IQWiG Reports – Commission No. A22-29

AR101
(peanut allergy 1) –
Addendum to Commission A21-135[1]

Addendum

Commission: A22-29
Version: 1.0
Status: 11 March 2022

[1] Translation of addendum A22-29 *AR101 (Erdnussallergie) – Addendum zum Auftrag A21-135* (Version 1.0; Status: 11 March 2022). 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 1) – Addendum to Commission A21-135

Commissioning agency
Federal Joint Committee

Commission awarded on
22 February 2022

Internal Commission No.
A22-29

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

IQWiG employees involved in the addendum

- Sascha Abbas
- Petra Kohlepp
- Daniela Preukschat
- Christoph Schürmann

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

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
CSR	clinical study report
DBPCFC	double-blind placebo-controlled food challenge
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PRACTALL	Practical-Allergy
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 22 February 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-135 (AR101 – Benefit assessment according to §35a Social Code Book V) [1].

The studies ARC003 and ARC010 were used for the benefit assessment of AR101 in the therapeutic indication of peanut allergy [1]. In the commenting procedure [2], the pharmaceutical company (hereinafter referred to as the "company") submitted additional explanations and analyses to supplement the dossier [3].

The G-BA commissioned IQWiG to assess the following outcomes presented in the dossier, taking into account the information in the commenting procedure, if applicable:

- tolerating 1000 mg peanut protein in the exit double-blind placebo-controlled food challenge (exit DBPCFC)
- maximum symptom severity at all tested doses of peanut protein in the exit DBPCFC
- use of adrenaline as rescue medication during DBPCFC
- use of adrenaline as rescue medication during the entire course of the study

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Outcomes recorded within the framework of the exit DBPCFC

Basic comments on outcomes and analyses

Dossier assessment A21-135 describes that DBPCFC is not to be considered per se as a valid surrogate for the occurrence of allergic reactions after accidental exposure to peanuts [1]. In the studies ARC003 and ARC010, allergic reactions after accidental exposure to peanuts were also recorded as a directly patient-relevant outcome. The results of the outcome "absence of symptoms at all tested doses (in the DBPCFC)" were thus only presented as supplementary information in the dossier assessment [1]. The criticism described in the dossier assessment correspondingly applies also to the additional outcomes presented in this addendum, which were also collected within the framework of the exit DBPCFC. There are currently no data showing that the DBPCFC allows sufficiently reliable predictions regarding the future risk or frequency of allergic reactions after peanut exposure and the severity of future allergic reactions after peanut exposure [4-6]. The results of these outcomes were therefore not used for the benefit assessment and are presented in Appendix A.

When interpreting the results, it should also be taken into account that measurement results in the exit DBPCFC were missing for 76 (20.4%) vs. 8 (6.5%) patients in study ARC003 and 26 (19.7%) vs. 3 (7.0%) patients in study ARC010 (intervention vs. comparator arm). This is mainly due to the patients who discontinued treatment prematurely and who, with a few exceptions, did also not participate in the exit DBPCFC. In the case of missing measurement results in the exit DBPCFC, the values from the screening DBPCFC of the patients concerned were used as a substitute. The proportion of patients with premature treatment discontinuation was clearly higher in the intervention arms than in the control arms. The high proportion of missing or imputed values, which differs significantly between the treatment groups, can result in a relevant bias in the effect estimation, the direction and extent of which must be assessed separately depending on the outcome. In particular, however, it is conceivable for some situations that the available effect estimations overestimate the actual treatment differences in terms of magnitude. According to analyses by the Food and Drug Administration (FDA), it can be assumed that especially the patients who were more sensitive to allergic reactions (i.e. those who had a lower peanut tolerance) discontinued treatment with AR101 before [7]. Thus, the possible bias in the direction of an advantage for the intervention must be taken into account especially in the case of effects in favour of the intervention.

Tolerating 1000 mg peanut protein in the exit DBPCFC

In the study documents (protocol, clinical study report [CSR]) and in Module 4 A of the dossier, the outcome is referred to as tolerating 1000 mg (cumulative 2043 mg) of peanut protein with no or mild symptoms in the exit DBPCFC. However, the study protocol shows that the outcome "tolerating 1000 mg peanut protein in the exit DBPCFC" was operationalized as the occurrence of at most moderate symptoms in connection with predefined tolerance criteria, each based on the investigator's discretion. Besides of minor deviations, grading of the severity of reactions

was in line with the Practical-Allergy (PRACTALL) guidelines [8]. In the case of mild symptoms, a dose was assessed as tolerated if the following criteria were met: only a single organ system affected, resolution without drug treatment, at most one oral administration of an H1 antihistamine, no administration of adrenaline, no worsening over time in terms of intensity or distribution of symptoms, resolution or occurrence of clear signs of resolution of symptoms in less than 1 hour and no objective respiratory disorders. A dose was assessed as tolerated for moderate symptoms if they were transient or self-limiting, affected only one organ system or were subjective. Examples for subjective symptoms include dyspnoea (without objective signs), nausea, abdominal pain or malaise. According to the study protocol, doses that involved severe symptoms were assessed as not tolerated in almost all cases.

Maximum symptom severity at all tested doses of peanut protein in the exit DBPCFC

Besides of minor deviations, the severity of reactions was graded in line with the PRACTALL guidelines by the investigator [8].

Use of adrenaline as rescue medication during DBPCFC (screening and exit)

The use of adrenaline as rescue medication during the exit DBPCFC as well as the comparison with the use of adrenaline during the screening DBPCFC were predefined outcomes in both studies. In Module 4 A of the dossier, the company presented analyses on each the use of adrenaline in the screening and in the exit DBPCFC. In addition, it presented 2 analyses comparing the use of adrenaline in the screening and the exit DBPCFC, each of which, however, only includes the subpopulation of patients who received or did not receive adrenaline in the screening DBPCFC (peanut provocation).

The results for the outcome “use of adrenaline as rescue medication during the exit DBPCFC in the peanut provocation”, which consider all patients of the intention to treat (ITT) population, are presented in Appendix A.

2.2 Use of adrenaline as rescue medication during the entire course of the study without DBPCFC

Basic comments on operationalization of the outcome and on the available analyses

The use of adrenaline as rescue medication during the treatment phases (initial dose escalation, dose increase and maintenance phase; excluding events during the DBPCFC) is one of the predefined outcomes in both studies. At the start of the study, the included patients and their respective family members were trained on when and how to use adrenaline (using an auto-injector). Adrenaline should only be used to treat an allergic reaction, and it was further analysed whether treatment with adrenaline was associated with accidental exposure to peanuts or other food allergens. The analysis in the CSR was done as the number of patients with at least one adrenaline episode, where 1 episode was defined as 1 or several adrenaline doses within a 2-hour window.

The outcome is not used for the benefit assessment because the outcomes used in the benefit assessment already provide a direct comprehensive picture of the allergic reactions occurring during the course of the study. For example, the outcome "systemic allergic reactions" covers events that are directly noticeable for the patient.

Separation of morbidity and side effects in the therapeutic indication as well as assignment of the outcome "use of adrenaline as rescue medication"

In the present therapeutic indication, there is a close correlation between outcomes on morbidity and side effects, as AR101 is a peanut powder, i.e. AR101 itself represents the allergen through the administration of which desensitisation is sought. Thus, in the present therapeutic indication, allergic reactions may even be caused primarily by 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 adverse events (AEs), is not possible with sufficient certainty for each event in the present therapeutic indication. For the 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 dossier assessment A21-135 [1]).

It is assumed that the outcomes of the outcome category "side effects" basically also represent the disease-related morbidity. For the analyses on side effects presented by the company in the dossier, it was unclear at the time of the dossier assessment whether allergic reactions due to accidental exposure to peanuts were also included in these analyses. In its comments [2], the company clarified that the analyses on side effects comprised all events, i.e. also those that occurred due to accidental exposure to peanuts. Equally, the analyses on adrenaline as rescue medication presented in this addendum include both the use of adrenaline following accidental exposure to peanuts or other food allergens and the use of adrenaline following allergic reactions in general (regardless of cause).

In the analyses presented on the use of adrenaline as rescue medication, events involving the use of adrenaline for allergic reactions due to accidental exposure to peanuts (or other food allergens), and thus events reflecting the underlying disease/disease-related morbidity, represent almost all of the events that occurred in the comparator arm (7 out of 8 [ARC003] and 1 out of 1 [ARC010] events in the comparator arm, respectively). In the intervention arm, in contrast, adrenaline was mostly used for allergic reactions that were not ascribed to accidental exposure to peanuts (or other food allergens). The outcome was therefore interpreted as a combination of symptoms (morbidity) and side effects.

The results of the outcome "use of adrenaline as rescue medication" are presented in Appendix A.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of AR101 from dossier assessment A21-135.

The following Table 1 shows the result of the benefit assessment of AR101 under consideration of dossier assessment A21-135 and the present addendum.

Table 1: 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 G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. AR101 (Erdnussallergie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 25.01.2022]. URL: https://www.iqwig.de/download/a21-135_ar101_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Aimmune Therapeutics Germany. Stellungnahme zum IQWiG-Bericht Nr. 1272: AR101 (Erdnussallergie) - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. 2021: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/748/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Aimmune Therapeutics Germany. AR101, entfettetes Pulver von Arachis hypogaea L., semen (Erdnüsse) (Palforzia); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 21.01.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/748/#dossier.

4. 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.

5. 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.

6. 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.

7. Food and Drug Administration. Peanut (Arachis hypogaea) Allergen Powder; BLA Clinical Review Memorandum [online]. 2020 [Accessed: 09.03.2022]. URL: https://www.fda.gov/media/135488/download.

8. 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.

Anhang A Results

Table 2: Results (morbidity, side effects) - RCT, direct comparison: AR101 versus 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]
Morbidity					
Tolerating 1000 mg peanut protein in the exit DBPCFC[b]					
ARC003	372	187 (50.3)	124	3 (2.4)	20.78 [6.76; 63.83]; < 0.001
ARC010	132	77 (58.3)	43	1 (2.3)	25.08 [3.60; 174.97]; < 0.001
Total[c]					21.86 [8.27; 57.77]; < 0.001
Maximum symptom severity at all doses of peanut protein in the exit DBPCFC					
ARC003					
Mild	372	119 (32.0)	124	35 (28.2)	–
Moderate	372	94 (25.3)	124	73 (58.9)	–
Severe	372	19 (5.1)	124	13 (10.5)	0.49 [0.25; 0.96]; 0.045
ARC010					
Mild:	132	55 (41.7)	43	16 (37.2)	–
Moderate	132	24 (18.2)	43	20 (46.5)	–
Severe	132	6 (4.6)	43	7 (16.3)	0.28 [0.10; 0.79]; 0.018
Total[c]					0.41 [0.24; 0.73]; 0.002
Use of adrenaline as rescue medication during the exit DBPCFC in the peanut provocation					
ARC003	372	28 (7.5)	124	62 (50)	0.15 [0.10; 0.22]; < 0.001
ARC010	132	3 (2.3)	43	7 (16.3)	0.14 [0.04; 0.52]; 0.002
Total[c]					0.15 [0.10; 0.22]; < 0.001
Side effects/morbidity					
Use of adrenaline as rescue medication[d]					
ARC003					
Entire treatment phase[e]	372	52 (14.0)	124	8 (6.5)	2.17[f] [1.06; 4.43]; 0.030[g]
Maintenance phase	310[h]	24 (7.7)	118[h]	4 (3.4)	–
ARC010					
Entire treatment phase[e]	132	9 (6.8)	43	1 (2.3)	2.93[f] [0.38; 22.48]; 0.324[g]
Maintenance phase	108[h]	4 (3.7)	41[h]	0 (0)	–
Total[c]					2.25 [1.15; 4.43]; 0.019

Table 2: Results (morbidity, side effects) - RCT, direct comparison: AR101 versus 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]
a. Chi-square test. b. Defined as the occurrence of at most moderate symptoms in connection with pre-defined tolerance criteria (see Section 2.1). c. Institute's calculation, fixed-effect model (Mantel-Haenszel method). d. 1 or more adrenaline doses within a 2-hour window. It is assumed that the outcome basically reflects both side effects and the underlying disease/disease-related morbidity, as events relating to the use of adrenaline as rescue medication for allergic reactions due to accidental exposure to peanuts (or other food allergens) are also included (see Section 2.2). e. Without events that occurred in the exit DBPCFC. f. Institute's calculation of effect and CI (asymptotic). g. Institute's calculation, CSZ text. h. Number of patients who reached the maintenance phase. CI: confidence interval; DBPCFC: double-blind placebo-controlled food challenge; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk					