cohorts used by the company, patients exclusively received AR101. A comparison with the ACT (watchful waiting) is not available. ARC004 in combination with study ARC003 does not allow conclusions to be drawn about sustainable effects. The ARC004 study was not included in the present benefit assessment.

Study ARC007: no maintenance phase and overall too short study duration

Study ARC007 is a double-blind, placebo-controlled RCT that was conducted in North America and included children from 4 to 17 years of age with IgE-mediated peanut allergy. The diagnosis was explicitly not based on a DBPCFC, but exclusively on clinical symptoms of allergy in temporal association with oral peanut exposure as well as a serum IgE antibody concentration ≥ 14 kU_A/L and a ≥ 8 mm larger mean hive diameter after a peanut skin prick test compared with the negative control. A total of 506 patients were randomly assigned to the treatment arms in a 2:1 ratio stratified by the age classes 4 to 11 years and 12 to 17 years (338 patients in the intervention arm and 168 patients in the placebo arm).

The study comprised an initial dose escalation phase as well as a dose increase phase in line with the regimen used in the studies ARC003 and ARC010 (see Table 7 in Section 2.3.2). A total treatment duration between 20 and a maximum of 48 weeks was planned, depending on how quickly the dose escalation from one level to the next could take place. A maximum treatment duration of 48 weeks was possible by means of permitted dose reductions and re-escalations. In both arms, the median treatment duration was 5.6 months; the mean treatment duration was 5.4 months in the intervention arm and 5.5 months in the placebo arm. Primary outcome of the study was the frequency of AEs during the course of the study.

Treatment with AR101 provides for a maintenance phase with 300 mg AR101 daily after the initial dose escalation phase and dose-increase phase [16]. A maintenance phase was not planned in study ARC007, the patients were only on the maintenance dose for about 2 weeks. However, the maintenance treatment presents an essential component of the AR101 treatment concept and is indispensable for the assessment of the treatment success. In addition, the median and mean treatment durations of less than 6 months are too short to allow conclusions about short-term effects (see Section 2.2). The ARC007 study was therefore not relevant for the benefit assessment.

2.3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: AR101 versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ARC003	RCT, double-blind, parallel	Patients aged 4 to 55 years with peanut allergy: ▪ serum IgE antibodies against peanut ≥ 0.35 kU_A/L (within the last 12 months) and/or peanut prick test of ≥ 3 mm compared to the negative control ▪ dose-limiting symptoms at ≤ 100 mg peanut protein during the screening DBPCFC[b, c]	AR101 (N = 416) placebo (N = 139) relevant subpopulation thereof (patients aged 4 to 17 years): ▪ AR101 (n = 374)[d] ▪ placebo (N = 125)[d]	▪ Screening: 28 days (incl. screening DBPCFC)[b] ▪ treatment (44–68 weeks in total[e]): ▫ 2 days (initial dose escalation phase) ▫ 20–40 weeks[e] (dose increase) ▫ 24–28 weeks[e] (maintenance) ▪ exit DBPCFC[b] ▪ observation: up to 30 days[f,g]	69 centres in: Canada, Denmark, Germany, Great Britain, Netherlands, Ireland, Italy, Spain, Sweden, USA 12/2015–12/2017	Primary: tolerating 1000 mg peanut protein (cumulative 2043 mg) in Europe or 600 mg (cumulative 1043 mg) peanut protein in North America with no or mild symptoms at exit DBPCFC. secondary: morbidity, health-related quality of life, AEs
ARC010	RCT, double-blind, parallel	Patients aged 4 to 17 years with peanut allergy: ▪ serum IgE antibodies against peanut ≥ 0.35 kU_A/L (within the last 12 months) and/or peanut prick test of ≥ 3 mm compared to the negative control. ▪ dose-limiting symptoms at ≤ 300 mg peanut protein during the screening DBPCFC[b, c]	AR101 (N = 132) placebo (N = 43)	▪ Screening: 28 days (incl. screening DBPCFC)[b] ▪ treatment (32–56 weeks[e] in total): ▫ 2 days (initial dose escalation phase) ▫ 20–40 weeks[e] (dose increase) ▫ 12–16 weeks[e] (maintenance) ▪ exit DBPCFC[b] ▪ observation: up to 30 days[f,g]	18 centres in: France, Germany, Ireland, Italy, Spain, Sweden, United Kingdom 06/2017–02/2019	Primary: tolerating 1000 mg (cumulative 2043 mg) of peanut protein with no or mild symptoms at exit DBPCFC secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: AR101 versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. A double-blind, placebo-controlled food provocation (screening or exit DBPCFC) was performed each before the start of treatment with the study medication and at the end of the maintenance phase (for description see running text).
c. According to slightly modified PRACTALL guidelines (Figure 3 in [17])
d. Of these, 2 patients in the intervention arm and 1 patient in the placebo arm received no study medication.
e. The upper limit refers to the maximum allowed duration of treatment that allows dose reductions and re-escalations; the lower limit refers to the duration needed if all dose escalation steps are completed as planned.
f. In case of a premature treatment discontinuation (i.e. before having reached the maximum treatment duration of the maintenance treatment), patients were only followed up for 14 days (ARC003) or 14 to 16 days (ARC010).
g. After completion of the study, further treatment with AR101 was possible in the follow-up studies ARC004 (for study ARC003) and ARC008 (for study ARC010).

AE: adverse event; DBPCFC: double-blind placebo-controlled food challenge; IgE: immunoglobulin E; kU_A: kilo units of allergen-specific IgE; n: relevant subpopulation; N: number of randomized patients; PRACTALL: Practical Allergy; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: AR101 vs. placebo (multipage table)

Study	Intervention	Comparison
ARC003	AR101 orally, mixed into carrier food ▪ 1. initial dose escalation (2 days) ▫ day1: 0.5/1/1.5/3/6 mg in increasing doses every 20–30 minutes ▫ day 2: 3 mg ▪ 2. dose increase (20–40 weeks) ▫ daily: dose increases at 2-week intervals until a daily dose of 300 mg is reached: 3/6/12/20/40/80/120/160/200/240/300 mg ▪ 3. maintenance (24–28 weeks)[a] ▫ daily: 300 mg	Placebo same administration as in the intervention arm
	▪ temporary deviations from the planned dose regimen were allowed in the dose increase and maintenance phase due to the occurrence of allergic reactions (dose reduction or dose delay[b]). ▪ patients should adhere to a peanut-avoiding diet.	
	Non-permitted pretreatment ▪ immunotherapy against another allergen in which the maintenance dose had not been reached yet ▪ steroid-based drugs (IV, IM, orally)[c] ▪ antihistamines 5 half-lives before the first day of initial dose escalation, prick test or screening DBPCFC ▪ therapeutic antibodies (e.g. omalizumab), peanut immunotherapy immunomodulating therapy (except corticosteroids) within the last 6 months **non-permitted concomitant treatment** ▪ omalizumab, systemic oral corticosteroids for > 3 consecutive weeks, oral beta-blockers, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, tricyclic antidepressants ▪ immunomodulatory drugs (including immunosuppressants) ▪ prophylactic administration of antihistamines[d] **permitted concomitant treatment** ▪ continuation of medication for the treatment of asthma, allergic rhinitis and atopic dermatitis ▪ topical use of steroids after skin prick test ▪ treatment of acute allergic reactions with antihistamines and/or adrenaline, if indicated with IV infusions, beta-adrenoceptor agonists, oxygen and/or steroids[e] ▪ symptomatic treatment of chronic and/or recurrent AEs[f]	
ARC010	AR101 orally, mixed into carrier food ▪ initial dose escalation and dose increase see ARC003 study ▪ maintenance (12–16 weeks)[a] ▫ daily: 300 mg	placebo same administration as in the intervention arm
	▪ temporary deviations from the planned dose regimen were allowed in the dose increase and maintenance phase due to the occurrence of allergic reactions (dose reduction or dose delay[b]). ▪ patients should adhere to a peanut-avoiding diet.	

Table 7: Characteristics of the intervention – RCT, direct comparison: AR101 vs. placebo (multipage table)

Study	Intervention	Comparison
	non-permitted pretreatment ▪ peanut-specific or other food-related immunotherapy within the previous 5 years ▪ oral or parenteral high-dose corticosteroid therapy[g] ▪ antihistamines 5 half-lives before initial dose escalation, prick test or DBPCFC ▪ therapeutic antibodies or other immunomodulators (excluding aeroallergens, immunotherapies with venom or corticosteroids) within the previous 6 months **non-permitted concomitant treatment** ▪ therapeutic antibodies (e.g. omalizumab), systemic oral corticosteroids for > 3 consecutive weeks, oral beta-blockers, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, tricyclic antidepressants ▪ immunomodulatory drugs (including immunosuppressants) ▪ prophylactic administration of antihistamines[d] **permitted concomitant treatment** ▪ continuation of medication for the treatment of asthma, allergic rhinitis and atopic dermatitis, as well as use of topical steroids ▪ topical steroids after skin prick test ▪ treatment of acute reactions with antihistamines and/or adrenaline, if indicated with IV infusions, beta-adrenoceptor agonists, oxygen and/or steroids[e] ▪ symptomatic treatment of chronic and/or recurrent AEs[f]	

a. If a dose reduction of the stable dose of 300 mg/day was necessary within the last weeks of the planned maintenance phase, the maintenance phase could be extended up to 4 weeks.
b. For dose delays of ≥ 15 consecutive days for any reason during the study period (excluding dose delays due to chronic or recurrent gastrointestinal AEs at or before reaching a dose level of 20 mg), patients were classified as escalation failures and treatment was discontinued.
c. Daily oral intake > 1 month within the previous year or pulse therapy (orally, IV, IM) within the last 3 months or more than 2 pulse therapies (orally, IV, IM) within the previous year with a duration of ≥ 1 week.
d. Antihistamines and other drugs that may impair the assessment of an allergic reaction should be discontinued 5 half-lives of the drug before the first day of the first dose escalation, skin prick test or DBPCFCs, respectively.
e. Patients who did not already have an adrenaline autoinjector were prescribed one before the first dose.
f. Symptomatic treatment for chronic and/or recurrent AEs was allowed in addition to (but not as a substitute for) dose reduction. An attempt should be made to adjust the symptomatic therapy before a new dose escalation.
g. Daily intake > 1 month within the previous year or 1 treatment in the last 3 months or ≥ 2 treatments within the previous year with a duration of ≥ 1 week.

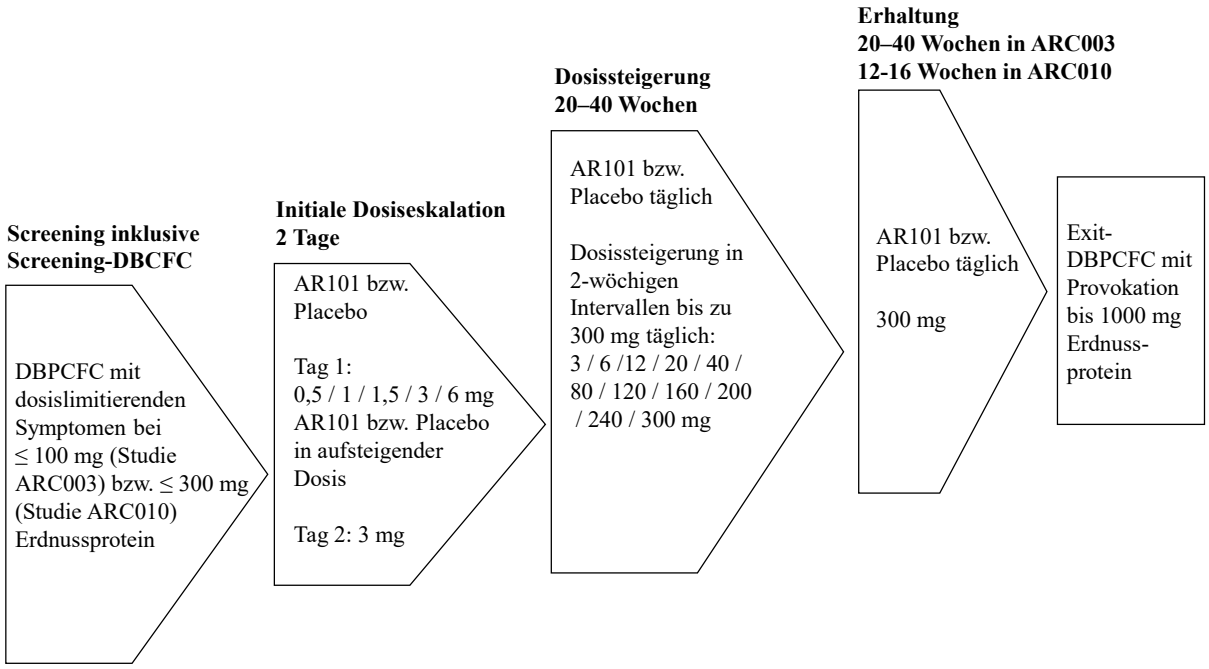
ACE: angiotensin converting enzyme inhibitor; AE: adverse event; ARB: angiotensin receptor blocker; DBPCFC: double-blind placebo-controlled food challenge; IM: intramuscular; IV: intravenous; RCT: randomized controlled trial

Study characteristics

The studies ARC003 and ARC010 are randomized, double-blind studies on the comparison of AR101 with placebo. Patients aged 4 to 55 years (ARC003) or patients aged 4 to 17 years (ARC010) were included. In accordance with the approval of AR101 [16], the company presented analyses for the population of the 4 to 17-year-olds for both studies in Module 4 A. In addition to a serum concentration ≥ 0.35 kU_A/L of IgE antibodies against peanut within the last 12 months and/or a mean hive diameter ≥ 3 mm larger after a peanut skin prick test

compared with the negative control, the diagnosis was confirmed in a DBPCFC at screening (for information on DBPCFC see running text below). Inclusion criteria were dose-limiting symptoms at ≤ 100 mg peanut protein in study ARC003 or at ≤ 300 mg in study ARC010. Thus, according to the study protocol, patients who tolerated more peanuts compared to those in study ARC003 and were thus less severely affected by peanut allergy were in principle also included in study ARC010. The proportion of these less affected patients was 21% (see Table 9). In the ARC003 study, 555 patients were randomly assigned either to treatment with AR101 (N = 416) or placebo (N = 139) in a 3:1 ratio, stratified by region (North America Europe). The relevant subpopulation of children and adolescents aged 4 to 17 years included 374 children in the AR101 arm and 125 children in the placebo arm. The following comments on study ARC003 refer to the subpopulation relevant for the benefit assessment. In the ARC010 study, 175 patients were randomly assigned either to treatment with AR101 (N = 132) or placebo (N = 43) in a 3:1 ratio. The ARC010 study was only conducted in Europe.

In both studies, the dosage of AR101 was in compliance with the SPC [16]. Since, according to the SPC, the probability of allergy symptoms occurring after the intake of AR101 may be higher in patients if certain co-factors (e.g. physical exertion, empty stomach, hot showers/baths) are present, there are corresponding specifications on this in both the study protocols and the SPC.



DBPCFC: double-blind placebo-controlled food challenge

Figure 1: Study design of the studies ARC003 and ARC010

The dosing regimen of AR101 is divided into an initial dose escalation of 1 day (on day 2, the 3 mg dose was administered again to decide about the transition to the next treatment phase

based on the severity of symptoms encountered), a dose increase phase, in which the medication was dosed up daily at 2-week intervals starting with 3 mg up to a maintenance dose of 300 mg, and a maintenance phase with a daily dose of 300 mg (see Table 7 and Figure 1). The initiation of a new dose level always took place in the study centre under medical supervision. After the 300 mg dose had been reached, further study visits took place, the first after 2 weeks, then every 4 weeks. Allergic reactions or AEs that occurred between study visits were documented in an electronic patient diary and the entries were reviewed at each study visit.

Patients who developed dose-limiting symptoms during the initial dose escalation phase after administration of the 3 mg dose or moderate or severe symptoms after administration of the confirmatory 3 mg dose on day 2, were not allowed to proceed to the dose increase phase. In both studies, the dose increase phase was limited to a maximum of 40 weeks. Ideally, that is, if each dose escalation level was reached at 14-day intervals and no dose delay or dose reduction with subsequent re-escalation was necessary, the dose increase phase could be completed after 20 weeks.

The planned duration of the maintenance phase was 24 weeks in study ARC003, and thus longer than the planned 12 weeks in study ARC010. In the case of a necessary dose reduction of the stable 300 mg dose at the end of the maintenance phase, this could be extended by up to 4 weeks in both studies, resulting in a maximum duration of the maintenance phase of 28 and 16 weeks, respectively.

Patients had to adhere to a peanut-avoiding diet during the entire study duration. Allergic reactions were recorded within the framework of the dose escalation in the study centre according to specified criteria and rated by the degree of severity. For the treatment of acute allergic reactions, antihistamines and/or adrenaline could be administered as rescue medication, and, if indicated, also together with IV infusions, beta-adrenoceptor agonists, oxygen and/or steroids. Prophylactic administration of antihistamines before the dose increases was not allowed, and antihistamines had to be discontinued in time (5 half-lives) before the DBPCFC. Overall, in both trials, the proportion of patients with rescue medication over the course of the study in the initial dose escalation and dose increase phase was about 20% higher in the intervention arm than in the comparator arm (ARC003: 69% and 48% [initial dose escalation and dose increase phase]; ARC010: initial dose escalation: 16% vs. 1%, dose increase phase: 51% vs. 33%). The differences in the use of rescue medication were smaller in the maintenance phase. In the ARC003 study, 45% of patients in the intervention arm and 42% in the comparator arm received a rescue medication. The proportion was 31% and 24% in the ARC101 study.

Symptomatic treatment for chronic and/or recurrent AEs was allowed in addition to (but not as a substitute for) dose reduction. An attempt should be made to adjust symptomatic therapy before a new dose escalation.

After reaching the maximum duration of the maintenance phase, treatment with the study medication was terminated and the DBPCFC was performed (see the following Section below).

Patients were then observed for AEs for another 30 days. Primary outcome in both studies was tolerating 1000 mg of peanut protein (in study ARC003, 600 mg of peanut protein only in North America) with no more than mild symptoms during the exit DBPCFC. Moreover, patient-relevant outcomes on morbidity and AEs were recorded.

DBPCFC

The DBPCFC is a double-blind, placebo-controlled provocation to food and involves 2 provocation tests: on one day the food to be tested is used and on another day a placebo preparation. In the ARC003 and ARC010 studies, patients in DBPCFC received peanut flour on one day and of oat flour (placebo provocation) on another day in increasing doses at 20- to 30-minute intervals. The maximum allowed interval between the provocation tests was 7 days. In both studies, 2 DBPCFCs took place during the course of the study, at the time of screening (screening DBPCFC) and at the end of the treatment phase (exit DBPCFC). In the DBPCFC, the patient was tested for tolerance to consecutive single doses of peanut protein (or placebo). In the screening DBPCFC, provocation took place by up to a maximum of 100 mg peanut protein (cumulative 143 mg) in the ARC003 study, and by up to a maximum of 300 mg peanut protein (cumulative 443 mg) in the ARC010 study (see Table 8). In the exit DBPCFC, provocation was up to a maximum of 1000 mg (cumulative 2043 mg) in both studies. For the administration of the provocation dose, the same carrier food should be used in both the screening DBPCFC and the exit DBPCFC. Antihistamines and other drugs that may impair the assessment of an allergic reaction should be discontinued about 5 half-lives of the respective drugs before the DBPCFC. The patients were medically monitored during DBPCFC by a physician who was not involved in the administration or escalation of the study medication and who also did not assess AEs occurring in this context. Besides of minor deviations, grading of the severity of reactions was in line with the Practical-Allergy (PRACTALL) guidelines [17]. The severity of the symptoms occurring within the framework of the exit DBPCFC was assessed according to the PRACTALL guidelines [18]. A dose was considered tolerated if either ingestion entailed no symptoms or the symptoms developed were mild or moderate and non-systemic, resolving on their own without therapeutic intervention. Patients who had not reached the 300 mg dose by week 40 were not allowed to participate in the exit DBPCFC. Symptomatic therapies for the treatment of AEs that occurred under the study medication had to be discontinued 4 weeks prior to the exit DBPCFC.

Table 8: Dose levels in the screening and exit DBPCFC in the studies ARC003 and ARC00

Screening/exit DBPCFC	Dose in mg	Study ARC003	Study ARC010	Cumulative dose of peanut protein (mg) exit DBPCFC[a]
Screening	1	x	x	0 (or1)
Screening and exit	3	x	x	3 (or 4)
Screening and exit	10	x	x	13 (or 14)
Screening and exit	30	x	x	43 (or 44)
Screening and exit	100	x	x	143 (or 144)
Screening and exit	300	x (Exit only)	X (Screening and exit)	443 (or 444)
Exit	600	x	x	1043 (or 1044)
Exit	1000	x	x	2043 (or 2044)

a. Patients who had not tolerated the 1 mg dose of peanut protein in the screening DBPCFC had to start with a dose of 1 mg in the exit DBPCFC. A dose of 1 mg could be added in the exit DBPCFC at the testing staff's discretion.

DBPCFC: double-blind placebo-controlled food challenge

Implementation of the ACT

The G-BA specified watchful waiting as ACT.

In the studies ARC003 and ARC010, watchful waiting was operationalized as adherence to a peanut-avoiding diet. In addition, a placebo was administered in the comparator arm to ensure blinding. Accidental exposure to peanuts was documented in the electronic patient diary. The documentation also included the occurrence of allergic reactions in connection with accidental peanut exposure. If clinically necessary, rescue medication could be administered in both arms (see above).

In summary, the ACT was adequately implemented in the studies ARC003 and ARC010.

Patient characteristics

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations – RCT, direct comparison: AR101 versus placebo (multipage table)

Study characteristic category	ARC003		ARC010	
	AR101	placebo	AR101	placebo
	N[a] = 374	N[a] = 125	N[a] = 132	N[a] = 43
Age [years], mean (SD)	9.7 (3.6)	9.6 (3.6)	9 (3.7)	9.5 (3.9)
Age group, n (%)				
4–11 years	238 (64)	89 (72)	97 (73)	30 (70)
12–17 years	134 (36)	35 (28)	35 (27)	13 (30)
Sex [F/M], %	44/56	39/61	48/52	37/63
Family origin, n (%)				
White	292 (79)	97 (78)	108 (82)	35 (81)
Asian	41 (11)	8 (7)	2 (2)	2 (5)
Black/African American	6 (2)	3 (2)	1 (< 1)	0 (0)
Native Americans	1 (< 1)	0 (0)	0 (0)	0 (0)
Hawaiian/pacific Islanders	1 (< 1)	0 (0)	0 (0)	0 (0)
Other	31 (8)	16 (13)	12 (9)	3 (7)
Not specified	0 (0)	0 (0)	11 (8)	4 (9)
Geographical region, n (%)				
North America	306 (81)	100 (81)	0 (0)	0 (0)
Europe	70 (19)	24 (19)	132 (100)	43 (100)
Ps IgE [kU_A/L], median [Q1; Q3]	69.0 [18.6; 194.3]	74.8 [28.9; 251]	43.5 [5.2; 147]	69.7 [20.7; 103]
Hive diameter [mm], median [Q1; Q3]	11 [9; 14.5]	12 [9; 15.3]	9.5 [7.5; 12.3]	9.8 [8; 12.5]
Maximum tolerated dose in screening DBPCFC				
Median [Q1; Q3]	10 [ND[b]]	10 [ND[b]]	10 [ND[b]]	10 [ND[b]]
Mean (SD)	14.8 (12.2)	16.0 (12.5)	34.0 (45.0)	24.8 (32.6)
Categories, n (%)				
None	20 (5)	6 (5)	16 (12)	3 (7)
1 mg	31 (8)	9 (7)	13 (10)	6 (14)
3 mg	77 (21)	25 (20)	15 (11)	6 (14)
10 mg	104 (28)	31 (25)	29 (22)	11 (26)
30 mg	140 (38)	53 (43)	28 (21)	11 (26)
100 mg	0 (0)	0 (0)	31 (23)	6 (14)
300 mg	-	-	0 (0)	0 (0)
Asthma[c], n (%)	198 (53)	77 (56)	56 (42)	14 (33)
Duration of the disease: months since diagnosis [months], median [Q1; Q3]	87.5 [53.6; 128.3]	84.5 [59.3; 126.0]	59.9 [37.3; 93.0]	56.5 [28.7; 107.2]
number of previous anaphylactic reactions, n (%)				
0	103 (28)	35 (28)	74 (56)	21 (49)
1	161 (43)	48 (39)	33 (25)	16 (37)

Table 9: Characteristics of the study populations – RCT, direct comparison: AR101 versus placebo (multipage table)

Study characteristic category	ARC003		ARC010	
	AR101	placebo	AR101	placebo
	N[a] = 374	N[a] = 125	N[a] = 132	N[a] = 43
2	56 (15)	27 (22)	13 (10)	5 (12)
3	29 (8)	7 (6)	8 (6)	0 (0)
> 3	23 (6)	7 (6)	4 (3)	1 (2)
Former and current further allergies (excluding peanut allergy), n (%)	353 (94)[d]	118 (95)[d]	120 (91)[d]	40 (93)[d]
Treatment discontinuation, n (%)	80 (21[e])[f]	10 (8[e])[f]	26 (19[e])[g]	3 (7[e])[g]
Study discontinuation, n (%)	ND	ND	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. For [Q1; Q3], values are only available for the total population or, in ARC003, for the relevant subpopulation of the 4- to 17-year-olds and not per study arm: [3; 30].
c. According to the inclusion criteria, patients with i) severe asthma and ii) uncontrolled mild or moderate asthma were excluded from study participation.
d. Including patients with further food allergies: 245 (66%) vs. 80 (65%) in study ARC003 and 81 (61%) vs. 21 (49%) in study ARC010.
e. Institute's calculation.
f. Common reasons for treatment discontinuation included: AEs (9% vs. 2%) and withdrawal of consent (8% vs. 5%). Percentages refer to the number of randomized patients.
g. The most common reason for treatment discontinuation were AEs (11% vs. 2%). Percentages refer to the number of randomized patients.

DBPCFC: double-blind placebo-controlled food challenge; F: female; kU_A: kilo units of allergen-specific IgE; M: male; n: number of patients in the category, N: number of randomized patients; ND: not data; PS IgE: peanut-specific immunoglobulin E; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Within the individual studies, the patient characteristics are comparable between the two treatment groups. The characteristics were also largely balanced between the two studies. In both studies, the mean age of the patients was between 9 and 10 years. The proportion of 4- to 11-year olds is about 70% of the study population, and about 80% of the patients in both studies were white. Just under 20% of patients in the ARC003 study were enrolled in Europe and about 80% in North America; the ARC010 study was conducted exclusively in Europe. The mean maximum tolerated dose of peanut protein at the time of screening was higher in study ARC010 (34.0 mg and 24.8 mg) than in study ARC003 (14.8 mg and 16.0 mg). At screening, the median tolerance of patients in both arms of ARC003 and ARC010 was at most 10 mg peanut protein.

Course of the study

The treatment regimen of AR101 consists of several phases: initial dose increase, dose increase and maintenance (see above).

In studies ARC003 and ARC010, the median duration of the initial dose escalation was 2 days in each of the two study arms, the median dose increase phase was 154 and 149 days in ARC003

and 153 days in both study arms of ARC010; the median maintenance phase was 175 days in both study arms of the ARC003 study and 104 or 97 days in the ARC010 study. The mean treatment duration in days (standard deviation [SD]) was slightly higher in study ARC003 (302 [104] vs. 320 [68] days) than in study ARC010 (248 [107] vs. 264 [58] days). The median total treatment duration was 331 and 328 days in study ARC003, and 259 and 257 days in study ARC010 in the intervention and the control arms, respectively.

Comparability of the studies ARC003 and ARC010 for the quantitative interpretation of the results

The studies ARC003 and ARC010 are largely comparable with regard to the study design, the inclusion and exclusion criteria and the characteristics of the patients included. Differences exist in the maximum tolerated dose of peanut protein at study inclusion as defined by the protocol, the duration of treatment and the location of the study. Study ARC003 was mostly conducted in North America, study ARC010 exclusively in Europe. Due to the different lengths of the planned maintenance phases, the actual treatment duration was longer in study ARC003 compared with study ARC010 (see above). Due to the different inclusion criteria regarding the occurrence of dose-limiting symptoms at a maximum of 100 mg (study ARC003) or 300 mg peanut protein (study ARC010), the study ARC010 also included patients who, according to the doses tested in the screening DBPCFC (see Table 8), only developed symptoms at a higher amount of peanut protein (maximum tolerated dose 100 mg instead of 30 mg in study ARC003). However, in the ARC010 study, the proportion of patients with a maximum tolerated dose at 100 mg was only 21%. Moreover, the mean maximum tolerated dose of peanut protein at the time of screening was also in a low range in study ARC010 (34.0 mg and 24.8 mg, respectively, see Table 9). Overall, the described differences are not serious, so that the two studies ARC003 and ARC010 can be pooled in a meta-analysis.

This approach deviates from that of the company. The company based its assessment of the feasibility of meta-analyses on all of the studies included by it, ARC003, ARC010, ARC007 and the non-comparative study ARC004. On the basis of this study pool, the company came to the conclusion that a meta-analytical summary was not appropriate due to relevant differences in study design and in the characteristics of the respective patient populations included.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: AR101 versus placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ARC003	Yes	Yes	Yes	Yes	Yes	Yes	Low
ARC010	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies.

Transferability of the study results to the German health care context

The company assumed the study results to be transferable to the German healthcare context and in doing so considered the included studies ARC003, ARC004, ARC007 and ARC010.

As the ARC003 and ARC004 studies were partly conducted in Europe and the ARC010 study was completely conducted in Europe, the European healthcare context was represented. Although according to various publications [7,19-23], the frequency of peanut allergy is estimated to be higher in the USA, where the ARC003 and ARC004 studies were predominantly conducted and ARC007 was almost exclusively conducted (in addition to the USA, there were also study centres in Canada), than in Europe, the general nature and type of development was to be regarded as largely independent of regional differences. In addition, the same comorbidities such as allergic rhinitis or asthma would occur in both regions [24,25]. Furthermore, the company stated that the use of adrenaline as rescue medication for anaphylactic reactions was the standard treatment for acute treatment and management of anaphylaxis according to the German guideline [26] and could therefore be transferred to the German healthcare context, even if the use of adrenaline would differ regionally.

The company also stated that there was no register of patients with peanut allergy in Germany for a comparison with the patient characteristics in the studies and that the proportion of patients included in the ARC003 and ARC010 studies in Germany was too small to allow a direct comparison with the other countries within the respective study. Nevertheless, the company considered the nature of the disease as well as the recommended treatment to be largely comparable within Europe, citing various guidelines, position papers and expert panels [26-34].

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - allergic reactions due to accidental exposure to peanuts
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs ≥ grade ≥ 3
    - severity classification for allergic reactions according to the Consortium for Food Allergy Research (CoFAR) [35], for systemic allergic reactions according to European Academy of Allergy and Clinical Immunology (EAACI) [29], and for all other AEs according to the Common Terminology Criteria for Adverse Events (CTCAE)
  - discontinuation due to AEs
  - systemic allergic reactions
  - severe (according to EAACI criteria [29]) systemic allergic reactions
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 11shows for which outcomes data were available in the studies included.

Table 11: Matrix of outcomes – RCT, direct comparison: AR101 versus placebo

Study	Outcomes								
	All-cause mortality	Allergic reactions due to accidental exposure to peanuts	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Systemic allergic reactions[b, c]	Severe systemic allergic reactions[b, d]	Further specific AEs[e]
ARC003	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes
ARC010	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs ≥ grade 3: classification of the severity of allergic reactions according to CoFAR [35], of systemic allergic reactions according to EAACI [29] and of all other AEs according to CTCAE.
g. Referred to as "anaphylactic reaction" in Module 4 A; defined according to Sampson's diagnosis criteria [18]; coded as PT "anaphylactic reaction".
c. Severity grade 1 to 3 (mild, moderate, severe) according to EAACI criteria [29]
d. Severity grade 3 (severe) according to EAACI criteria [29]; also includes anaphylactic shock.
e. The following events (MedDRA coding) are considered: abdominal pain (PT, AE), pain in the upper abdomen (PT, AE), itching in the oral cavity (PT, AE), paraesthesia oral (PT, AE), tightness in the throat (PT, AE), ear and labyrinth disorders (SOC, AE).
f. No usable data available; see running text for reasons.

AE: adverse event; CoFAR: Consortium for Food Allergy Research; CTCAE: Common Terminology Criteria for Adverse Events; DBPCFC: double-blind placebo-controlled food challenge; EAACI: European Academy of Allergy and Clinical Immunology; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Allergic reactions due to accidental exposure to peanuts

In the studies ARC003 and ARC010, patients had to adhere to a peanut-avoiding diet during the entire course of the study. In case of accidental peanut exposure during the course of the study, patients were instructed to contact the study centre for the recording of possible allergic reactions. Furthermore, documentation was made in the electronic patient diary. If necessary, this was followed by a study visit. In addition to accidental exposure to peanut, exposure to other food allergens was also documented. A special case report form for an accidental exposure to food allergens was used to record the accidental exposure and any reaction to it.

In Module 4 A, the company presented analyses on allergic reactions caused by accidental exposure to peanuts, which are part of the outcome "adverse events associated with accidental exposure to food allergens" predefined in the study protocol. The analyses on allergic reactions due to accidental exposure to peanuts are included in the benefit assessment. However, in the

present therapeutic indication, there is a close correlation between outcomes on morbidity and side effects, as AR101 is a standardized peanut powder, i.e. AR101 itself represents the allergen through the administration of which desensitisation is sought. In the studies ARC003 and ARC010, the assessment of whether an accidental peanut exposure occurred was exclusively based on the assessment of the patient or the patient's custodian. This also determines whether an allergic event that has occurred is classified as an allergic reaction due to accidental peanut exposure (if an accidental exposure was perceived by the patient or his/her custodian) or as a (systemic) allergic reaction, i.e. an AE (if no accidental exposure was perceived by the patient or his/her custodian). This differentiation is subject to uncertainty, for example, when the administration of the intervention (AR101 or placebo) and the accidental peanut exposure/allergic reaction are close in time. This results in a reduced certainty of conclusions for the results of the outcome “allergic reactions due to accidental exposure to peanuts” (see Section 2.4.2).

Allergic reactions due to accidental exposure to peanuts represent the morbidity in the present therapeutic indication. On the other hand, analyses that allow for a consideration of side effects without these events are also necessary. In the overall consideration, the interpretation of the results on the outcome "allergic reactions due to accidental exposure to peanuts" takes into account the results on the side effect outcomes (see Section 2.5.2).

When interpreting the results, it should also be noted that it cannot be clearly inferred from the company's dossier whether allergic reactions due to accidental exposure to peanuts are included in the analyses on side effects (e.g. in the systemic allergic reactions). It is thus unclear whether analyses are available that allow conclusions on AEs, e.g. on (systemic) allergic reactions overall - independent of the cause (e.g. the suspected accidental exposure). However, since from the patient's point of view the primary focus is on the experienced symptom (e.g. the abdominal pain or the systemic allergic reaction), regardless of the cause, such analyses are basically useful as supplementary analyses.

Absence of symptoms at all tested doses (maximum 1000 mg) in the exit DBPCFC

The outcome “absence of symptoms” was defined as no symptoms up to the maximum tested dose of 1000 mg peanut protein in the exit DBPCFC (for information on DBPCFC, see Section 2.3.2). The outcome was analysed post hoc by the company.

DBPCFC simulates accidental peanut exposure under medical supervision by administering increasing doses of peanut protein or placebo at short time intervals. In the studies ARC003 and ARC010, patients were only allowed to participate in the DBPCFC if there was no wheezing or acute disease flare-up in the case of an additionally existing asthma or atopic disease such as atopic dermatitis. In order to participate in the DBPCFC, patients were also not allowed to have an acute disease. In everyday life, however, accidental peanut exposure is possible at any time, regardless of whether there is an acute disease, for example.

The successful passing of a medically supervised food provocation is described as a surrogate for the effectiveness of desensitization [36,37]. However, the DBPCFC does not represent an everyday situation, so that its outcome does not allow predictions to be made regarding the future risk and frequency of allergic reactions after peanut exposure [36]. In everyday life, various parameters (co-factors), such as showering, alcohol consumption, sports or acute disease can have an influence on the allergic reaction after accidental peanut exposure [36,38,39]. Some of these co-factors are modifiable/avoidable (such as alcohol consumption, sports), some are not modifiable/avoidable (such as infections) and lead to the fact that patients can react to considerably smaller amounts of peanuts than in the provocation test in the interaction of factors in everyday life. Even if an amount of 1000 mg peanut protein initially appears theoretically important in view of the average amounts in accidental peanut exposures in everyday life (there are data stating that these are around 125 mg [40]), a successful passing (in this case absence of symptoms at all tested doses) of the DBPCFC is therefore not to be regarded per se as a valid surrogate for the occurrence of allergic reactions after accidental peanut exposure in the course of out-of-hospital setting. In the studies ARC003 and ARC010, allergic reactions after accidental exposure to peanuts were also recorded as a directly patient-relevant outcome (see above). The results of the outcome "absence of symptoms at all tested doses" are therefore only presented as supplementary information.

Anaphylactic shock

An anaphylactic shock is potentially life-threatening and thus represents a patient-relevant outcome. The company analysed “anaphylactic shock” as a separate outcome of the outcome category “morbidity” for a severe systemic allergic reaction (see below). On the one hand, events that occurred independently of the study medication - and thus in connection with the DBPCFC - were included in the analysis of the company. In addition, events occurring outside the hospital setting were considered in the analysis within the framework of the recording of allergic reactions (see below). The severity of allergic reactions was classified according to PRACTALL (see Section 2.3.2) within the framework of the DBPCFC, and according to CoFAR in everyday out-of-hospital settings. Separate case report forms were used for recording in each case. For the recording of allergic reactions, anaphylactic shocks were recorded via the symptom "shock" in the symptom case report form.

In the present benefit assessment, anaphylactic shock was not used as a separate outcome, as occurring events were already recorded via the included outcome “severe systemic allergic reactions” (see below).

FAQLQ and FAIM

The company presented analyses on the FAQLQ and FAIM instruments in its dossier. The FAQLQ is an instrument for the recording of morbidity/health-related quality of life [41-44] in patients with food allergies. FAIM is a tool to record the patient's perceived risk of food allergy. [45]. For both instruments, the company presented analyses on patient-reported versions (for

the age groups 8 to 12 years and 13 to 17 years) as well as analyses on interviews with parents (for the age groups 4 to 12 years and 13 to 17 years).

Regardless of the examination of the instruments' validity, the recording of the FAQLQ and FAIM instruments planned in the studies is not suitable to adequately capture patient-reported morbidity/health-related quality of life in the present indication. Both instruments were recorded at the time of screening before the screening DBPCFC and once at the end of the therapy. The time and circumstances of the recording differed with regard to the end of treatment: in the case of premature treatment discontinuation, recording was blinded (and without exit DBPCFC in the "early discontinuation visit"); for patients who took the medication until the planned end of treatment, recording was carried out unblinded after the exit DBPCFC in the "exit visit". A single measurement at the end of the treatment cannot adequately capture the burden in the different therapy phases (initial dose escalation phase, maintenance), nor the burden of the allergy after successful desensitization. This requires several documentation time points during the study phase as well as recordings beyond the exit DBPCFC. Irrespective of this, it cannot be clearly understood from the FAIM and FAQLQ data collection forms to which period the questions refer, even in case of a single recording after the start of the study medication. In the analyses of patients who have undergone the exit DBPCFC used by the company for the added benefit, it can at least be assumed that the result of the DBPCFC will have an important influence on the assessment of the patient.

Regardless of the previously described fundamental problem of recording patient-reported morbidity/health-related quality of life with only 2 recordings and missing follow-up in the present indication, the analysis of the company is not adequate. The analyses used by the company to derive the added benefit only include patients who took the medication until the end of the study; a relevant proportion of randomized patients is therefore not taken into account. Accordingly, for the patient-reported outcomes of FAIM and FAQLQ, there are mostly consideration proportions < 70% related to both study arms or differences > 15 percentage points between the study arms depending on the study and instrument.

Due to the described general limitation in data collection, neither the validity of the two instruments nor the suitability of the versions used (parents/children) was examined in the context of the benefit assessment. The company's analyses on FAIM and FAQLQ were not used for the benefit assessment.

Notes across outcomes on side effects

According to the study protocol, the following events were recorded in separate case report forms and not via the AE case report form in the submitted analyses on side effects:

- According to the study protocol, events that occurred within the framework of the DBPCFC were not taken into account in the presented analyses on side effects, since no study medication was administered in the DBPCFC or allergic reactions that occurred were assigned to the administration of peanut flour in the provocation test.

- Accidental exposure to food allergens (including exposure to peanut) was recorded in a special case report form for accidental exposure and any reaction to it. Simultaneous recording of occurred events in the AE case report form only took place when the occurred event was an SAE (however, there was no SAE after accidental exposure to food allergens either). It is unclear whether these events are included in the analyses on side effects (e.g. on systemic allergic reactions) presented by the company.

In the dossier, the company submitted analyses on AEs with and without consideration of events of the underlying disease. The company explained that all allergic reactions to peanut or other allergens were considered disease-related. According to the company, this not only referred to AEs that occurred outside of the treatment with the study medication, but also to AEs that, based on the investigators' opinion, were assessed as treatment-associated due to their temporal correlation with the study medication. The company did not specify the exact AEs that remained unconsidered in the analyses on AEs without consideration of events of the underlying disease. In the present situation, the analyses on AEs that also include allergic reactions to peanut or its allergens are used. This is due to the fact that in the present therapeutic indication allergic reactions are also or, due to the peanut-avoiding diet, possibly even primarily caused by the treatment with AR101. An exact separation or differentiation as to whether the occurred events are allergic reactions which are an expression of the underlying disease and can thus be assigned to morbidity, or AEs, is not possible with sufficient certainty for each event in the present therapeutic indication. For the present benefit assessment, it is nevertheless considered useful to (additionally) consider the outcome "allergic reactions due to accidental exposure to peanuts" separately as a morbidity outcome (see above).

It is assumed that the outcomes of the outcome category "side effects" basically also represent the disease-related morbidity. According to the patients, however, few allergic reactions occurred as a result of accidental exposure to peanuts in the present data situation. Moreover, it is unclear whether these were included in the analyses on side effects presented by the company (see above). Overall, conclusions on side effects and harm are possible on the basis of the available analyses.

Systemic and severe systemic allergic reactions (including anaphylactic shock)

A modified version of Sampson's criteria was used to classify AEs as systemic allergic reactions (also referred to as "anaphylactic reactions" or "anaphylaxis" by the company) [18]. AEs that affected more than one organ system were classified as systemic allergic reactions based on these criteria. The severity grades were classified according to EAACI criteria (mild, moderate, severe) [29]. An EAACI severity grade of 3 meant the presence of a severe systemic allergic reaction. Such reaction could be serious or potentially life-threatening. A severe anaphylactic reaction also includes anaphylactic shock.

Systemic allergic reactions were recorded on a special case report form and were coded via the PT "anaphylactic reaction".

Severe AEs (according to CTCAE/CoFAR/EAACI)

The severity of allergic reactions was classified according to CoFAR [35], of systemic allergic reactions according to EAACI [29] and of all other AEs according to CTCAE. The summary of 3 different severity classifications (CoFAR, EAACI and CTCAE) is basically subject to uncertainty, especially as the EAACI criterion for a severe allergic reaction (hypoxia, hypotension or neurologic impairment) appears more restrictive than the corresponding criteria according to CTCAE (symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; low blood pressure) or the general CoFAR criterion (symptoms may include bronchospasm with dyspnoea, severe abdominal pain, tightness in the throat with hoarseness, transient low blood pressure or other symptoms). Moreover, there are more specific severity criteria for individual PTs that represent allergic reactions (such as diarrhoea) in the CTCAE categorization than are provided by the non-PT-specific general CoFAR classification. In the present data situation, the analyses are nevertheless assessed as usable for conclusions on the outcome “severe AEs” despite these uncertainties. In this context, it is important to note that a severity classification was made for each recorded AE.

Allergic reactions

The company presented analyses on allergic reactions (referred to as “hypersensitivity” by the company in its dossier). In the ARC003 and ARC010 studies, electronic diaries and interviews with patients and/or their guardians were used for the recording. For an event to be classified as an allergic reaction, the investigator had to label the symptom(s) that occurred as an allergic reaction. The severity of an allergic reactions was classified according to CoFAR [35].

In principle, an aggregated analysis of all allergic reactions across PTs is desirable as a supplementary analysis. However, with the operationalization presented, events are only included in the analysis if the physician labelled such event correspondingly in the case report form. Therefore, the outcome “allergic reactions” was not included in the benefit assessment. Instead, specific AEs that result from the frequencies and that are not limited by an "allergic reaction" label applied by the physician are presented. This reflects a wide range of potential allergic reactions. However, the results on the outcome "allergic reactions” are presented as supplementary information in Appendix B.

2.4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: AR101 vs. placebo

Study	Study level	Outcomes								
		All-cause mortality	Allergic reactions due to accidental exposure to peanuts	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Systemic allergic reactions[b, c]	Severe systemic allergic reactions[b, d]	Further specific AEs[e]
ARC003	N	N	H[f]	–[g]	H[f, h]	H[f, h]	N	H[f]	H[f]	H[f, h]
ARC010	N	N	H[f]	–[g]	H[f, h]	H[f, h]	N	H[f]	H[f]	H[f, h]

a. Severe AEs ≥ grade 3: classification of the severity of allergic reactions according to CoFAR [35], of systemic allergic reactions according to EAACI [29] and of all other AEs according to CTCAE.
b. Referred to as "anaphylactic reaction" in Module 4 A; defined according to Sampson's diagnosis criteria [18] (see Section 2.4.1); coded as PT "anaphylactic reaction".
c. Severity grade 1 to 3 (mild, moderate, severe) according to EAACI criteria [29]
d. Severity grade 3 (severe) according to EAACI criteria [29]; also includes anaphylactic shock.
e. The following events (MedDRA coding) are considered: abdominal pain (PT, AE), pain in the upper abdomen (PT, AE), itching in the oral cavity (PT, AE), paraesthesia oral (PT, AE), tightness in the throat (PT, AE), ear and labyrinth disorders (SOC, AE).
f. High and differential proportions of patients who were not fully observed over the entire treatment period.
g. No usable data available; see Section 2.4.1 for reasons.
h. Patients were only observed for 14 days (study ARC003) or 14 to 16 days (study ARC010) after treatment discontinuation.

AE: adverse event; CoFAR: Consortium for Food Allergy Research; CTCAE: Common Terminology Criteria for Adverse Events; DBPCFC: double-blind placebo-controlled food challenge; EAACI: European Academy of Allergy and Clinical Immunology; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event

The risk of bias for the results on the outcomes "all-cause mortality" and "discontinuation due to AEs" must be rated as low. For the other outcomes used in the analysis, there is a high risk of bias of the results, which is due to the possibly incomplete observations of some of the patients: Of these, 21.5% vs. 8.1% (ARC003) and 19.7% vs. 7.0% (ARC010) discontinued the study prematurely, and the respective outcomes were not followed up until the end of the study. For the outcomes on AEs, follow-up was only up to 14 (study ARC003) or 14 to 16 days (study ARC010) after premature discontinuation of treatment. Events that might have been captured under AE outcomes were thus not recorded over the entire course of the study.

The impact of a possibly incomplete observation with regard to adverse events was investigated in sensitivity analyses calculated by the Institute, provided that a statistically significant result

was shown in the meta-analysis. For incompletely observed patients in the control group, it was assumed that they had not experienced the respective event by the time the treatment was discontinued, but would experience it with a probability corresponding to the observed risk in the intervention arm during the remaining course of the study. Conversely, for incompletely observed patients in the intervention arm, it was assumed that they would have experienced a respective event with the probability corresponding to the observed risk for the event in the control arm. According to the procedure in Higgins et al [46], an adjustment of the variance was made in the resulting confidence intervals of the effect estimations. In the meta-analyses, this approach leads to a decrease in value of the effects. In all situations, statistically significant effects of the original effect estimation were confirmed (for forest plots on the meta-analyses conducted, see Appendix C), so that the certainty of results is not downgraded despite the high risk of bias.

No sensitivity analysis was performed for the outcome “allergic reactions due to accidental exposure to peanuts”, as the observed effect was not statistically significant. Since the proportion of patients with premature treatment discontinuation was higher in the intervention arms than in the control arms, the proportion of missing observable events is probably also higher in the intervention arms than in the control arms. An unbiased recording would then result in a numerically higher relative risk, i.e. a shift of the currently present effect towards an advantage for the control treatment.

Based on the available information, no more than proof, e.g. of an added benefit, can be determined for all outcomes with the exception of the outcome “allergic reactions due to accidental exposure to peanuts”. However, or the outcome "allergic reactions due to accidental exposure to peanuts", there is a reduced certainty of conclusions (see Section 2.4.1) so that at most indications can be determined for this outcome.

2.4.3 Results

Table 13 summarizes the results for the comparison of AR101 in comparison with placebo in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy.

The meta-analytical summary of the results of the studies ARC003 and ARC010 were used in the present benefit assessment.

The results for the entire treatment phase are presented. For the maintenance phase, the proportions of patients with event are presented for the respective outcomes as supplementary information (see Section 2.4.1). The forest plots of the meta-analyses calculated by the Institute can be found in Appendix D of the full dossier assessment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

Common AEs, common SAEs, common severe AEs as well as discontinuations due to AEs are presented in Appendix E.

Table 13: Results (outcome categories, dichotomous) – RCT, direct comparison: AR101 vs. placebo (multipage table)

Outcome category outcome study	AR101 N	AR101 patients with event n (%)	placebo N	placebo patients with event n (%)	AR101 vs. placebo RR [95% CI]; p-value[a]
Mortality					
All-cause mortality[b]					
ARC003	372	0 (0)	124	0 (0)	–
ARC010	132	0 (0)	43	0 (0)	–
Morbidity					
Allergic reactions due to accidental exposure to peanuts					
ARC003					
Entire treatment phase[c]	372	32 (8.6)[d]	124	13 (10.5)[d]	0.82 [0.45; 1.51]; 0.528
Maintenance phase	*310[e]*	*11 (3.5[f])*	*118[e]*	*6 (5.1[f])*	–
ARC010					
Entire treatment phase[c]	132	3 (2.3)[d]	43	2 (4.7)[d]	0.49 [0.08; 2.83][g]; 0.481[h]
Maintenance phase	*108[e]*	*1 (0.9)*	*41[e]*	*0 (0)*	–
Total[i]					0.78 [0.44; 1.38]; 0.388
Supplementary: absence of symptoms at all tested doses (maximum 1000 mg) in the exit DBPCFC					
ARC003	*372[j]*	*140 (37.6)*	*124[j]*	*3 (2.4)*	*15.56 [5.05; 47.94]; < 0.001*
ARC010	*132[j]*	*47 (35.6[f])[k]*	*43[j]*	*0 (0)*	*31.43 [1.98; 499.27][g]; > 0.001[h]*
Total[i]					*17.83 [6.28; 50.58]; < 0.001*
Health-related quality of life	No usable data[l]				
Side effects					
AEs (supplementary information)					
ARC003					
Entire treatment phase[c]	372	367 (98.7)	124	118 (95.2)	–
Maintenance phase	*310[e]*	*270 (87.1)*	*118[e]*	*94 (79.7)*	–
ARC010					
Entire treatment phase[c]	132	130 (98.5)	43	42 (97.7)	–
Maintenance phase	*108[e]*	*95 (88.0)*	*41[e]*	*32 (78.0)*	–
SAEs					
ARC003					
Entire treatment phase[c]	372	8 (2.2)	124	1 (0.8)	2.67 [0.34; 21.11]; 0.462
Maintenance phase	*310[e]*	*4 (1.3)*	*118[e]*	*1 (0.8)*	–
ARC010					
Entire treatment phase[c]	132	1 (0.8)	43	2 (4.7)	0.16 [0.02; 1.18]; 0.150
Maintenance phase	*108[e]*	*0 (0)*	*41[e]*	*0 (0)*	–
Total[i]					0.99 [0.27; 3.63]; 0.993
Severe AEs[m]					
ARC003					

Table 13: Results (outcome categories, dichotomous) – RCT, direct comparison: AR101 vs. placebo (multipage table)

Outcome category outcome study	AR101 N	AR101 patients with event n (%)	placebo N	placebo patients with event n (%)	AR101 vs. placebo RR [95% CI]; p-value[a]
Entire treatment phase[c]	372	16 (4.3)	124	1 (0.8)	5.33 [0.71; 39.81]; 0.085
Maintenance phase	*310[e]*	*8 (2.6)*	*118[e]*	*0 (0)*	–
ARC010					
Entire treatment phase[c]	132	1 (0.8)	43	0 (0)	0.99 [0.04; 23.92]; > 0.999
Maintenance phase	*108[e]*	*0 (0)*	*41[e]*	*0 (0)*	–
Total[i]					3.88 [0.74; 20.40]; 0.109
Discontinuation due to AEs					
ARC003					
Entire treatment phase[c]	372	43 (11.6)	124	2 (1.6)	7.17 [1.76; 29.15]; < 0.001
Maintenance phase	*310[e]*	*4 (1.3)*	*118[e]*	*0 (0)*	–
ARC010					
Entire treatment phase[c]	132	12 (9.1)	43	1 (2.3)	3.91 [0.52; 29.20]; 0.191
Maintenance phase	*108[e]*	*0 (0)*	*41[e]*	*0 (0)*	–
Total[i]					6.08 [1.93; 19.16]; 0.002
Systemic allergic reactions[n]					
ARC003					
Entire treatment phase[c]	372	53 (14.3)	124	4 (3.2)	4.42 [1.63; 11.96]; < 0.001
Maintenance phase	*310[e]*	*27 (8.7[f])*	*118[e]*	*2 (1.7[f])*	–
ARC010					
Entire treatment phase[c]	132	16 (12.1)	43	1 (2.3)	5.21 [0.71; 38.16]; 0.075
Maintenance phase	*108[e]*	*8 (7.4[f])*	*41[e]*	*1 (2.4[f])*	–
Total[i]					4.58 [1.88; 11.15]; < 0.001
Severe systemic allergic reactions[n, o]					
ARC003					
Entire treatment phase[c]	372	1 (0.3)	124	0 (0)[p]	1.01 [0.04; 24.52][g]; 0.728[h]
Maintenance phase	*310[e]*	*1 (0.3)*	*118[e]*	*0 (0)*	–
ARC010					
Entire treatment phase[c]	132	0 (0)	43	0 (0)	–
Total					–[l]
Abdominal pain (PT, AE)					
ARC003					
Entire treatment phase[c]	372	194 (52.2)	124	30 (24.2)	2.16 [1.56; 2.99][g]; < 0.001[h]
Maintenance phase	*310[e]*	*46 (14.8)*	*118[e]*	*7 (5.9)*	–
ARC010					
Entire treatment phase[c]	132	88 (66.7)	43	19 (44.2)	1.51 [1.06; 2.16][g]; 0.009[h]
Maintenance phase	*108[e]*	*24 (22.2)*	*41[e]*	*4 (9.8)*	–
Total[i]					1.90 [1.49; 2.43]; < 0.001

Table 13: Results (outcome categories, dichotomous) – RCT, direct comparison: AR101 vs. placebo (multipage table)

Outcome category outcome study	AR101 N	AR101 patients with event n (%)	placebo N	placebo patients with event n (%)	AR101 vs. placebo RR [95% CI]; p-value[a]
Pain in the upper abdomen (PT, AE)					
ARC003					
Entire treatment phase[c]	372	152 (40.9)	124	26 (21.0)	1.95 [1.36; 2.80][g]; < 0.001[h]
Maintenance phase	*310[e]*	*41 (13.2)*	*118[e]*	*9 (7.6)*	–
ARC010					
Entire treatment phase[c]	132	14 (10.6)	43	5 (11.6)	0.91 [0.35; 2.39][g]; 0.886[h]
Maintenance phase	*108[e]*	*4 (3.7)*	*41[e]*	*0 (0)*	–
Total[i]					1.78 [1.27; 2.49]; < 0.001
Itching in the oral cavity (PT, AE)					
ARC003					
Entire treatment phase[c]	372	151 (40.6)	124	20 (16.1)	2.52 [1.65; 3.83][g]; < 0.001[h]
Maintenance phase	*310[e]*	*39 (12.6)*	*118[e]*	*5 (4.2)*	–
ARC010					
Entire treatment phase[c]	132	28 (21.2)	43	1 (2.3)	9.12 [1.28; 65.06][g]; 0.007[h]
Maintenance phase	*108[e]*	*6 (5.6)*	*41[e]*	*0 (0)*	–
Total[i]					2.83 [1.87; 4.28]; < 0.001
Paraesthesia, oral (PT, AE)					
ARC003					
Entire treatment phase[c]	372	65 (17.5)	124	8 (6.5)	2.71 [1.34; 5.48][g]; 0.005[h]
Maintenance phase	*310[e]*	*23 (7.4)*	*118[e]*	*2 (1.7)*	–
ARC010					
Entire treatment phase[c]	132	52 (39.4)	43	9 (20.9)	1.88 [1.01; 3.49][g]; 0.028[h]
Maintenance phase	*108[e]*	*18 (16.7)*	*41[e]*	*1 (2.4)*	–
Total[i]					2.27 [1.42; 3.63]; < 0.001
Tightness in the throat (PT, AE)					
ARC003					
Entire treatment phase[c]	372	86 (23.1)	124	8 (6.5)	3.58 [1.79; 7.18][g]; < 0.001[h]
Maintenance phase	*310[e]*	*20 (6.5)*	*118[e]*	*0 (0)*	–
ARC010					
Entire treatment phase[c]	132	10 (7.6)	43	1 (2.3)	3.26 [0.43; 24.72][g]; 0.225[h]
Maintenance phase	*108[e]*	*1 (0.9)*	*41[e]*	*0 (0)*	–
Total[i]					3.55 [1.84; 6.85]; < 0.001
Ear and labyrinth disorders (SOC, AE)					
ARC003					
Entire treatment phase[c]	372	48 (12.9)	124	3 (2.4)	5.33 [1.69; 16.82][g]; 0.001[h]
Maintenance phase	*310[e]*	*17 (5.5)*	*118[e]*	*0 (0)*	–
ARC010					

Table 13: Results (outcome categories, dichotomous) – RCT, direct comparison: AR101 vs. placebo (multipage table)

Outcome category outcome study	AR101		placebo		AR101 vs. placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Entire treatment phase[c]	132	21 (15.9)	43	5 (11.6)	1.37 [0.55; 3.41][g]; 0.582[h]
Maintenance phase	*108[e]*	*6 (5.6)*	*41[e]*	*1 (2.4)*	–
Total[i]					2.85 [1.40; 5.79]; 0.004

a. Chi-square test.
b. Deaths were recorded within the framework of the AEs.
c. Without events that occurred in the exit DBPCFC.
d. The study report of study ARC003 shows that only few of the events (maximum 8 vs. 3 patients) were systemic allergic reactions. The study report of the ARC010 study, in contrast, shows that possibly almost all (maximum 3 patients vs. 1 patient) of the (altogether few) events were systemic allergic reactions. The "maximum" data result from the fact that only the results for the predefined outcome "allergic reaction after accidental food exposure" are reported in the study reports, independent of the food allergen. In both studies, neither severe systemic allergic reactions nor serious reactions occurred after accidental food exposure.
e. Number of patients who reached the maintenance phase.
f. Institute's calculation.
g. Institute's calculation (asymptotic).
h. Institute's calculation, CSZ test [47]
i. Institute's calculation, fixed-effect model (Mantel-Haenszel method).
j. There were missing measurement results in the exit DBPCFC (intervention vs. comparator arm) in 76 (20.4%) vs. 8 (6.5%) patients in study ARC003 and 26 (19.7%) vs. 3 (7.0%) patients in study ARC010. For these patients, it was assumed that no event occurred.
k. Module 4 A provides contradictory information on the number of patients with event in the intervention arm (47 and 52). An RR = 34.74 [2.19; 551.03] resulted from the analysis with 52 patients with event in the intervention arm.
d. The company presented analyses on the instruments FAIM and FAQLQ and assigned them to health-related quality of life. Regardless of the examination of the instruments' validity, the recording planned in the studies is not suitable to adequately capture patient-reported morbidity/health-related quality of life in the indication (see Section 2.4.1).
m. Severe AEs ≥ grade 3: classification of the severity of allergic reactions according to CoFAR [35], of systemic allergic reactions according to EAACI [29] and of all other AEs according to CTCAE.
n. Defined according to Sampson's diagnosis criteria [18] (see Section 2.4.1); coded as PT "anaphylactic reaction".
o. Severity grade 3 (= severe) according to EAACI criteria [29]
p. 1 event occurred within the framework of the exit DBPCFC during the provocation with peanut.

AE: adverse event; CI: confidence interval; CoFAR: Consortium for Food Allergy Research; CTCAE: Common Terminology Criteria for Adverse Events; DBPCFC: double-blind placebo-controlled food challenge; EAACI: European Academy of Allergy and Clinical Immunology; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy Quality of Life Questionnaire; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Based on the available information, no more than proof, e.g. of an added benefit, can be determined for all outcomes with the exception of the outcome "allergic reactions due to accidental exposure to peanuts" (see Section 2.4.2). For the outcome "allergic reactions due to

accidental exposure to peanuts", there is a reduced certainty of conclusions (see Section 2.4.1) so that at most indications can be determined for this outcome.

Mortality

All-cause mortality

No deaths occurred in the studies ARC003 and ARC010. This resulted in no hint of an added benefit of AR101 in comparison with watchful waiting for the outcome “all-cause mortality”; an added benefit is therefore not proven.

Morbidity

Allergic reactions due to accidental exposure to peanuts

There was no statistically significant difference between the treatment groups for the outcome "allergic reactions due to accidental exposure to peanuts”. This resulted in no hint of an added benefit of AR101 in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

There were no usable data on health-related quality of life. The company presented analyses on the instruments FAIM and FAQLQ and assigned them to health-related quality of life (for the lack of usability of the data, see Section 2.4.1). This resulted in no hint of an added benefit of AR101 in comparison with watchful waiting for the outcome "health-related quality of life”; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm from AR101 in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs

There was no statistically significant difference between the treatment groups for the outcome "severe AEs". This resulted in no hint of greater or lesser harm from AR101 in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome “discontinuation due to AEs”, there is a statistically significant difference to the disadvantage of AR101. This resulted in proof of greater harm from AR101 in comparison with watchful waiting.

Systemic allergic reactions

For the outcome “systemic allergic reactions”, there is a statistically significant difference to the disadvantage of AR101. This resulted in proof of greater harm from AR101 in comparison with watchful waiting.

Severe systemic allergic reactions

There was no statistically significant difference between the treatment groups for the outcome "severe systemic allergic reactions". This resulted in no hint of greater or lesser harm from AR101 in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Abdominal pain, pain in the upper abdomen, itching in the oral cavity, paraesthesia oral, tightness in the throat (preferred term [PT], adverse event [AE] each) and ear and labyrinth disorders (SOC, AE)

There is a statistically significant difference to the disadvantage of AR101 for each of the outcomes “abdominal pain”, “pain in the upper abdomen”, “itching in the oral cavity”, “paraesthesia oral”, “tightness in the throat” (PT, AE each) and “ear and labyrinth disorders” (SOC, AE). This results in a proof of greater harm from AR101 compared to watchful waiting for these outcomes.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- Sex (female versus male)
- Age (4 to 11 years vs. 12 to 17 years)

The age groups for the subgroup characteristic “age” were predefined for both studies, ARC003 and ARC010. The subgroup characteristic “sex” was not predefined.

For the studies ARC003 and ARC010, correct information on the number of patients in the corresponding two-by-two tables for the subgroup characteristic “sex” was only available for the outcomes “systemic allergic reaction” and “discontinuation due to AEs”. For all other outcomes, no interaction tests for the characteristic “sex” could be calculated based on the meta-analytical summary of studies ARC003 and ARC010.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

There were no relevant effect modifications for the characteristic "age" for all outcomes considered, nor for the subgroup characteristic "sex" for the outcomes "systemic allergic reaction" and "discontinuation due to AEs".

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 14).

Determination of the outcome category for the outcomes on side effects

It cannot be directly inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification was justified for these outcomes.

Systemic allergic reactions

There was 1 severe systemic allergic reaction during the entire treatment phase (see Table 13). In addition, 1 severe systemic allergic reaction occurred in the exit DBPCFC (see Section 2.4.3). Therefore, the outcome "systemic allergic reactions" was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", there is no information available on the assignment of the severity grade that would result in a classification as serious/severe. Therefore, the outcome was assigned to the outcome category of non-serious/non-severe side effects.

Table 14: Extent of added benefit at outcome level: AR101 vs. watchful waiting (multipage table)

Outcome category **outcome**	**AR101 vs. placebo** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0 vs. 0 RR: -; p = -	Lesser benefit/added benefit not proven
Morbidity		
Allergic reactions due to accidental exposure to peanuts	2.3-8.6 vs. 4.7-10.5[c] RR: 0.78 [0.44; 1.38]; p = 0.388	Lesser benefit/added benefit not proven
Health-related quality of life		
There were no evaluable data[d].		
Side effects		
SAEs	0.8-2.2 vs. 0.8-4.7[c] 0.99 [0.27; 3.63]; p = 0.993	Greater/lesser harm not proven
Severe AEs[e]	0.8-4.3 vs. 0-0.8[c] RR: 3.88 [0.74; 20.40]; p = 0.109	Greater/lesser harm not proven
Discontinuation due to AEs	9.1-11.6 vs. 1.6-2.3[c] RR: 6.08 [1.93; 19.16] RR: 0.16 [0.05; 0.52][f]; p = 0.002 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Systemic allergic reactions[g]	12.1-14.3 vs. 2.3-3.2[c] RR: 4.58 [1.88; 11.15] RR: 0.22 [0.09; 0.53][f] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: “considerable”
Severe systemic allergic reactions[g, h]	0-0.3 vs. 0[c] RR: -[i]; p = -[i]	Greater/lesser harm not proven
Abdominal pain (AE)	52.2-66.7 vs. 24.2-44.2[c] RR: 1.90 [1.49; 2.43] RR: 0.53 [0.41; 0.67][f]; p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: “considerable”
Pain in the upper abdomen (AE)	10.6-40.9 vs. 11.6-21.0[c] RR: 1.78 [1.27; 2.49] RR: 0.56 [0.40; 0.79][f] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: “considerable”

Table 14: Extent of added benefit at outcome level: AR101 vs. watchful waiting (multipage table)

Outcome category **outcome**	**AR101 vs. placebo** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Itching in the oral cavity (AE)	21.2-40.6 vs. 2.3-16.1[c] RR: 2.83 [1.87; 4.28] RR: 0.35 [0.23; 0.53][f]; p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: “considerable”
Paraesthesia, oral (AE)	17.5-39.4 vs. 6.5-20.9[c] RR: 2.27 [1.42; 3.63] RR: 0.44 [0.28; 0.70][f]; p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: “considerable”
Tightness in the throat (AE)	7.6-23.1 vs. 2.3-6.5[c] RR: 3.55 [1.84; 6.85] RR: 0.28 [0.15; 0.54][f]; p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: “considerable”
Ear and labyrinth disorders (AE)	12.9-15.9 vs. 2.4-11.6[c] RR: 2.85 [1.40; 5.79] RR: 0.35 [0.17; 0.71][f]; p = 0.004 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: “considerable”

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum proportions of events in each treatment arm in the studies included.
d. The company presented analyses on the instruments FAIM and FAQLQ and assigned them to health-related quality of life. Regardless of the examination of the instruments’ validity, the recording planned in the studies is not suitable to adequately capture patient-reported morbidity/health-related quality of life in the indication (see Section 2.4.1).
e. Severe AEs ≥ grade 3: classification of the severity of allergic reactions according to CoFAR [35], of systemic allergic reactions according to EAACI [29] and of all other AEs according to CTCAE.
f. Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
g. Defined according to Sampson’s diagnosis criteria [18]; coded as PT “anaphylactic reaction”.
h. Severity grade 3 according to EAACI criteria [29].
i. Calculation of a pooled effect not possible.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; CoFAR: Consortium for Food Allergy Research; CTCAE: Common Terminology Criteria for Adverse Events; EAACI: European Academy of Allergy and Clinical Immunology; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy Quality of Life Questionnaire; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of AR101 in comparison with watchful waiting

Positive effects	Negative effects
-	Non-serious/non-severe side effects[a] ▪ systemic allergic reactions, abdominal pain, pain in the upper abdomen, itching in the oral cavity, paraesthesia oral, tightness in the throat and ear and labyrinth disorders: proof of greater harm – extent: “considerable” ▪ discontinuation due to AEs proof of greater harm – extent: "considerable"
There were no usable data for the outcome category "health-related quality of life".	
a. It is assumed that outcomes of the outcome category “side effects” also represent the underlying disease/disease-related morbidity. AE: adverse event	

The available data only allow statements on short-term effects.

The overall consideration showed only negative effects for AR101 versus the ACT watchful waiting in the outcome category of non-serious/non-severe side effects, each with the extent “considerable”.

Treatment with AR101 is a permanent therapy in which patients must still maintain a peanut-free diet throughout [16] and follow recommended measures to mitigate the risks associated with co-factors during treatment (e.g. no physical exertion immediately before and 3 hours after treatment). This means that patients continue to be restricted in terms of their diet and lifestyle even during treatment with AR101. Moreover, the observed disadvantages of AR101 - with the exception of discontinuations due to AEs - were not exclusively limited to the initial phase of the dose increase, but still occurred in the maintenance phase. Particularly in the case of systemic allergic reactions, no decrease in the risk, which was significantly increased compared to the control arm, could be seen in the course of the study. The absolute proportions of events decrease in the maintenance phase, but this is probably due to the fact that the patients who were more sensitive to allergic reactions (i.e. those who had a lower peanut tolerance) discontinued treatment with AR101 before.

Although an advantage of AR101 over placebo was observed with respect to the absence of symptoms in the exit DBPCFC”, this was not reflected in the patient-relevant outcome “allergic reactions due to accidental exposure to peanuts”. It is unclear whether this is due to the short study duration. Whether the advantages in provocation testing are reflected in a reduction of the allergic reactions (both reactions due to accidental exposure as well as in general) in the further course can only be answered by a longer study duration/follow-up observation.

Moreover, there were no usable data on health-related quality of life. These data would be important to assess the impact of permanent treatment with AR101 o patients while at the same time maintaining a peanut-avoiding diet.

In summary, there is proof of lesser benefit of AR101 compared to the ACT "observational waiting" for patients aged 4-17 years with a confirmed diagnosis of peanut allergy.

The result of the assessment of the added benefit of AR101 in comparison with the ACT is summarized in Table 16.

Table 16: AR101 – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy[b]	Watchful waiting[c]	Proof of lesser benefit[d]

a. Presentation of the ACT specified by the G-BA.
b. The use can be continued in patients who are 18 years and older. Use of the drug has to be accompanied by a peanut-free diet.
c. A peanut-avoiding diet was assumed in both study arms. It is assumed that in the event of accidental exposure, the use of a rescue medication is possible in both arms in case of clinical necessity.
d. The available data only allow statements on short-term effects. In the studies relevant for the present assessment, the diagnosis of peanut allergy was confirmed within the framework of a DBPCFC at screening (inclusion criteria were dose-limiting symptoms at ≤ 100 mg peanut protein in the ARC003 study or at ≤ 300 mg in the ARC010 study). It is unclear whether the observed effects are transferable to patients with peanut allergy who did not undergo DBPCFC to confirm the diagnosis and/or who are less severely affected (i.e. who only show dose-limiting symptoms in DBPCFC at > 300 mg). According to the SPC, no DBPCFC is required.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; DBPCFC: double-blind placebo-controlled food challenge

The assessment described above deviates from that of the company, which derived proof of a considerable added benefit based on the studies ARC003, ARC004, ARC007 and ARC010.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. European Medicines Agency. Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases [online]. 2008 [Accessed: 23.12.2021]. URL: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-development-products-specific-immunotherapy-treatment-allergic-diseases_en.pdf.

4. Aimmune Therapeutics. Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE), study ARC003; clinical study report [unpublished]. 2018.

5. Aimmune Therapeutics. Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (the Palisade Study) [online]. [Accessed: 09.11.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004257-41.

6. Aimmune Therapeutics. Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) [online]. 2019 [Accessed: 09.11.2021]. URL: https://ClinicalTrials.gov/show/NCT02635776.

7. Vickery BP, Vereda A, Casale TB et al. AR101 Oral Immunotherapy for Peanut Allergy. N Engl J Med 2018; 379(21): 1991-2001. https://dx.doi.org/10.1056/NEJMoa1812856.

8. Aimmune Therapeutics. AR101 Trial in Europe Measuring Oral Immunotherapy Success in Peanut Allergic Children (ARTEMIS), study ARC010; clinical study report [unpublished]. 2019.

9. Aimmune Therapeutics. Ar101 Trial in Europe Measuring Oral Immunotherapy Success in Peanut Allergic Children (Artemis) [online]. [Accessed: 09.11.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-005004-26.

10. Aimmune Therapeutics. ARTEMIS Peanut Allergy In Children [online]. 2021 [Accessed: 09.11.2021]. URL: https://ClinicalTrials.gov/show/NCT03201003.

11. O'B Hourihane J, Beyer K, Abbas A et al. Efficacy and safety of oral immunotherapy with AR101 in European children with a peanut allergy (ARTEMIS): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. Lancet Child Adolesc Health 2020; 4(10): 728-739. https://dx.doi.org/10.1016/S2352-4642(20)30234-0.

12. Aimmune Therapeutics. PALISADE Follow-on Study (ARC004) [online]. 2019 [Accessed: 09.11.2021]. URL: https://ClinicalTrials.gov/show/NCT02993107.

13. Aimmune Therapeutics. Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) Follow-on Study [online]. [Accessed: 06.10.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-004941-94.

14. Vickery BP, Vereda A, Nilsson C et al. Continuous and Daily Oral Immunotherapy for Peanut Allergy: Results from a 2-Year Open-Label Follow-On Study. J Allergy Clin Immunol Pract 2020. https://dx.doi.org/10.1016/j.jaip.2020.12.029.

15. Aimmune Therapeutics. Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children (RAMSES) [online]. 2021 [Accessed: 09.11.2021]. URL: https://clinicaltrials.gov/show/NCT03126227.

16. Aimmune Therapeutics Ireland. PALFORZIA Pulver zum Einnehmen zur Entnahme aus Kapseln [online]. 2021 [Accessed: 17.12.2021]. URL: https://www.fachinfo.de.

17. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012; 130(6): 1260-1274. https://dx.doi.org/10.1016/j.jaci.2012.10.017.

18. Sampson HA, Munoz-Furlong A, Campbell RL et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117(2): 391-397. https://dx.doi.org/10.1016/j.jaci.2005.12.1303.

19. Gupta RS, Springston EE, Warrier MR et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011; 128(1): e9-17. https://dx.doi.org/10.1542/peds.2011-0204.

20. Nwaru BI, Hickstein L, Panesar SS et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy 2014; 69(8): 992-1007. https://dx.doi.org/10.1111/all.12423.

21. Sicherer S, Munoz-Furlong A, Burks AW et al. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. J Allergy Clin Immunol 1999.

22. Sicherer SH, Munoz-Furlong A, Godbold JH et al. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010; 125(6): 1322-1326. https://dx.doi.org/10.1016/j.jaci.2010.03.029.

23. Vierk KA, Koehler KM, Fein SB et al. Prevalence of self-reported food allergy in American adults and use of food labels. J Allergy Clin Immunol 2007; 119(6): 1504-1510. https://dx.doi.org/10.1016/j.jaci.2007.03.011.

24. Worm M, Scherer K, Kohli-Wiesner A et al. Food-induced anaphylaxis and cofactors - data from the anaphylaxis registry. Allergol Select 2017; 1(1): 21-27. https://dx.doi.org/10.5414/ALX01401E.

25. Munoz-Cano R, Pascal M, Araujo G et al. Mechanisms, Cofactors, and Augmenting Factors Involved in Anaphylaxis. Front Immunol 2017; 8: 1193. https://dx.doi.org/10.3389/fimmu.2017.01193.

26. Ring J, Beyer K. Guideline for acute therapy and management of anaphylaxis. 2014. https://dx.doi.org/10.1007/10.1007/s40629-014-0009-1.

27. Boyce JA, Assa'ad A, Burks AW et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. Nutr Res 2011; 31(1): 61-75. https://dx.doi.org/10.1016/j.nutres.2011.01.001.

28. Muraro A, Dubois AE, DunnGalvin A et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. Allergy 2014; 69(7): 845-853. https://dx.doi.org/10.1111/all.12405.

29. Muraro A, Roberts G, Clark A et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007; 62(8): 857-871. https://dx.doi.org/10.1111/j.1398-9995.2007.01421.x.

30. Pajno GB, Fernandez-Rivas M, Arasi S et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy 2018; 73(4): 799-815. https://dx.doi.org/10.1111/all.13319.

31. Stiefel G, Anagnostou K, Boyle RJ et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. Clin Exp Allergy 2017; 47(6): 719-739. https://dx.doi.org/10.1111/cea.12957.

32. Waserman S, Chad Z, Francoeur MJ et al. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. Allergy 2010; 65(9): 1082-1092. https://dx.doi.org/10.1111/j.1398-9995.2010.02418.x.

33. Worm M, Eckermann O, Dolle S et al. Triggers and treatment of anaphylaxis: an analysis of 4,000 cases from Germany, Austria and Switzerland. Dtsch Arztebl Int 2014; 111(21): 367-375. https://dx.doi.org/10.3238/arztebl.2014.0367.

34. Worm M, Reese I, Ballmer-Weber B et al. Guidelines on the management of IgE-mediated food allergies. Allergo J Int 2015; 24: 256-293. https://dx.doi.org/10.1007/s40629-015-0074-0.

35. Burks AW, Jones SM, Wood RA et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012; 367(3): 233-243. https://dx.doi.org/10.1056/NEJMoa1200435.

36. Chu DK, Wood RA, French S et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet 2019; 393(10187): 2222-2232. https://dx.doi.org/10.1016/s0140-6736(19)30420-9.

37. Institute for Clinical and Economic Review. Oral Immunotherapy and Viaskin Peanut for Peanut Allergy: Effectiveness and Value [online]. 2019 [Accessed: 23.12.2021]. URL: https://icer.org/wp-content/uploads/2020/10/ICER_PeanutAllergy_Final_Report_071019.pdf.

38. Rodriguez Del Rio P, Escudero C, Sanchez-Garcia S et al. Evaluating primary end points in peanut immunotherapy clinical trials. J Allergy Clin Immunol 2019; 143(2): 494-506. https://dx.doi.org/10.1016/j.jaci.2018.09.035.

39. Sim K, Mijakoski D, Stoleski S et al. Outcomes for clinical trials of food allergy treatments. Ann Allergy Asthma Immunol 2020; 125(5): 535-542. https://dx.doi.org/10.1016/j.anai.2020.06.023.

40. Deschildre A, Elegbede CF, Just J et al. Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. Clin Exp Allergy 2016; 46(4): 610-620. https://dx.doi.org/10.1111/cea.12681.

41. DunnGalvin A, Cullinane C, Daly DA et al. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges. Clin Exp Allergy 2010; 40(3): 476-485. https://dx.doi.org/10.1111/j.1365-2222.2010.03454.x.

42. DunnGalvin A, de BlokFlokstra BM, Burks AW et al. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy 2008; 38(6): 977-986. https://dx.doi.org/10.1111/j.1365-2222.2008.02978.x.

43. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008; 122(1): 139-144, 144 e131-132. https://dx.doi.org/10.1016/j.jaci.2008.05.008.

44. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009; 39(1): 127-137. https://dx.doi.org/10.1111/j.1365-2222.2008.03120.x.

45. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2010; 65(5): 630-635. https://dx.doi.org/10.1111/j.1398-9995.2009.02216.x.

46. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials 2008; 5(3): 225-239. https://dx.doi.org/10.1177/1740774508091600.

47. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-135.html.