Clinical trial results:
PEANUT ALLERGY ORAL IMMUNOTHERAPY STUDY OF AR101 FOR DESENSITIZATION IN CHILDREN AND ADULTS (PALISADE) FOLLOW-ON STUDY

Summary

EudraCT number	2016-004941-94
Trial protocol	IE GB SE DE ES NL IT
Global end of trial date	31 May 2019

Results information

Result version number	v1 (current)
This version publication date	02 July 2021
First version publication date	02 July 2021

Trial information

Trial identification

Sponsor protocol code	ARC004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02993107
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aimmune Therapeutics Inc.
Sponsor organisation address	8000 Marina Blvd, Suite 300, Brisbane, United States, 94005
Public contact	Director of Regulatory Affairs, Aimmune Therapeutics Inc., +1 (650)409-5164, RegulatoryAffairs@aimmune.com
Scientific contact	Director of Regulatory Affairs, Aimmune Therapeutics Inc., +1 (650)409-5164, RegulatoryAffairs@aimmune.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001734-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2019
Global end of trial reached?	Yes
Global end of trial date	31 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

- Education of patients to notify sites of allergic symptoms occurring at home.
- Patient emergency card, dos and don't card, home dosing card.
- Patients/caregivers asked to carry epi-pen with them at all times during study.
- Patient advised to go to local emergency unit outside of normal clinical working hours.
- Patient advised to report rare or unforeseen AEs immediately.
- Advised to practice usual peanut avoidance
- Specific reporting/monitoring of AEIs, Gastrointestinal AEs (monitoring and follow-up for EOE), capture of AEs in patient diaries, EDC, SAE reporting, study and individual stopping rules & in clinic, supervised up-dosing, including observation timelines prior to Clinic departure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Ireland: 15
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	United States: 290
Worldwide total number of subjects	388
EEA total number of subjects	75

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	230
Adolescents (12-17 years)	128
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 442 subjects who completed the ARC003 (PALISADE) study were eligible for participation in this study and were screened for inclusion of which 388 were enrolled in this study.

Pre-assignment

Screening details:

Subjects who met all of the following criteria were eligible for enrolment:
- Completion of ARC003
- Written informed consent and/or assent from subject/guardian as appropriate
- Continued use of effective birth control by female subjects of childbearing potential

Period 1

Period 1 title	Post-Allocation (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Group 1

Arm description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative) was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be dosed at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks.

Arm type	Experimental
Investigational medicinal product name	AR101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

AR101 drug product was supplied in 2 presentations. These were capsules containing 0.5, 1, 10, 20 and 100mg of peanut protein and sealed sachets containing 300mg of peanut protein. Subjects in initial escalation and up-dosing phases received the capsule presentation. Subjects in maintenance phase received the sachet presentation according to their allocated dosing schedules. If dose-reduction was required, subjects were dispensed the appropriate capsule packs.

Arm title	Group 2, Cohort 1

Arm description:

Group 2, Cohort 1 subjects were the first 120 (approximately) of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day (once daily, QD) for 28 weeks.

Arm type	Experimental
Investigational medicinal product name	AR101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

AR101 drug product was supplied in 2 presentations. These were capsules containing 0.5, 1, 10, 20 and 100mg of peanut protein and sealed sachets containing 300mg of peanut protein. Subjects in initial escalation and up-dosing phases received the capsule presentation. Subjects in maintenance phase received the sachet presentation according to their allocated dosing schedules. If dose-reduction was required, subjects were dispensed the appropriate capsule packs.

Arm title	Group 2, Cohort 2

Arm description:

Group 2, Cohort 2 subjects comprised 50(approximately) of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every other day (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks for a total of 28 weeks.

Arm type	Experimental
Investigational medicinal product name	AR101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

AR101 drug product was supplied in 2 presentations. These were capsules containing 0.5, 1, 10, 20 and 100mg of peanut protein and sealed sachets containing 300mg of peanut protein. Subjects in initial escalation and up-dosing phases received the capsule presentation. Subjects in maintenance phase received the sachet presentation according to their allocated dosing schedules. If dose-reduction was required, subjects were dispensed the appropriate capsule packs.

Arm title	Group 2, Cohort 3A

Arm description:

Group 2, Cohort 3A subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 56 weeks.

Arm type	Experimental
Investigational medicinal product name	AR101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

AR101 drug product was supplied in 2 presentations. These were capsules containing 0.5, 1, 10, 20 and 100mg of peanut protein and sealed sachets containing 300mg of peanut protein. Subjects in initial escalation and up-dosing phases received the capsule presentation. Subjects in maintenance phase received the sachet presentation according to their allocated dosing schedules. If dose-reduction was required, subjects were dispensed the appropriate capsule packs.

Arm title	Group 2, Cohort 3B

Arm description:

Group 2, Cohort 3B subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks (total of 56 weeks).

Arm type	Experimental
Investigational medicinal product name	AR101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

AR101 drug product was supplied in 2 presentations. These were capsules containing 0.5, 1, 10, 20 and 100mg of peanut protein and sealed sachets containing 300mg of peanut protein. Subjects in this treatment arm received the sealed sachets containing 300mg of peanut protein every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks (total of 56 weeks). If dose-reduction was required, subjects were dispensed the appropriate capsule packs.

Arm title	Group 2, Cohort 3C

Arm description:

Group 2, Cohort 3C subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, twice weekly (BIW) for 24 weeks then once weekly (QW) for 28 weeks (total of 84 weeks).

Arm type	Experimental
Investigational medicinal product name	AR101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

AR101 drug product was supplied in 2 presentations. These were capsules containing 0.5, 1, 10, 20 and 100mg of peanut protein and sealed sachets containing 300mg of peanut protein. Subjects in this treatment arm received the sealed sachets containing 300mg of peanut protein every day (QD) for 4 weeks, 300 mg/day every other (QOD) for 4 weeks, twice weekly (BIW) for 24 weeks then once weekly (QW) for 28 weeks (total of 84 weeks). If dose-reduction was required, subjects were dispensed the appropriate capsule packs.

Number of subjects in period 1	Group 1	Group 2, Cohort 1	Group 2, Cohort 2
Started	113	120	50
Completed	62	107	39
Not completed	51	13	11
Physician decision	1	-	1
Consent withdrawn by subject	32	7	7
Adverse event, non-fatal	12	4	1
Other	2	1	1
Sponsor Decision	4	-	1
Lost to follow-up	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	Group 2, Cohort 3A	Group 2, Cohort 3B	Group 2, Cohort 3C
Started	35	34	36
Completed	29	22	21
Not completed	6	12	15
Physician decision	-	-	-
Consent withdrawn by subject	3	6	2
Adverse event, non-fatal	1	3	5
Other	1	2	3
Sponsor Decision	1	-	4
Lost to follow-up	-	-	1
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Post-Allocation

Reporting group description:

Subjects aged 4 to 55 years who completed study ARC003 (PALISADE).

Reporting group values	Post-Allocation	Total	
Number of subjects	388	388	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	230	230	
Adolescents (12-17 years)	128	128	
Adults (18-64 years)	30	30	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Subject age at screening (years)			
Units: years			
median	10		
full range (min-max)	4 to 17	-	
Gender categorical Units: Subjects			
Female	165	165	
Male	223	223	

Subject analysis sets

Subject analysis set title	Safety Population Ages 4-17: Group 1 (All Study Periods)
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (IDE; day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC, using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative), was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be doses at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks. This analysis set evaluates all the above study phases. This analysis set includes events from subjects in all study (IDE, Updosing and maintenance) periods.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 1
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 1 subjects were the first 120 of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day (once daily, QD) for 28 weeks.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 2
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 2 subjects comprised 50 of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every other day (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks for a total of 28 weeks.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 3A
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 3A subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 56 weeks.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 3B
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 3B subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks (total of 56 weeks).

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 3C
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 3C subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 4 weeks, 300 mg/day every other (QOD) for 4 weeks, twice weekly (BIW) for 24 weeks then once weekly (QW) for 28 weeks (total of 84 weeks).

Subject analysis set title	Safety Population Ages 4-17: Group 1 (IDE and Updosing)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (IDE; day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC, using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative), was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be doses at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks. This analysis set includes events from subjects in the IDE and Updosing periods only.

Subject analysis set title	Safety Population Ages 4-17: Group 1 (Maintenance)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (IDE; day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC, using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative), was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be doses at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks. This analysis set includes event from subjects in the maintenance period only.

Subject analysis set title	Safety Population Ages 18-55
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Adult population data not reported.

Reporting group values	Safety Population Ages 4-17: Group 1 (All Study Periods)	Safety Population Ages 4-17: Group 2, Cohort 1	Safety Population Ages 4-17: Group 2, Cohort 2
Number of subjects	102	112	48

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	69	63	31
Adolescents (12-17 years)	33	46	15
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Subject age at screening (years)			
Units: years			
median	9.5	11	10
full range (min-max)	5 to 17	5 to 17	4 to 17
Gender categorical Units: Subjects			
Female	37	52	22
Male	65	60	26

Reporting group values	Safety Population Ages 4-17: Group 2, Cohort 3A	Safety Population Ages 4-17: Group 2, Cohort 3B	Safety Population Ages 4-17: Group 2, Cohort 3C
Number of subjects	31	31	34
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	22	20	23
Adolescents (12-17 years)	9	11	11
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Subject age at screening (years)			
Units: years			
median	9	9	9
full range (min-max)	5 to 17	5 to 16	5 to 16
Gender categorical Units: Subjects			
Female	14	12	16
Male	17	19	18

Reporting group values	Safety Population Ages 4-17: Group 1 (IDE and Updosing)	Safety Population Ages 4-17: Group 1 (Maintenance)	Safety Population Ages 18-55
Number of subjects	100	85	30

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	69	61	0
Adolescents (12-17 years)	31	24	0
Adults (18-64 years)	0	0	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Subject age at screening (years)			
Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female	35	30	12
Male	65	55	18

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative) was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be dosed at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks.

Reporting group title	Group 2, Cohort 1

Reporting group description:

Group 2, Cohort 1 subjects were the first 120 (approximately) of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day (once daily, QD) for 28 weeks.

Reporting group title	Group 2, Cohort 2

Reporting group description:

Group 2, Cohort 2 subjects comprised 50(approximately) of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every other day (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks for a total of 28 weeks.

Reporting group title	Group 2, Cohort 3A

Reporting group description:

Group 2, Cohort 3A subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 56 weeks.

Reporting group title	Group 2, Cohort 3B

Reporting group description:

Group 2, Cohort 3B subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks (total of 56 weeks).

Reporting group title	Group 2, Cohort 3C

Reporting group description:

Group 2, Cohort 3C subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, twice weekly (BIW) for 24 weeks then once weekly (QW) for 28 weeks (total of 84 weeks).

Subject analysis set title	Safety Population Ages 4-17: Group 1 (All Study Periods)
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (IDE; day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC, using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative), was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be doses at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks. This analysis set evaluates all the above study phases. This analysis set includes events from subjects in all study (IDE, Updosing and maintenance) periods.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 1
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 1 subjects were the first 120 of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day (once daily, QD) for 28 weeks.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 2
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 2 subjects comprised 50 of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every other day (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks for a total of 28 weeks.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 3A
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 3A subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 56 weeks.

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 3B
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 3B subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks (total of 56 weeks).

Subject analysis set title	Safety Population Ages 4-17: Group 2, Cohort 3C
Subject analysis set type	Safety analysis

Subject analysis set description:

Group 2, Cohort 3C subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 4 weeks, 300 mg/day every other (QOD) for 4 weeks, twice weekly (BIW) for 24 weeks then once weekly (QW) for 28 weeks (total of 84 weeks).

Subject analysis set title	Safety Population Ages 4-17: Group 1 (IDE and Updosing)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (IDE; day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC, using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative), was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be doses at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks. This analysis set includes events from subjects in the IDE and Updosing periods only.

Subject analysis set title	Safety Population Ages 4-17: Group 1 (Maintenance)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during initial dose escalation (IDE; day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 to 300 mg/day for 22 to 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 to 28 weeks). A DBPCFC, using peanut protein (not AR101) of doses up to 2000 mg (4043 mg cumulative), was conducted after approximately 6 months of maintenance treatment. This was followed by an extended maintenance period in subjects tolerating at least 300mg in the DBPCFC where the subjects may be doses at gradually dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks. This analysis set includes event from subjects in the maintenance period only.

Subject analysis set title	Safety Population Ages 18-55
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Adult population data not reported.

Primary: Overall Summary of Treatment Emergent Adverse Events

End point title	Overall Summary of Treatment Emergent Adverse Events[1]

End point description:

All Treatment Emergent AEs and AEs by Severity

End point type	Primary

End point timeframe:

Group 1: Total duration varies, ranging from approximately 88 to 136 weeks
Group 2, Cohort 1: 28 weeks

Group 2, Cohort 2: 28 weeks
Group 2, Cohort 3A: 56 weeks
Group 2, Cohort 3B: 56 weeks
Group 2, Cohort 3C: 84 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data were summarised using descriptive statistics by group/cohort. No specific hypothesis testing or comparisons between treatment groups were performed.

End point values	Safety Population Ages 4-17: Group 1 (All Study Periods)	Safety Population Ages 4-17: Group 2, Cohort 1	Safety Population Ages 4-17: Group 2, Cohort 2	Safety Population Ages 4-17: Group 2, Cohort 3A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	109	46	31
Units: Percentage of Subjects Reporting				
number (not applicable)				
All AEs	98.0	82.6	78.3	87.1
SAEs	0	0.9	0	0
Grade 1: Mild	37.0	53.2	47.8	48.4
Grade 2: Moderate	58.0	26.6	30.4	38.7
Grade 3: Severe	3.0	2.8	0	0
Grade 4: Life-Threatening	0	0	0	0
Grade 5: Death	0	0	0	0

End point values	Safety Population Ages 4-17: Group 2, Cohort 3B	Safety Population Ages 4-17: Group 2, Cohort 3C	Safety Population Ages 4-17: Group 1 (IDE and Updosing)	Safety Population Ages 4-17: Group 1 (Maintenance)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	34	100	85
Units: Percentage of Subjects Reporting				
number (not applicable)				
All AEs	90.3	97.1	94.0	89.4
SAEs	3.2	2.9	0	0
Grade 1: Mild	41.9	35.3	41.0	52.9
Grade 2: Moderate	48.4	52.9	51.0	35.3
Grade 3: Severe	0	8.8	2.0	1.2
Grade 4: Life-Threatening	0	0	0	0
Grade 5: Death	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Subjects who tolerated a single dose of 300 mg peanut protein (response rate)

End point title	Subjects who tolerated a single dose of 300 mg peanut protein (response rate)

End point description:

Desensitisation Response Rates at Exit DBPCFC (Completer Population). Maintenance DBPCFC results were used for Group 1 subjects who did not complete the Exit DBPCFC.

End point type	Other pre-specified

End point timeframe:

Group 1: Total duration varies, ranging from approximately 88 to 136 weeks
Group 2, Cohort 1: 28 weeks
Group 2, Cohort 2: 28 weeks
Group 2, Cohort 3A: 56 weeks
Group 2, Cohort 3B: 56 weeks
Group 2, Cohort 3C: 84 weeks

End point values	Safety Population Ages 4-17: Group 1 (All Study Periods)	Safety Population Ages 4-17: Group 2, Cohort 1	Safety Population Ages 4-17: Group 2, Cohort 2	Safety Population Ages 4-17: Group 2, Cohort 3A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	103	38	26
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	98.6 (92.5 to 100)	98.1 (93.2 to 99.8)	94.7 (82.3 to 99.4)	100.0 (86.8 to 100)

End point values	Safety Population Ages 4-17: Group 2, Cohort 3B	Safety Population Ages 4-17: Group 2, Cohort 3C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	81.8 (59.7 to 94.8)	90.5 (69.6 to 98.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Subjects who tolerated a single dose of 600 mg peanut protein (response rate)

End point title	Subjects who tolerated a single dose of 600 mg peanut protein (response rate)

End point description:

Desensitisation Response Rates at Exit DBPCFC (Completer Population). Maintenance DBPCFC results were used for Group 1 subjects who did not complete the Exit DBPCFC.

End point type	Other pre-specified

End point timeframe:

Group 1: Total duration varies, ranging from approximately 88 to 136 weeks
Group 2, Cohort 1: 28 weeks
Group 2, Cohort 2: 28 weeks
Group 2, Cohort 3A: 56 weeks
Group 2, Cohort 3B: 56 weeks
Group 2, Cohort 3C: 84 weeks

End point values	Safety Population Ages 4-17: Group 1 (All Study Periods)	Safety Population Ages 4-17: Group 2, Cohort 1	Safety Population Ages 4-17: Group 2, Cohort 2	Safety Population Ages 4-17: Group 2, Cohort 3A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	103	38	26
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	86.1 (75.9 to 93.1)	89.3 (81.7 to 94.5)	71.1 (54.1 to 84.6)	96.2 (80.4 to 99.9)

End point values	Safety Population Ages 4-17: Group 2, Cohort 3B	Safety Population Ages 4-17: Group 2, Cohort 3C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	77.3 (54.6 to 92.2)	76.2 (52.8 to 91.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Subjects who tolerated a single dose of 1000 mg peanut protein (response rate)

End point title	Subjects who tolerated a single dose of 1000 mg peanut protein (response rate)

End point description:

Desensitisation Response Rates at Exit DBPCFC (Completer Population). Maintenance DBPCFC results were used for Group 1 subjects who did not complete the Exit DBPCFC.

End point type	Other pre-specified

End point timeframe:

Group 1: Total duration varies, ranging from approximately 88 to 136 weeks
Group 2, Cohort 1: 28 weeks
Group 2, Cohort 2: 28 weeks

Group 2, Cohort 3A: 56 weeks
Group 2, Cohort 3B: 56 weeks
Group 2, Cohort 3C: 84 weeks

End point values	Safety Population Ages 4-17: Group 1 (All Study Periods)	Safety Population Ages 4-17: Group 2, Cohort 1	Safety Population Ages 4-17: Group 2, Cohort 2	Safety Population Ages 4-17: Group 2, Cohort 3A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	103	38	26
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	72.2 (60.4 to 82.1)	80.6 (71.6 to 87.7)	57.9 (40.8 to 73.7)	96.2 (80.4 to 99.9)

End point values	Safety Population Ages 4-17: Group 2, Cohort 3B	Safety Population Ages 4-17: Group 2, Cohort 3C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	68.2 (45.1 to 86.1)	66.7 (43.0 to 85.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Subjects who tolerated a single dose of 2000 mg peanut protein (response rate)

End point title	Subjects who tolerated a single dose of 2000 mg peanut protein (response rate)

End point description:

Desensitisation Response Rates at Exit DBPCFC (Completer Population). Maintenance DBPCFC results were used for Group 1 subjects who did not complete the Exit DBPCFC.

End point type	Other pre-specified

End point timeframe:

Group 1: Total duration varies, ranging from approximately 88 to 136 weeks
Group 2, Cohort 1: 28 weeks
Group 2, Cohort 2: 28 weeks
Group 2, Cohort 3A: 56 weeks
Group 2, Cohort 3B: 56 weeks
Group 2, Cohort 3C: 84 weeks

End point values	Safety Population Ages 4-17: Group 1 (All Study Periods)	Safety Population Ages 4-17: Group 2, Cohort 1	Safety Population Ages 4-17: Group 2, Cohort 2	Safety Population Ages 4-17: Group 2, Cohort 3A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	103	38	26
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	51.4 (39.3 to 63.3)	48.5 (38.6 to 58.6)	36.8 (21.8 to 54.0)	80.8 (60.6 to 93.4)

End point values	Safety Population Ages 4-17: Group 2, Cohort 3B	Safety Population Ages 4-17: Group 2, Cohort 3C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Responder %	45.5 (24.4 to 67.8)	42.9 (21.8 to 66.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Group 1: Total duration varies, ranging from approximately 88 to 136 weeks
Group 2, Cohort 1: 28 weeks
Group 2, Cohort 2: 28 weeks
Group 2, Cohort 3A: 56 weeks
Group 2, Cohort 3B: 56 weeks
Group 2, Cohort 3C: 84 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Group 1 (Age 4-17)

Reporting group description:

Group 1 (placebo treated subjects in ARC003): Subjects received AR101 during IDE (day 1, 0.5 to 3 or 6 mg; day 2, 3 mg), up dosing (3 300 mg/day for 22 40 weeks, with dose escalations every 2 weeks), and maintenance (300 mg/day for 24 28 weeks). A DBPCFC after approximately 6 months of maintenance treatment evaluated up to a single highest dose of 2000 mg peanut protein food challenge material (4043 mg cumulative) (hereafter, peanut protein when referring to food challenge material; not AR101). Subjects who tolerated a single highest dose of at least 300 mg in the DBPCFC could receive AR101 during extended maintenance in gradually increasing dosing intervals depending on the results from group 2. The total duration of AR101 treatment in group 1 was 88 to 136 weeks.

Reporting group title	Group 2, Cohort 1 (Age 4-17)

Reporting group description:

Group 2, Cohort 1 subjects were the first 120 (approximately) of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day (once daily, QD) for 28 weeks.

Reporting group title	Group 2, Cohort 2 (Age 4-17)

Reporting group description:

Group 2, Cohort 2 subjects comprised 50(approximately) of the AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every other day (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks for a total of 28 weeks.

Reporting group title	Group 2, Cohort 3A (Age 4-17)

Reporting group description:

Group 2, Cohort 3A subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 56 weeks.

Reporting group title	Group 2, Cohort 3B (Age 4-17)

Reporting group description:

Group 2, Cohort 3B subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 28 weeks, 300 mg/day every other (QOD) for 4 weeks, then twice weekly (BIW) for 24 weeks (total of 56 weeks).

Reporting group title	Group 2, Cohort 3C (Age 4-17)

Reporting group description:

Group 2, Cohort 3C subjects were AR101-treated subjects in ARC003 who tolerated >/= 300 mg peanut protein in the exit DBPCFC. These subjects received 300 mg/day every day (QD) for 4 weeks, 300 mg/day every other (QOD) for 4 weeks, twice weekly (BIW) for 24 weeks then once weekly (QW) for 28 weeks (total of 84 weeks).

Serious adverse events	Group 1 (Age 4-17)	Group 2, Cohort 1 (Age 4-17)	Group 2, Cohort 2 (Age 4-17)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 100 (0.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Streptococcal infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 100 (0.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 2, Cohort 3A (Age 4-17)	Group 2, Cohort 3B (Age 4-17)	Group 2, Cohort 3C (Age 4-17)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	1 / 34 (2.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Streptococcal infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1 (Age 4-17)	Group 2, Cohort 1 (Age 4-17)	Group 2, Cohort 2 (Age 4-17)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 100 (98.00%)	90 / 109 (82.57%)	36 / 46 (78.26%)
Vascular disorders			
Flushing			
subjects affected / exposed	6 / 100 (6.00%)	3 / 109 (2.75%)	2 / 46 (4.35%)
occurrences (all)	6	3	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	24 / 100 (24.00%)	20 / 109 (18.35%)	4 / 46 (8.70%)
occurrences (all)	51	27	5
Influenza like illness			
subjects affected / exposed	1 / 100 (1.00%)	0 / 109 (0.00%)	1 / 46 (2.17%)
occurrences (all)	2	0	1
Malaise			
subjects affected / exposed	6 / 100 (6.00%)	0 / 109 (0.00%)	2 / 46 (4.35%)
occurrences (all)	10	0	3
Chest pain			

subjects affected / exposed	9 / 100 (9.00%)	0 / 109 (0.00%)	1 / 46 (2.17%)
occurrences (all)	14	0	3
Fatigue			
subjects affected / exposed	4 / 100 (4.00%)	2 / 109 (1.83%)	1 / 46 (2.17%)
occurrences (all)	4	2	1
Chest discomfort			
subjects affected / exposed	9 / 100 (9.00%)	3 / 109 (2.75%)	0 / 46 (0.00%)
occurrences (all)	19	4	0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	17 / 100 (17.00%)	7 / 109 (6.42%)	0 / 46 (0.00%)
occurrences (all)	22	13	0
Hypersensitivity			
subjects affected / exposed	6 / 100 (6.00%)	1 / 109 (0.92%)	1 / 46 (2.17%)
occurrences (all)	11	1	1
Seasonal allergy			
subjects affected / exposed	8 / 100 (8.00%)	2 / 109 (1.83%)	0 / 46 (0.00%)
occurrences (all)	18	2	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 100 (1.00%)	2 / 109 (1.83%)	1 / 46 (2.17%)
occurrences (all)	1	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	44 / 100 (44.00%)	16 / 109 (14.68%)	8 / 46 (17.39%)
occurrences (all)	147	29	15
Throat irritation			
subjects affected / exposed	32 / 100 (32.00%)	15 / 109 (13.76%)	9 / 46 (19.57%)
occurrences (all)	753	38	77
Oropharyngeal pain			
subjects affected / exposed	23 / 100 (23.00%)	7 / 109 (6.42%)	4 / 46 (8.70%)
occurrences (all)	82	9	8
Rhinorrhoea			
subjects affected / exposed	28 / 100 (28.00%)	7 / 109 (6.42%)	2 / 46 (4.35%)
occurrences (all)	65	23	19
Wheezing			

subjects affected / exposed	17 / 100 (17.00%)	3 / 109 (2.75%)	2 / 46 (4.35%)
occurrences (all)	54	5	5
Asthma			
subjects affected / exposed	4 / 100 (4.00%)	3 / 109 (2.75%)	4 / 46 (8.70%)
occurrences (all)	5	3	12
Nasal congestion			
subjects affected / exposed	22 / 100 (22.00%)	8 / 109 (7.34%)	6 / 46 (13.04%)
occurrences (all)	61	13	8
Dyspnoea			
subjects affected / exposed	12 / 100 (12.00%)	1 / 109 (0.92%)	1 / 46 (2.17%)
occurrences (all)	57	2	2
Sneezing			
subjects affected / exposed	18 / 100 (18.00%)	8 / 109 (7.34%)	4 / 46 (8.70%)
occurrences (all)	54	24	5
Pharyngeal paraesthesia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 109 (0.00%)	1 / 46 (2.17%)
occurrences (all)	2	0	1
Rhinitis allergic			
subjects affected / exposed	7 / 100 (7.00%)	3 / 109 (2.75%)	3 / 46 (6.52%)
occurrences (all)	48	4	3
Throat tightness			
subjects affected / exposed	12 / 100 (12.00%)	1 / 109 (0.92%)	1 / 46 (2.17%)
occurrences (all)	26	2	2
Productive cough			
subjects affected / exposed	2 / 100 (2.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	4 / 100 (4.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
occurrences (all)	6	1	0
Arthropod sting			
subjects affected / exposed	1 / 100 (1.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Procedural pain			

subjects affected / exposed	2 / 100 (2.00%)	1 / 109 (0.92%)	1 / 46 (2.17%)
occurrences (all)	2	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 100 (27.00%)	12 / 109 (11.01%)	12 / 46 (26.09%)
occurrences (all)	69	22	22
Dizziness			
subjects affected / exposed	1 / 100 (1.00%)	0 / 109 (0.00%)	1 / 46 (2.17%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 100 (2.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 100 (3.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
occurrences (all)	5	1	0
Ear pruritus			
subjects affected / exposed	2 / 100 (2.00%)	1 / 109 (0.92%)	3 / 46 (6.52%)
occurrences (all)	3	3	9
Eye disorders			
Eye pruritus			
subjects affected / exposed	8 / 100 (8.00%)	5 / 109 (4.59%)	4 / 46 (8.70%)
occurrences (all)	16	6	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	38 / 100 (38.00%)	11 / 109 (10.09%)	7 / 46 (15.22%)
occurrences (all)	315	22	13
Vomiting			
subjects affected / exposed	42 / 100 (42.00%)	18 / 109 (16.51%)	6 / 46 (13.04%)
occurrences (all)	116	32	10
Oral pruritus			
subjects affected / exposed	17 / 100 (17.00%)	6 / 109 (5.50%)	5 / 46 (10.87%)
occurrences (all)	354	232	40
Nausea			
subjects affected / exposed	33 / 100 (33.00%)	9 / 109 (8.26%)	9 / 46 (19.57%)
occurrences (all)	241	15	14

Abdominal pain upper			
subjects affected / exposed	31 / 100 (31.00%)	9 / 109 (8.26%)	6 / 46 (13.04%)
occurrences (all)	223	136	75
Lip pruritus			
subjects affected / exposed	11 / 100 (11.00%)	3 / 109 (2.75%)	2 / 46 (4.35%)
occurrences (all)	88	4	12
Lip swelling			
subjects affected / exposed	8 / 100 (8.00%)	3 / 109 (2.75%)	4 / 46 (8.70%)
occurrences (all)	11	3	5
Paraesthesia oral			
subjects affected / exposed	6 / 100 (6.00%)	0 / 109 (0.00%)	2 / 46 (4.35%)
occurrences (all)	62	0	2
Abdominal discomfort			
subjects affected / exposed	17 / 100 (17.00%)	6 / 109 (5.50%)	5 / 46 (10.87%)
occurrences (all)	46	20	20
Diarrhoea			
subjects affected / exposed	10 / 100 (10.00%)	5 / 109 (4.59%)	1 / 46 (2.17%)
occurrences (all)	67	11	4
Tongue pruritus			
subjects affected / exposed	11 / 100 (11.00%)	3 / 109 (2.75%)	1 / 46 (2.17%)
occurrences (all)	114	5	6
Toothache			
subjects affected / exposed	5 / 100 (5.00%)	0 / 109 (0.00%)	1 / 46 (2.17%)
occurrences (all)	5	0	2
Oral discomfort			
subjects affected / exposed	1 / 100 (1.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
occurrences (all)	5	1	0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	37 / 100 (37.00%)	16 / 109 (14.68%)	6 / 46 (13.04%)
occurrences (all)	96	32	12
Pruritus			
subjects affected / exposed	19 / 100 (19.00%)	7 / 109 (6.42%)	6 / 46 (13.04%)
occurrences (all)	47	11	10
Rash			

subjects affected / exposed	14 / 100 (14.00%)	6 / 109 (5.50%)	1 / 46 (2.17%)
occurrences (all)	16	6	1
Eczema			
subjects affected / exposed	7 / 100 (7.00%)	2 / 109 (1.83%)	1 / 46 (2.17%)
occurrences (all)	10	2	1
Dermatitis atopic			
subjects affected / exposed	3 / 100 (3.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Swelling face			
subjects affected / exposed	1 / 100 (1.00%)	1 / 109 (0.92%)	1 / 46 (2.17%)
occurrences (all)	1	1	1
Erythema			
subjects affected / exposed	8 / 100 (8.00%)	1 / 109 (0.92%)	1 / 46 (2.17%)
occurrences (all)	26	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 100 (2.00%)	2 / 109 (1.83%)	0 / 46 (0.00%)
occurrences (all)	2	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 100 (16.00%)	5 / 109 (4.59%)	5 / 46 (10.87%)
occurrences (all)	31	9	7
Upper respiratory tract infection			
subjects affected / exposed	23 / 100 (23.00%)	20 / 109 (18.35%)	6 / 46 (13.04%)
occurrences (all)	49	27	7
Sinusitis			
subjects affected / exposed	6 / 100 (6.00%)	2 / 109 (1.83%)	1 / 46 (2.17%)
occurrences (all)	8	2	1
Viral infection			
subjects affected / exposed	10 / 100 (10.00%)	9 / 109 (8.26%)	1 / 46 (2.17%)
occurrences (all)	13	12	1
Conjunctivitis			
subjects affected / exposed	4 / 100 (4.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
occurrences (all)	5	1	0
Gastroenteritis			

subjects affected / exposed	5 / 100 (5.00%)	2 / 109 (1.83%)	1 / 46 (2.17%)
occurrences (all)	5	2	1
Influenza			
subjects affected / exposed	7 / 100 (7.00%)	7 / 109 (6.42%)	1 / 46 (2.17%)
occurrences (all)	8	7	1
Rhinitis			
subjects affected / exposed	6 / 100 (6.00%)	1 / 109 (0.92%)	0 / 46 (0.00%)
occurrences (all)	11	1	0
Gastrointestinal viral infection			
subjects affected / exposed	2 / 100 (2.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Tonsillitis			
subjects affected / exposed	2 / 100 (2.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis viral			
subjects affected / exposed	9 / 100 (9.00%)	7 / 109 (6.42%)	1 / 46 (2.17%)
occurrences (all)	12	7	1
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 100 (4.00%)	5 / 109 (4.59%)	0 / 46 (0.00%)
occurrences (all)	4	6	0
Ear infection			
subjects affected / exposed	2 / 100 (2.00%)	4 / 109 (3.67%)	3 / 46 (6.52%)
occurrences (all)	2	5	3
Pharyngitis streptococcal			
subjects affected / exposed	4 / 100 (4.00%)	5 / 109 (4.59%)	5 / 46 (10.87%)
occurrences (all)	4	5	8
Respiratory tract infection viral			
subjects affected / exposed	1 / 100 (1.00%)	0 / 109 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Group 2, Cohort 3A (Age 4-17)	Group 2, Cohort 3B (Age 4-17)	Group 2, Cohort 3C (Age 4-17)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 31 (87.10%)	28 / 31 (90.32%)	33 / 34 (97.06%)
Vascular disorders			
Flushing			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 31 (25.81%)	6 / 31 (19.35%)	13 / 34 (38.24%)
occurrences (all)	19	14	24
Influenza like illness			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Malaise			
subjects affected / exposed	4 / 31 (12.90%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	4	0	2
Chest pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Chest discomfort			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	5 / 31 (16.13%)	2 / 31 (6.45%)	10 / 34 (29.41%)
occurrences (all)	14	2	13
Hypersensitivity			
subjects affected / exposed	5 / 31 (16.13%)	2 / 31 (6.45%)	3 / 34 (8.82%)
occurrences (all)	8	2	3
Seasonal allergy			
subjects affected / exposed	2 / 31 (6.45%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	2	4	3
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	4	5	0
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	8 / 31 (25.81%)	10 / 31 (32.26%)	16 / 34 (47.06%)
occurrences (all)	57	40	47
Throat irritation			
subjects affected / exposed	5 / 31 (16.13%)	5 / 31 (16.13%)	9 / 34 (26.47%)
occurrences (all)	14	6	289
Oropharyngeal pain			
subjects affected / exposed	7 / 31 (22.58%)	6 / 31 (19.35%)	8 / 34 (23.53%)
occurrences (all)	28	11	12
Rhinorrhoea			
subjects affected / exposed	3 / 31 (9.68%)	4 / 31 (12.90%)	7 / 34 (20.59%)
occurrences (all)	15	10	22
Wheezing			
subjects affected / exposed	2 / 31 (6.45%)	2 / 31 (6.45%)	7 / 34 (20.59%)
occurrences (all)	12	3	10
Asthma			
subjects affected / exposed	0 / 31 (0.00%)	4 / 31 (12.90%)	6 / 34 (17.65%)
occurrences (all)	0	7	8
Nasal congestion			
subjects affected / exposed	2 / 31 (6.45%)	4 / 31 (12.90%)	6 / 34 (17.65%)
occurrences (all)	37	15	14
Dyspnoea			
subjects affected / exposed	3 / 31 (9.68%)	5 / 31 (16.13%)	5 / 34 (14.71%)
occurrences (all)	5	5	7
Sneezing			
subjects affected / exposed	3 / 31 (9.68%)	4 / 31 (12.90%)	4 / 34 (11.76%)
occurrences (all)	7	14	11
Pharyngeal paraesthesia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	3 / 34 (8.82%)
occurrences (all)	0	1	5
Rhinitis allergic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Throat tightness			

subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Productive cough			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	4	2	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	3 / 34 (8.82%)
occurrences (all)	1	1	4
Arthropod sting			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Procedural pain			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	1	4	1
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 31 (25.81%)	5 / 31 (16.13%)	14 / 34 (41.18%)
occurrences (all)	19	12	51
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	0	3	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	4
Ear pruritus			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	2
Eye disorders			
Eye pruritus			

subjects affected / exposed	1 / 31 (3.23%)	3 / 31 (9.68%)	6 / 34 (17.65%)
occurrences (all)	1	4	36
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 31 (16.13%)	7 / 31 (22.58%)	16 / 34 (47.06%)
occurrences (all)	43	14	95
Vomiting			
subjects affected / exposed	6 / 31 (19.35%)	9 / 31 (29.03%)	9 / 34 (26.47%)
occurrences (all)	8	21	25
Oral pruritus			
subjects affected / exposed	4 / 31 (12.90%)	3 / 31 (9.68%)	7 / 34 (20.59%)
occurrences (all)	10	9	16
Nausea			
subjects affected / exposed	5 / 31 (16.13%)	5 / 31 (16.13%)	5 / 34 (14.71%)
occurrences (all)	5	9	12
Abdominal pain upper			
subjects affected / exposed	5 / 31 (16.13%)	6 / 31 (19.35%)	4 / 34 (11.76%)
occurrences (all)	28	10	8
Lip pruritus			
subjects affected / exposed	2 / 31 (6.45%)	3 / 31 (9.68%)	4 / 34 (11.76%)
occurrences (all)	4	13	31
Lip swelling			
subjects affected / exposed	3 / 31 (9.68%)	2 / 31 (6.45%)	4 / 34 (11.76%)
occurrences (all)	16	2	24
Paraesthesia oral			
subjects affected / exposed	2 / 31 (6.45%)	2 / 31 (6.45%)	4 / 34 (11.76%)
occurrences (all)	2	3	237
Abdominal discomfort			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	3 / 34 (8.82%)
occurrences (all)	0	5	4
Diarrhoea			
subjects affected / exposed	4 / 31 (12.90%)	4 / 31 (12.90%)	2 / 34 (5.88%)
occurrences (all)	15	9	3
Tongue pruritus			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	3	0	43

Toothache			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Oral discomfort			
subjects affected / exposed	0 / 31 (0.00%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	0	4	1
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	7 / 31 (22.58%)	6 / 31 (19.35%)	9 / 34 (26.47%)
occurrences (all)	34	9	19
Pruritus			
subjects affected / exposed	1 / 31 (3.23%)	7 / 31 (22.58%)	5 / 34 (14.71%)
occurrences (all)	2	8	12
Rash			
subjects affected / exposed	1 / 31 (3.23%)	3 / 31 (9.68%)	5 / 34 (14.71%)
occurrences (all)	1	3	6
Eczema			
subjects affected / exposed	2 / 31 (6.45%)	3 / 31 (9.68%)	3 / 34 (8.82%)
occurrences (all)	4	4	3
Dermatitis atopic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	9
Swelling face			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Erythema			
subjects affected / exposed	1 / 31 (3.23%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	1	7	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences (all)	2	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 31 (16.13%)	5 / 31 (16.13%)	9 / 34 (26.47%)
occurrences (all)	5	7	18

Upper respiratory tract infection			
subjects affected / exposed	3 / 31 (9.68%)	5 / 31 (16.13%)	7 / 34 (20.59%)
occurrences (all)	7	11	17
Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	4 / 34 (11.76%)
occurrences (all)	0	1	4
Viral infection			
subjects affected / exposed	5 / 31 (16.13%)	1 / 31 (3.23%)	4 / 34 (11.76%)
occurrences (all)	7	1	11
Conjunctivitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	3 / 34 (8.82%)
occurrences (all)	0	0	3
Gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	3 / 31 (9.68%)	3 / 34 (8.82%)
occurrences (all)	0	4	5
Influenza			
subjects affected / exposed	1 / 31 (3.23%)	5 / 31 (16.13%)	3 / 34 (8.82%)
occurrences (all)	1	5	3
Rhinitis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	3 / 34 (8.82%)
occurrences (all)	3	1	4
Gastrointestinal viral infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Tonsillitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Gastroenteritis viral			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	0	3	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Ear infection			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	6	1	0

Pharyngitis streptococcal			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	4	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2016	• Text and schematic modified to clarify procedures.
07 February 2017	• Changed the up dosing period duration from 20 to 40 weeks to 22 to 40 weeks for accuracy based on the dosing intervals. • Defined severe adverse events and adverse events associated with epinephrine use as adverse events of clinical interest. • Added: o a 4 week QOD dosing interval before transitioning to BIW dosing. o instructions for adjusting doses and managing missed doses for nondaily dosing regimens. o an allowance for screening procedures to be performed over 3 consecutive days o instructions for reporting an accidental food allergen exposure. o rationale and formula for cohort stopping rules. o that an adjudication committee will be used in the safety monitoring committee. • Text modified to clarify procedures.
12 June 2017	• Changed the interval extension periods for group 1 extended maintenance from 8 to 24 weeks to 8 to 28 weeks. • Added: o instructions for repeat up dosing for group 2 subjects who did not tolerate nondaily dosing. o guidelines for modifying QD dosing for group 1. o guidance for continuation of treatment for subjects with severe symptoms. o requirement to counsel and provide contraception information to postmenarchal subjects. o both parents must sign the informed consent form when required. o study product shipment and dispensation information. o subjects should not administer AR101 on the day of the DBPCFC. o end of study definition. • Text modified to clarify procedures.
05 March 2018	• Text modified to clarify procedures.
12 April 2018	• Added a maximum 26 week requirement for completion of repeat up dosing. • Text modified to clarify procedures and correct discrepancies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported