Peanut allergy oral immunotherapy study of AR101 for desensitization in children and adults (Palisade) follow-on study.

Published: 22-05-2017
Last updated: 13-04-2024

The primary objective of this study is to determine the safety, tolerability and efficacy of AR101 characterized oral desensitization immunotherapy (CODITTM) using alternative maintenance dosing intervals.The secondary objectives are:* To confirm...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON48551

Source
ToetsingOnline

Brief title
PALISADE Follow-on Study

Condition

- Allergic conditions

Synonym
peanut allergy

Research involving
Human

Sponsors and support

Primary sponsor: Aimmune Therapeutics UK Limited
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: AR101, Immunotherapy, open-label, Peanut allergy

Outcome measures

Primary outcome

The primary endpoint is the frequency of treatment-related AEs, including SAEs, during the overall study period (from enrollment to the end of EM period).

Secondary outcome

Secondary endpoints include:

* Frequency of anaphylaxis

* Frequency of use of epinephrine as a rescue medication

* Frequency of AEs leading to withdrawal of AR101

* Frequency of AEs in each treatment regimen leading to discontinuation of extended interval dosing

* Frequency of GI AEs of interest (GI AEIs)

* Frequency of accidental food allergen exposure

* In subjects with asthma, change in asthma control using the Asthma Control Test questionnaire (Appendix 2)

* Frequency of all above safety endpoints by treatment period

* The proportion of subjects in each regimen tolerating * 1043 mg cumulative of peanut protein during their EM Exit DBPCFC

* The proportion of subjects in each regimen who tolerate * 443 mg cumulative of peanut protein during their EM Exit DBPCFC

* The proportion of subjects in each regimen who tolerate 4043 mg cumulative of peanut protein during their EM Exit DBPCFC

* Maximum tolerated dose and change from baseline* at Post-Maintenance** and each EM Exit DBPCFC

* Maximum severity of symptoms at each challenge dose at Post-Maintenance** and each EM Exit DBPCFC

* Frequency of use of epinephrine as a rescue medication at the Post-Maintenance** and each EM Exit DBPCFC

* Change in QoL as assessed by the food allergy related quality of life questionnaire (FAQLQ) and the food allergy independent measure (FAIM) questionnaire

* Satisfaction with AR101 treatment as assessed by the Treatment Satisfaction Questionnaire for Medication Version 9 (TSMQ-9) questionnaire and additional questions

* Changes in peanut-specific serum IgE and IgG4 levels

* Changes in peanut skin prick test (SPT) wheal diameter

*Baseline is defined as the Screening DBPCFC from ARC003 for both treatment groups.

**Post-Maintenance is defined as the ARC003 Exit DBPCFCs for Group 2.

Study description

Background summary

Peanut allergy is a common and serious condition that often affects children, and is commonly associated with severe reactions, including life-threatening anaphylaxis. Despite efforts at strict peanut avoidance, accidental exposure continues to be a major concern in peanut allergy because allergic responses

can be triggered after ingestion of just milligram quantities of peanut protein. Accidental exposures may result from commercial food products mislabeling as well as inattention to, or mistrust of, food warning labels. Oral immunotherapy for peanut allergy has been widely studied in recent years and has demonstrated encouraging safety and efficacy results in early clinical trials. In practical terms, this state of desensitization should be sufficient to protect a patient with peanut allergy in case of an accidental exposure to peanut while the patient is attempting to maintain a peanut avoidant diet.

Study objective

The primary objective of this study is to determine the safety, tolerability and efficacy of AR101 characterized oral desensitization immunotherapy (CODITTM) using alternative maintenance dosing intervals.

The secondary objectives are:
* To confirm the safety profile of AR101 as measured by the incidence of adverse events (AEs), including serious adverse events (SAEs)
* To confirm the efficacy of AR101 through reduction in clinical reactivity, measured in a double-blind, placebo-controlled food challenge (DBPCFC) to a cumulative dose of 4043 mg
* To evaluate subjects* quality of life (QoL) and treatment satisfaction during AR101 treatment on daily and non-daily treatment regimens
* To evaluate the long-term immunologic effects of AR101 treatment

Study design

This is an international, multicenter, open-label, 2-arm follow-on study that will explore alternate dosing interval regimens during extended maintenance with AR101.

Group 1 (Placebo Crossovers):
Subjects who complete the placebo arm of ARC003 are eligible to enroll in ARC004. Subjects will enter Group 1 and will undergo initial escalation, up-dosing, and maintenance with AR101 as in the active arm of ARC003. The Initial Escalation Period consists of a step-wise dose-escalation from 0.5 to 3 or 6 mg (as tolerated) on Day 1 and confirmation of the ability to tolerate a single dose of 3 mg on Day 2. The Up-dosing Period is 22 to 40 weeks in duration and consists of dose escalations every 2 weeks up to a maximum of 300 mg/d (as tolerated). The Maintenance Period consists of daily dosing at 300 mg/d for approximately 24 weeks, at which point Group 1 subjects will undergo a DBPCFC to a maximum cumulative dose of 4043 mg peanut protein to test the efficacy of AR101 in ARC003 placebo crossovers after 6 months of daily maintenance. All Group 1 subjects tolerating * 443 mg of cumulative peanut protein will be eligible to continue in ARC004, and enter the Extended Maintenance (EM) Period, initially consisting of ongoing daily maintenance

therapy at 300 mg/d. Dependent upon the EM results from ARC004 Group 2 (below), subjects in Group 1 EM will test the gradual lengthening of their dosing interval from daily (QD) to every other day (QOD), twice weekly (BIW), once weekly (QW), and finally every other week (QOW), as tolerated. Lengthening to each level will occur sequentially (QD then QOD then BIW then QW and finally QOW), and only if sufficient evidence exists, based on the analyses of the Group 2 EM subjects and the ongoing safety of Group 1 subjects, to support progression to each level.

Group 2 (Active Rollovers):
Subjects who complete the active arm of ARC003 and tolerate a challenge dose of * 443 mg cumulative of peanut protein at the ARC003 exit food challenge are eligible to enroll in ARC004. Group 2 subjects will have undergone the Initial Escalation, Up dosing, and Initial Maintenance Periods in ARC003 and will therefore enter the ARC004 EM period directly, where they will be evaluated in 1 of 3 cohorts as outlined below.

Extended Maintenance:
The EM periods will differ between and within the 2 groups in duration and dosing regimen. All EM subjects who complete their dosing regimen, regardless of group or cohort assignment, will have an Exit DBPCFC up to a single highest dose of 2000 mg of peanut protein (4043 mg cumulative). ARC004 will conclude after the last visit for the last subject is completed.

Group 1 Extended Maintenance:
Group 1 subjects who tolerate * 443 mg cumulative peanut protein in the Post-Maintenance DBPCFC will enter the EM period. Subjects who do not tolerate * 443mg cumulative peanut protein are not eligible to continue for safety reasons. The EM period for Group 1 subjects will initially consist of QD dosing. Conditional upon the safety and DBPCFC outcomes assessed in the Group 2 participants, Group 1 subjects may have their dosing interval serially lengthened from QD to QOD, QOD to BIW, BIW to QW, and QW to QOW, as tolerated. The duration of each of these interval extension periods will be adjusted, based on Group 2*s experience, from between 8 to 24 weeks, as tolerated. Following the completion of their longest tested dosing interval, Group 1 subjects will undergo an Exit DBPCFC.

Group 2 Extended Maintenance:
Upon entry into the EM phase of the study (Figure 1), Group 2 subjects will be consecutively enrolled into cohorts that will conditionally explore alternate dosing interval regimens over 28-week study periods, as follows:
1. EM Cohort 1: The first 120 Group 2 subjects to enter ARC004 will make up Cohort 1, and will continue on 300 mg of AR101 daily for 28 weeks before undergoing an Exit DBPCFC.
2. EM Cohort 2: The next 50 Group 2 subjects (subjects 121 to 170) enrolling in ARC004 will make up Cohort 2 and will take 300 mg of AR101 QOD for 4 weeks and then BIW (eg, Monday/Thursday) for 24 weeks as tolerated before undergoing an

Exit DBPCFC.
3. EM Cohort 3: All remaining Group 2 subjects recruited into ARC004 (subjects 171 to the end) will make up Cohort 3. This cohort will be randomized 1:1:1 to 1 of 3 initial strategies:
a. 300 mg QD for 56 weeks followed by an Exit DBPCFC (Cohort 3A)
b. 300 mg QD for 28 weeks, then 300 mg QOD for 4 weeks, then BIW for 24 weeks followed by an Exit DBPCFC (Cohort 3B)
c. 300 mg QD for 28 weeks, then 300 mg QOD for 4 weeks, then BIW for 24 weeks, then 300 mg QW for 28 weeks followed by an Exit DBPCFC (Cohort 3C)
Group 2 cohorts will produce evidence during the trial concerning the feasibility and safety of adjusting EM dosing from daily to a less frequent schedule. The information that becomes available as each cohort proceeds through the study will be evaluated before determining whether the next cohort is to advance to a longer interval between doses. Lengthening the dosing intervals in subsequent cohorts depends on the safety experience of previous cohorts, which will be reviewed by a Safety Monitoring Committee. Individual and cohort stopping rules are discussed further in Section 7.8.3.

End of Participation in ARC004 and Entry into ARC008:
After the end of participation in ARC004, subjects may enroll in the long-term, open-label extension study ARC008 to continue treatment with AR101 at their current dosing regimen (QD, BIW, QW, or QOW) or switch to AR101 daily dosing, until AR101 becomes commercially available or ARC008 is terminated, as follows:
* Subjects on any dosing regimen able to tolerate at least the 600 mg single dose of peanut protein (* 1043 mg cumulative) at their ARC004 Exit DBPCFC will continue their current dosing regimen in Treatment Pathway 1 of ARC008 when that study is available. If ARC008 is not available at the study site, these subjects may continue their current dosing regimen and have visits in ARC004 until they can enroll in ARC008.
* Subjects who tolerate their nondaily dosing regimen and tolerate at least the 300 mg single dose of peanut protein (* 443 mg cumulative) but are unable to tolerate the 600 mg single dose of peanut protein (1043 mg cumulative) at the ARC004 Exit DBPCFC will switch to daily dosing with 300 mg AR101 in Treatment Pathway 1 of ARC008, per investigator discretion. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until ARC008 is available, then continue dosing in ARC008.
* Subjects on a nondaily dosing regimen who tolerate less than the 300 mg single dose of peanut protein (443 mg cumulative) at the Exit DBPCFC may be eligible for treatment in ARC008 per investigator judgment and after discussion with the medical monitor. If continued treatment with AR101 is determined to be safe, these subjects will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not yet available or able to accept these subjects at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until they can enroll in ARC008.
* Subjects who do not tolerate their nondaily dosing regimen (described in

study procedures for Extended Maintenance) will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until
ARC008 is available, then continue dosing in ARC008.
* Subjects on a nondaily dosing regimen who miss or withhold their dose for > 3 days, including subjects receiving QOD, BIW, or QW dosing who miss or withhold their dose for > 14 days, will have the option to receive AR101 daily in Treatment Pathway 2 of ARC008, which consists of Repeat Up-dosing (dose escalation from 80, 120, or 160 mg to 300 mg daily), Initial Maintenance, and Extended Maintenance. If ARC008 is not available at the study site, these subjects may start AR101 daily dosing and have visits in ARC004 until they can enroll in ARC008.
Subjects are not eligible to enroll in ARC008 when continued treatment with AR101 is determined to be unsafe as follows:
* Subjects on a daily dosing regimen who are unable to tolerate at least the 300 mg single dose of peanut protein (443 mg cumulative) at the Exit DBPCFC.
* Subjects not tolerating their nondaily dosing regimen who begin Repeat Up-dosing in ARC004, but are unable to dose escalate to AR101 300 mg daily and tolerate that dose level for 2 weeks within 26 weeks.

Intervention

The investigational product is AR101.
Doses are expressed as mg of peanut protein. For the Initial Escalation and Up-dosing periods, AR101 will be provided in pull-apart capsules at doses of 0.5, 1.0, 10, 20, and 100 mg. For the Maintenance and EM periods, AR101 will be provided in foil-lined sachets at a dose of 300 mg. AR101 will be shipped directly to investigational sites and will be dispensed according to subject identification number, using an interactive response system. Trained investigational site personnel will administer AR101 directly or dispense AR101 to the subject/ guardian in a manner consistent with the assigned dose level. AR101 is administered by QD dosing during Initial Escalation, Up-dosing, and Maintenance, and by either QD, QOD, BIW, QW, or QOW dosing during EM.

Study burden and risks

Please Note: The number of visits per group / cohort varies. Please review Protocol Appendix 1 page 89 -104.
Please Note: Screening/Baseline is conducted at the same time as the End of Study Visit of the preceding ARC003 study. Procedures / Tests performed then are not counted as this has been done already in the ARC003 study.

Burden::
- Blood draw: 2 -5 times appr. 9 ml each time.
- number of visits: 3-29. lasting 1-3 hours. In case of updosing (group 1) and DBPCFC test the visit may last up till 7 hours.
- Physical Exam: full exam 3 times + at the investigator's discretion limited or symptom directed physical exams may be completed.
- Peak expiratory flow rate (PEFR) in subjects 6 years and older: each visit
- Spirometry (FEV1) in subjects 6 years and older when PEFR shows a clinically relevant reduction or the subject shows clinical deterioration (e.g., active wheeze on physical examination): each visit.
- questionnaires: once at end of study
- skin prick test: 2 to 5 times
- DBPCFC: once or twice
- Asthma test: 3 to 8 times
- Diary: entire duration of the study.

Side Effects Associated with the study drug (AR101)
Side effects are mostly allergic reactions and most subjects receiving AR101 experienced at least one side effect of allergic reaction during the course of treatment. These reactions were all of mild to moderate intensity and none was severe.
Symptoms included vomiting, abdominal pain, nausea, cough, mouth and throat discomfort or pain, throat irritation, hives, itching of the lips, lip swelling, lip blister, itchy tongue, runny nose, sneezing, nasal congestion, wheezing, skin itching, eye itching, ear itching, facial swelling, and fatigue.

Other common side effects experienced by 1% to 10% of subjects included gastrointestinal symptoms (nausea, vomiting, diarrhea), respiratory symptoms (nasal congestion, pain in the mouth and throat, cough, wheezing), skin disorders (itching, rash, redness), sleepiness, anaphylaxis, and eosinophilic esophagitis (EoE). Most of the side effects were mild to moderate and became less frequent over time. Although the episodes of anaphylaxis were infrequent and successfully managed, severe or life-threatening anaphylaxis is a potential risk of AR101. Also, whenever reoccurring gastrointestinal symptoms occur with AR101, there is a suspicion that EoE might be present.

It is expected that the chance of having an allergic reaction is reduced when the study drug is started at very small doses, and when the dosing is increased slowly while being observed by the Study Doctor.

There may be a risk that during study participation subjects may decrease their vigilance against accidental peanut ingestion because they believe they are protected from it. This phenomenon has been reported in previous trials. Subjects (and partents/guardians) will be warned that they should continue to practice their usual vigilance against accidental ingestion of peanuts or peanut containing food.

Side Effects Associated with Oral Food Challenges
Oral food challenges are expected to induce an allergic response in food-allergic individuals. Allergic reactions can be severe, including life-threatening allergic reactions; however, the risk of an allergic reaction is reduced by beginning the challenge with a very small amount of the food, gradually increasing the dose, and stopping the challenge at the first sign of a significant reaction. In case of an allergic reaction during the challenges, medication will be administered (if needed) and the subject will be provided with the standard care.

Side Effects Associated with Collecting Blood Samples
- pain or bruising at the site where the blood will be drawn, fainting, swelling of the vein, infection or bleeding at the puncture site. *

Possible benifits:
-The study drug does not cure an allergy. However, it may lessen the body*s sensitivity or allergic response to the allergen, resulting in fewer symptoms.
-. Information from this study may help researchers to better understand peanut allergy or to develop future tests or treatments to help patients with this condition.

Contacts

Public
Aimmune Therapeutics UK Limited

Gray's Inn Road 344-354
London WC1X8BP
GB
Scientific
Aimmune Therapeutics UK Limited

Gray's Inn Road 344-354
London WC1X8BP
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Completion of ARC003
2. Written informed consent and/or assent from subjects/guardians as appropriate
3. Use of effective birth control by female subjects of child-bearing potential

Exclusion criteria

1. Early discontinuation from ARC003
2. Meets any longitudinally applicable ARC003 exclusion criteria
3. (Group 2 only) Failure to tolerate *443 mg cumulative of peanut protein with no or mild symptoms in the ARC Exit DBPCFC
4. Any other condition that, in the opinion of the investigator, precludes participation for reasons of safety.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2017
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AR101 (proprietary + generic name not yet set)
Generic name:	AR101

Ethics review

Approved WMO Date:	22-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-08-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-01-2019
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-004941-94-NL
ClinicalTrials.gov	NCT02993107
CCMO	NL61344.042.17