1393

PALISADE Follow-On Study (ARC004): Longer-Term Outcomes With AR101 Oral Immunotherapy for Peanut Allergy

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INTRODUCTION

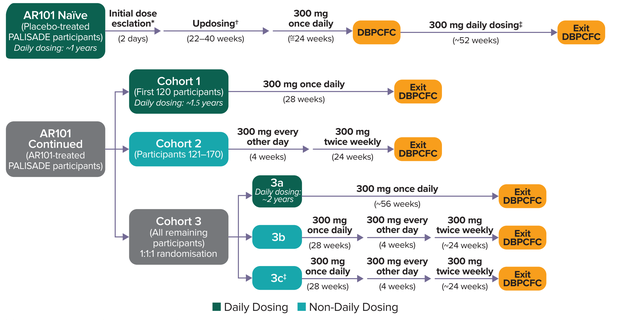
- AR101 is an oral biologic drug with a characterised peanut-protein profile for immunotherapy administration in individuals with peanut allergy (PA)[1]
- AR101 was recently approved in the United States to mitigate allergic reactions that may occur with accidental exposure to peanuts in individuals aged 4–17 years with a confirmed diagnosis of PA[1]
- The safety and efficacy of AR101 were demonstrated in the international phase 3 PALISADE trial in 551 children and adults with PA (randomised 3:1 to AR101:placebo)[2]
- ARC004 was an open-label follow-on study to PALISADE designed to explore the long-term safety, tolerability, and efficacy of AR101 as well as daily versus non-daily dosing regimens
  - The PALISADE study followed participants for ~1 year of treatment; ARC004 followed participants for ~2 years of treatment, at which time they were eligible to continue treatment in a longer-term safety study (ARC008)

METHODS

Trial Design and Participants

- Outcomes reported here are for participants aged 4–17 years enrolled in ARC004
  - Participants who received placebo in PALISADE (AR101 Naïve) crossed over to active treatment with AR101 (**Figure 1**)
  - Eligible participants who received AR101 in PALISADE (AR101 Continued) were assigned to either daily or non-daily continued treatment regimens of different durations (**Figure 1**)
- All AR101 Naïve participants remained on the once-daily dosing regimen for ~1 year; AR101 Continued participants in cohorts 3b and 3c remained on the twice-weekly regimen and had similar length of treatment: 300 mg/day AR101 for 28 weeks, 300 mg every other day for 4 weeks, and 300 mg twice weekly for ≥24 weeks

Figure 1. ARC004 Study Design



All treatments were administered as tolerated.
*Day 1, 0.5 to 3 mg or 6 mg AR101 as tolerated; day 2, confirmation of ability to tolerate 3 mg AR101. †From 3 mg to 300 mg once daily, with dose escalation every 2 weeks. ‡Administration of daily or non-daily dosing regimens was contingent on results; planned regimens were every other day, twice weekly, once weekly, or every other week. Regimens longer than twice weekly were not instituted due to small cohort size. DBPCFC, double-blind, placebo-controlled food challenge.

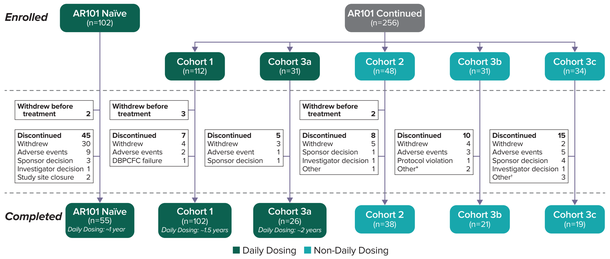
- All ARC004 participants who completed their dose regimen were administered exit double-blind, placebo-controlled food challenges (DBPCFCs) to a maximum single dose of 2000 mg peanut protein (4043 mg cumulative)
- Data were summarised using descriptive statistics and included:
  - Safety: serious and nonserious adverse events (AEs)
  - Efficacy: ability to tolerate 300, 600, 1000, and 2000 mg peanut protein with no more than mild symptoms at exit DBPCFC
  - Immunologic changes: mean wheal diameter on peanut skin prick test (SPT), peanut-specific serum immunoglobulin E (psIgE) and immunoglobulin G4 (psIgG4) concentrations, and psIgE/psIgG4 ratio

RESULTS

Study Population

- Of 409 participants completing the PALISADE study, 358 (87.5%) enrolled in ARC004
  - Of these, 7 withdrew consent before receiving treatment; the remaining 351 participants comprised the safety population (**Figure 2**)
  - 261 (74.4%) of treated participants completed the study: 55.0% of AR101 Naïve and 82.1% of AR101 Continued participants (**Figure 2**)
- Baseline characteristics were similar across all treatment groups (**Table 1**)

Figure 2. ARC004 Participant Disposition



*Reasons included exit DBPCFC failure and reverted to once-daily dosing for 1 participant and recurrent adverse events for 1 participant. †Reasons included anxiety related to dosing, no longer interested in participating in study, and study termination for 1 participant each. DBPCFC, double-blind, placebo-controlled food challenge.

Table 1. Baseline Characteristics (Safety Population, N=351)

	Daily Dosing			Non-Daily Dosing		
	AR101-Naïve (n=100) ~52 Weeks†	AR101 Continued Cohort 1 (n=109) ~28 Weeks	AR101 Continued Cohort 3a (n=31) ~56 Weeks	AR101 Continued Cohort 2 (n=46) ~28 Weeks	AR101 Continued Cohort 3b (n=31) ~56 Weeks	AR101 Continued Cohort 3c (n=34) ~56 Weeks
Median age, y (range)*	9.5 (5–17)	11 (5–17)	9 (5–17)	10 (4–17)	9 (5–16)	9 (5–16)
Sex, male, n (%)	65 (65.0)	57 (52.3)	17 (54.8)	25 (54.3)	19 (61.3)	18 (52.9)
Immunoglobulin and SPT results, median (IQR)						
Total IgE, IU/mL†	n=100 484.5 (258–1127)	n=105 355 (169–725)	n=30 377.5 (129–746)	n=46 575 (212–989)	n=31 542 (220–810)	n=34 389 (174–858)
psIgE, kU_A/L†	n=100 108.3 (32.9–277.8)	n=109 63.4 (20.1–172)	n=31 42.7 (4.1–207)	n=46 39.8 (6.5–100)	n=31 77.8 (12.3–213.5)	n=34 83.1 (36.6–169)
psIgG4, mg_A/L†	n=100 0.5 (0.3–1.4)	n=101 0.5 (0.2–1.1)	n=31 0.5 (0.3–0.8)	n=44 0.7 (0.3–1.5)	n=31 0.5 (0.2–1.5)	n=34 0.4 (0.2–1.2)
psIgE/IgG4 ratio†	n=100 187.5 (44.6–401.9)	n=101 137.8 (35.4–339.5)	n=31 137.5 (16.6–496.7)	n=44 64.0 (18.4–156.4)	n=31 111.1 (37.9–334)	n=34 175.8 (54.6–316.7)
SPT MWD, mm†	n=99 10.5 (8.5–13.5)	n=109 11.5 (9–15)	n=31 10 (8–15)	n=46 10.5 (8.5–15)	n=31 10.5 (8.5–13.5)	n=33 10.5 (9–13)
Peanut protein MTD at study entry, n (%)						
1 mg	8 (8.0)	0	0	0	0	0
3 mg	17 (17.0)	0	0	0	0	0
10 mg	27 (27.0)	0	0	0	0	0
30 mg	20 (20.0)	0	1 (3.2)	0	0	0
100 mg	21 (21.0)	0	0	1 (2.2)	1 (3.2)	0
300 mg	3 (3.0)	16 (14.7)	1 (3.2)	7 (15.2)	4 (12.9)	2 (5.9)
600 mg	2 (2.0)	25 (22.9)	10 (32.3)	10 (21.7)	4 (12.9)	7 (20.6)
1000 mg	2 (2.0)	68 (62.4)	19 (61.3)	28 (60.9)	22 (71.0)	25 (73.5)

*Calculated relative to the date of informed consent in ARC004. †Baseline values are relative to the start of ARC004, except for AR101 Continued participants (start of PALISADE). DBPCFC, double-blind, placebo-controlled food challenge; Ig, immunoglobulin; IQR, interquartile range; MTD, maximum tolerated dose; MWD, mean wheal diameter; ps, peanut-specific; SPT, skin prick test.

Safety

- Most participants experienced ≥1 AE, most of which were mild to moderate in maximum severity (**Table 2**)
  - The overall rate of AE-related discontinuations was low, with slightly higher rates seen in the longer-term non-daily dosing groups
- The incidence of systemic allergic reactions ranged from 6.4–16.1% in participants receiving daily dosing and from 0–29.4% in the non-daily dosing cohorts (**Table 2**)
  - Adrenaline use ranged from 6.4–12.9% in those receiving daily dosing and from 0–14.7% in participants receiving non-daily dosing
- Exposure-adjusted AE rates per participant–years at risk were lower in daily dosing groups than in the non-daily dosing groups (**Table 2**)
  - Within the daily dosing groups, exposure-adjusted total treatment-related AEs per participant–years improved with duration of therapy

Table 2. Summary of Treatment-Emergent AEs During Daily and Non-Daily Dosing in ARC004

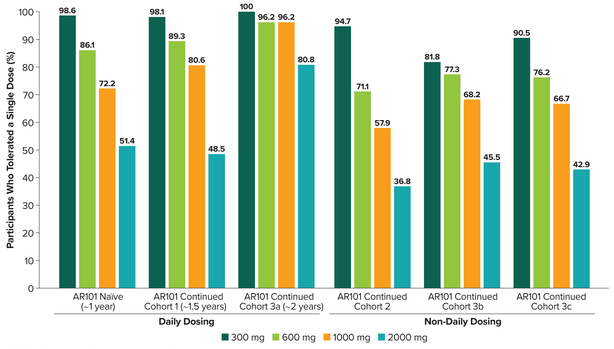
	Daily Dosing			Non-Daily Dosing*		
	AR101-Naïve (n=100) ~52 Weeks	AR101 Continued Cohort 1 (n=109) ~28 Weeks	AR101 Continued Cohort 3a (n=31) ~56 Weeks	AR101 Continued Cohort 2 (n=46) ~28 Weeks	AR101 Continued Cohort 3b (n=31) ~56 Weeks	AR101 Continued Cohort 3c (n=34) ~56 Weeks
≥1 AE, n (%)	76 (89.4)	90 (82.6)	27 (87.1)	36 (78.3)	28 (90.3)	33 (97.1)
AEs by grade						
Grade 1 (mild)	45 (52.9)	58 (53.2)	15 (48.4)	22 (47.8)	13 (41.9)	12 (35.3)
Grade 2 (moderate)	30 (35.3)	29 (26.6)	12 (38.7)	14 (30.4)	15 (48.4)	18 (52.9)
Grade 3 (severe)	1 (1.2)	3 (2.8)	0	0	0	3 (8.8)
Treatment-related AEs, n (%)	43 (50.6)	47 (43.1)	15 (48.4)	25 (54.3)	14 (45.2)	24 (70.6)
Serious AEs,† n (%)	0	1 (0.9)	0	0	1 (3.2)	1 (2.9)
AEs leading to discontinuation, n (%)	2 (2.4)	3 (2.8)	1 (3.2)	0	2 (6.5)	1 (2.9)
Systemic allergic reactions	11 (12.9)	7 (6.4)	5 (16.1)	0	2 (6.5)	10 (29.4)
Adrenaline use	8 (9.4)	7 (6.4)	4 (12.9)	0	2 (6.5)	5 (14.7)
Total exposure, participant-years	85.5	73.7	31.5	26.0	30.1	42.5
Total number of AEs (exposure-adjusted)‡	1551 (18.1)	954 (12.9)	553 (17.5)	537 (20.7)	417 (30.0)	1279 (42.5)
Total treatment-related AEs (exposure-adjusted)‡	1040 (12.2)	416 (5.6)	147 (4.7)	348 (13.4)	102 (3.4)	875 (20.6)

*Participants in cohorts 3b and 3c underwent initial once-daily dosing for 28 weeks. †None treatment-related. ‡Exposure-adjusted event rates were defined as the total number of events divided by the total number of participant–years at risk during the period. AE, adverse event.

Efficacy

- Desensitisation rates were higher in the daily dosing vs non-daily dosing cohorts (**Figure 3**)
- Within the daily dosing groups, desensitisation rates improved with duration of therapy

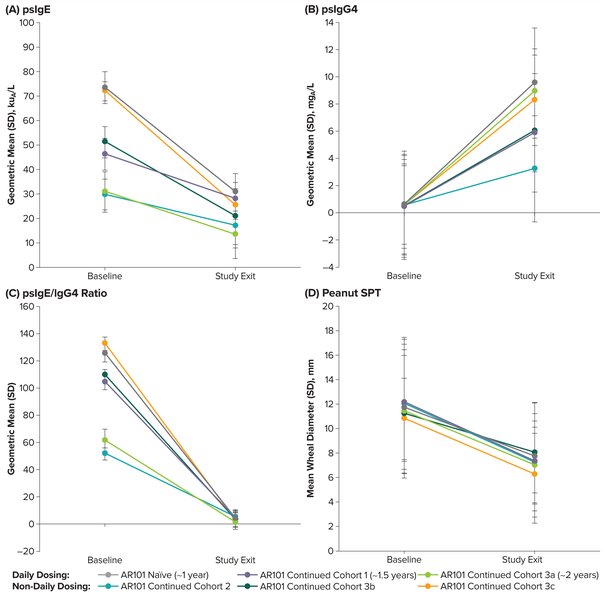
Figure 3. Desensitisation Response Rates at Exit DBPCFC (Completer Population)



DBPCFC, double-blind, placebo-controlled food challenge.

- Change from baseline in psIgE, psIgG4, and SPT mean wheal diameter were consistent with ongoing immunomodulation during extended dosing with AR101 (**Figure 4**)
- Longer duration of daily dosing was consistent with greater change from baseline in immune biomarkers

Figure 4. Change From Baseline to Study Exit in (A) psIgE, (B) psIgG4, (C) psIgE/IgG4 Ratio, and (D) Peanut SPT



Note: Baseline was defined as the last available measurement before the first dose of study product on day 1 of ARC004 for participants in the AR101-Naïve group and day 1 of PALISADE for participants in the AR101-Continued group. Ig, immunoglobulin; ps, peanut-specific; SD, standard deviation; SPT, skin prick test.

SUMMARY & CONCLUSIONS

- Long-term daily dosing with AR101 showed an improved safety and efficacy profile compared with shorter treatment durations
  - After ~2 years daily treatment with AR101 (PALISADE and ARC004 combined), 80% of participants who completed ARC004 showed desensitisation to 2000 mg peanut protein (4043 cumulative; equivalent to ~14 peanut kernels)
  - Changes in immunologic measures suggest ongoing immunomodulation during the first 2 years of treatment with AR101
  - Further modulation of immunologic measures and improvement in clinical parameters is anticipated with subsequent years of treatment with AR101
- The long-term safety and efficacy of peanut oral immunotherapy with AR101 were shown in the ARC004 study
- The overall benefit-risk profile of long-term AR101 daily dosing was better than that of less frequent (non-daily) dosing

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