National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

AR101 for treating peanut allergy ID1282

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Aimmune Therapeutics	Yes	Comment noted. No action required.
	The Anaphylaxis Campaign	It is appropriate that this topic is referred to NICE. The prevalence of allergy including peanut allergy is increasing and it is known that having an allergy can have a negative psychological impact. AR101 may reduce the number and severity of reactions from accidental exposure, and thereby increase quality of life of the allergic individual.	Comment noted. No action required.
	British Society for Allergy and Clinical Immunology (BSACI)	Yes	Comment noted. No action required.
Wording	Aimmune Therapeutics	More appropriate wording of the remit may be “AR101 for the treatment of peanut allergy in children aged 4 – 17 years old.”	Comment noted. The remit has been kept broad to align with the referral from the Department of Health and

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			Social Care. The committee will appraise the treatment within its marketing authorisation.
	The Anaphylaxis Campaign	Yes the remit reflects this.	Comment noted. No action required.
	BSACI	Yes	Comment noted. No action required.
Timing Issues	Aimmune Therapeutics	We believe there is an urgent requirement for NICE guidance on the use of AR101 as AR101 will potentially be the first licensed medicinal product to treat peanut allergy in Europe, addressing a significant unmet medical need in the absence of approved therapy. The current standard of care is strict avoidance of peanut and management of allergic reactions with emergency medication. Allergic reactions can be triggered by trace quantities of peanut and can range from mild to fatal in severity with no reliable way to predict the severity of a reaction with each exposure. This can lead to considerable anxiety about reactions and impairment of usual daily activities for many allergic individuals and their families, with commensurate reduction in quality of life.	Comment noted. The aim of the STA process is to provide guidance close to the MA being granted.
	The Anaphylaxis Campaign	With rising hospital admissions for anaphylaxis, there is a cost benefit to completing this appraisal.	Comment noted. No action required.
	BSACI	No urgency. Routine assessment appropriate.	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Aimmune Therapeutics	We have no comments on the background information.	Comment noted. No action required.
	The Anaphylaxis Campaign	The information is mostly correct, however, many people with peanut allergy can tolerate other nuts so it is not correct to say they must avoid all other tree nuts. It could also highlight how small an amount of peanut is sometimes needed to produce a severe allergic reaction.	Comment noted. The background section has been corrected to clarify the potential link between tree nuts and peanuts. The background section of the scope aims to provide a brief summary of the condition and how it is managed, it is not designed to be exhaustive in its detail. Where relevant, the quantity of peanut protein required to produce a severe allergic reaction will be considered during the appraisal.
	BSACI	Information sufficient. No inaccuracies.	Comment noted. No action required.
The technology/ intervention	Aimmune Therapeutics	We propose the following revised wording for description of the technology: “AR101 (PALFORZIA, Aimmune Therapeutics) is an oral immunotherapy that aims to desensitise peanut-allergic individuals to peanut, thereby mitigating allergic reactions, including anaphylaxis, that may occur with accidental exposure to the allergen. AR101 is an oral	Comment noted. The description of the technology aims to provide key details about the mechanism of action, administration route and clinical evidence base. The description has been

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		biologic drug derived from peanuts, manufactured in accordance with CGMPs to contain a standardized amount of all peanut allergens. The treatment involves taking a small dose of AR101 initially but gradually increasing under clinical supervision over approximately 6 months ("initial dose escalation" and "up-dosing" phases) until maintenance dose level is achieved. AR101 does not currently have marketing authorisation for peanut allergy in the UK and Europe, but was approved by the US FDA for use in children (aged 4-17) in the US in January 2020. It has been studied in clinical trials in comparison with placebo in children and adults with peanut allergy."	updated to reflect some of the suggested changes.
	The Anaphylaxis Campaign	It could mention a rough time frame as to how slowly the amount of peanut protein increases, as well as the maintenance phase that follows the dose escalation period. The amount of AR101 in the smallest dose can sometimes still cause a reaction in very sensitive individuals and is not successful for everyone. Does not describe the method of administration.	Comment noted. The description of the technology has been updated.
	BSACI	The description states that '*..AR101 contains a very small amount of the protein found in peanuts that is insufficient to cause a reaction'.* Is this correct? Does the submission imply that there is no risk of an adverse (allergic) reaction to AR101? Statement at odds with research into AR101 9reference: *N Engl J Med* November 22, 2018 pp 1991-2001.	Comment noted. The description of the technology has removed this inaccuracy.
Population	Aimmune Therapeutics	The intended licensed population in the first instance for initiation of AR101 treatment will be [redacted]	Comment noted. The population has been updated to children aged 4-17 years and adults who started treatment as a child.

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	The Anaphylaxis Campaign	AR101 is intended for children aged 4-17 years?	Comment noted. The population has been updated to children aged 4-17 years and adults who started treatment as a child.
	BSACI	Population described accurately. No groups that need to be considered separately.	Comment noted. No action required.
Comparators	Aimmune Therapeutics	We propose the following slightly amended wording: Established clinical management without AR101 (including allergen avoidance, symptomatic treatments such as antihistamines, and emergency medication).	Comment noted. The comparator treatment has been updated.
	The Anaphylaxis Campaign	Yes, allergen avoidance and use of emergency medication in the event of an allergic reaction is the only current management.	Comment noted. No action required.
	BSACI	Standard treatment is dietary avoidance and emergency preparedness as described. It is the only alternative care available on the NHS.	Comment noted. No action required.
Outcomes	Aimmune Therapeutics	We would propose the following amended list of outcomes: • Proportion of patients able to complete initial dose escalation and up-dosing phases of treatment (instead of tolerance to the treatment) • Peanut allergy desensitisation, as evaluated by challenge doses of 600 mg (1043 mg cumulatively),1000mg (2043 mg cumulatively) and 2000mg (4043mg) peanut protein in a double-blind placebo-controlled food challenge (DBPCFC)	Comments noted. The outcome section is set to specify clinically important outcomes needed for the committee to appraise the clinical effectiveness of the treatment and may not always align with trial evidence. For this reason, outcomes listed are less specific than as suggested

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		• Discontinuation of treatment • Reactions to accidental exposures to peanut and their severity • Treatment-related adverse events by type • Change in Immunoglobulin Values and Peanut Skin Prick Test • Health-related quality of life (patient and caregiver).	and have not been updated. However, after consensus at the scoping workshop, systemic allergic reactions and adverse effects of treatment have been added. The outcomes listed in the scope are not exhaustive, companies are encouraged to provide all relevant data that will be informative for the appraisal.
	The Anaphylaxis Campaign	discontinuation of treatment – efficacy data is currently only available for up to 24 months – treatment may need to continue at maintenance dose indefinitely?	Comment noted. Where relevant, uncertainties related to treatment duration or long-term treatment options will be considered during the appraisal.
	BSACI	Outcome measures not clearly presented. It is for example not clear what the statement 'symptom severity' refers to. There are two treatment outcomes: 1. Efficacy i.e. proportion of those treated who achieve tolerance. 2. Risk of treatment i.e. proportion of those treated who experience adverse events including death. Types of adverse events are not outcomes.	Comment noted. After the scoping workshop, the updated outcome section broadly aligns with outcomes suggested.

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		As previously mentioned under 'The technology/intervention' not consistent with the claim that peanut content insufficient to cause a reaction'.	
Economic analysis	Aimmune Therapeutics	We agree with the economic analysis approach outlined and anticipate a lifetime horizon will be appropriate for estimating clinical and cost-effectiveness of AR101.	Comment noted. No action required.
	The Anaphylaxis Campaign	Consider that reference data is only available for 24 months and treatment may be continued indefinitely	Comment noted. No action required.
	BSACI	Appropriate.	Comment noted. No action required.
Equality	Aimmune Therapeutics	No equality issues identified.	Comment noted. No action required.
	The Anaphylaxis Campaign	There are very few studies which consider the impact of allergy on different ethnic groups, an agenda that is currently the subject of working group under BSACI	Comment noted. The committee will consider whether the recommendation requires consideration of equalities issues during the appraisal.
	BSACI	No risk of discrimination. Treatment eligibility determined by allergy status only. Stakeholder list considered inclusive. No notable omissions.	Comment noted. No action required.
Innovation	Aimmune Therapeutics	We consider AR101 represents a potential step change in the management of peanut allergy (PA), as there are currently no licensed therapies for PA in Europe.	Comment noted. Where relevant and appropriate, the extent to which the

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		AR101 is the first application of Oral ImmunoTherapy (OIT) to provide both a standardised product and dosing protocol for desensitisation to peanut. Based on the data from the Phase 2 clinical trials, AR101 was granted Breakthrough Designation by the FDA. AR101 was approved by the FDA on 31st January 2020. We anticipate that the majority of health benefits of AR101 treatment will be included in the QALY calculation for patients and carers.	technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	The Anaphylaxis Campaign	The prevalence of allergy including peanut allergy is increasing and it is known that having an allergy can have a negative psychological impact. AR101 may reduce the number and severity of reactions from accidental exposure, and thereby increase quality of life of the allergic individual by reducing fear of an allergic reaction.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations.No action required.
	BSACI	Oral immunotherapy (OI) is now a well-recognised widely applied treatment option in the active management of allergy to milk and egg. It has replaced the traditional approach of avoidance only with significant positive impact on the quality of life of affected individuals and their families and probable impact on tolerance acquisition. Peanut OI will be a step-change in the management of individuals with peanut allergy. Health related benefits: 1. Diminish/remove constant risk of anaphylaxis.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations . No action required.

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		2. Diminish/remove need to practice emergency preparedness i.e. carry emergency medication. 3. Improve quality of life for affected individual and family. Data available is studies on efficacy of peanut OI.	
Questions for consultation	Aimmune Therapeutics	Within the population of people with peanut allergy, who would receive immunotherapy treatment? Would this be affected by age or severity of peanut allergy? [redacted] We do not believe that there is a clinical consensus on the definition of peanut allergy severity, rather all children diagnosed with peanut allergy are at risk of having a systemic allergic reaction upon accidental exposure to peanut. The frequency and severity of these reactions are unpredictable, and the severity of symptoms experienced during an initial reaction may not be consistent with the severity of future reactions (Vander Leek 2000). Thus, we believe it is not an appropriate way to identify patients in most need. Would AR101 be used in conjunction with a peanut-avoidance diet? Yes. AR101 should be used in conjunction with a peanut-avoidant diet and is not intended for the immediate relief of peanut allergy symptoms. Additionally, patients are encouraged to carry self-injectable adrenaline (epinephrine) at all times.	Comments noted. No action required.

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		Would immunotherapy treatment be expected to last for a lifetime? [redacted] Are there any subgroups of people in whom AR101 is expected to be more clinically effective and cost effective or other groups that should be examined separately? We have conducted a review of AR101 clinical trial data to identify any subgroups of patients, as defined by their baseline clinical characteristics, who might benefit more or less from AR101 treatment. However current analysis has not identified any clinically relevant subgroups (data on file). Are the outcomes listed appropriate? See comments above under “Outcomes” section. What outcomes are important for people with peanut allergy and clinicians? We consider that desensitisation to peanut is probably the most important outcome for patients, their families and clinicians. An	

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		increased level of desensitisation enables patients and their families to feel safer about potential traces of peanut in their environment and to have a greater sense of control over accidental exposures, thereby reducing both anxiety about reactions and the impact of the disease on their usual daily activities. Ultimately this can lead to a substantial improvement in health-related quality of life for both patients and their families.	
	The Anaphylaxis Campaign	The demographic of those receiving the immunotherapy must be similar to those who do not receive it. AR101 should be used in conjunction with a peanut-avoidance diet, which must continue even during successful treatment. The most important outcomes, particularly to patients, would be peanut allergy desensitisation and improvement in health-related quality of life. There would be an expectation by patients that desensitisation would last a substantially long time.	Comments noted. No action required.
	BSACI	AR101 would be used initially in conjunction with a peanut-avoidance diet until treatment completion if successful i.e. tolerance achieved. Once tolerance is achieved patients would be expected to eat peanuts to maintain tolerance. It is hoped/expected that tolerance will be lifelong. There are however no long-term studies to substantiate/refute these expectations.	Comments noted. No action required.