At-Home Dosing Adherence During Characterized Oral Desensitization Immunotherapy for Peanut Allergy

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ABSTRACT #803

- **Rationale:** AR101, a pharmaceutical-grade peanut protein formulation, was studied in a Phase 2, double-blind, placebo (PBO)-controlled trial in subjects aged 4 to 21 years. We now report results on at-home dosing adherence
- **Methods:** Subjects took their daily dose at home by mixing the capsules' content in non-allergenic food, and consuming the entire serving. Subjects documented doses taken at home using diary logs and returned unused capsules to the clinic at every visit. At-home adherence, defined as full, partial (at least half the dose was taken), and missed home doses, was expressed as a percentage of planned at-home doses
- **Results:** 55 subjects (AR101, n=29; PBO, n=26) received at least 1 dose of randomized study treatment. The number of days of planned at-home doses was 139.8 (standard deviation [SD]: 38.63) for the overall group. The percentage of days (% [SD]) with any at-home dose (either a full or partial dose) was similar for AR101 and PBO groups (94.7 [6.80] vs 96.9 [3.37], respectively), as was the percentage of days with full doses (93.6 [6.86] for AR101 and 96.7 [3.41] for PBO; 95.1 [5.68] overall). The percentage of days (% [SD]) with partial doses was higher for AR101 than PBO (1.1 [1.94] vs 0.2 [0.50], respectively) as was the mean percentage of days (% [SD]) with missed doses (4.7 [6.84] for AR101 and 2.4 [2.84] for PBO)
- **Conclusions:** Overall adherence in the combined analysis of AR101 and PBO was 95%

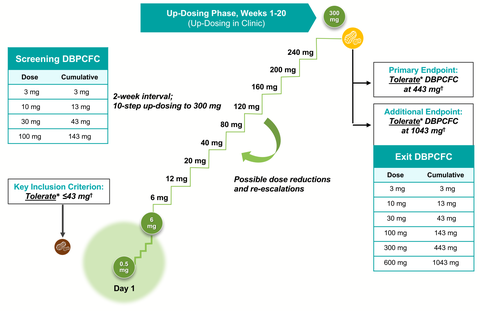
BACKGROUND

- Currently, there is no FDA-approved therapy for peanut allergy
  - Prevalence is increasing, affecting >5 million individuals in the United States and Europe today[1]
  - Reactions to the allergen can be severe and include potentially fatal anaphylaxis[2]
  - Peanut allergies tend to be lifelong, with only approximately 20% of those afflicted outgrowing the allergy[2]
- AR101 is an investigational, characterized, oral biologic drug product with the protein profile found in peanuts being studied for peanut allergy desensitization
- In a previously reported double-blind, PBO-controlled Phase 2 study (ARC001)[3]
  - AR101 or PBO was administered daily using the Characterized Oral Desensitization Immunotherapy (CODIT™) approach
  - 95% of active-treated patients experienced a hypersensitivity reaction; >90% were mild reactions and the rest were moderate
  - After 2 weeks of maintenance dose, 79% of subjects were desensitized to 443 mg peanut protein on an intention-to-treat basis and 100% of subjects on a completer basis
- In any oral immunotherapy (OIT) protocol, most of the doses are taken at home, without direct physician supervision
- Adherence to therapy is important, not only for efficacy, but also for patient safety

METHODS

- In ARC001, the oral dosing of AR101 or PBO was given daily **(Figure 1)**
  - Subjects were up-dosed every 2 weeks (in-clinic dosing), and the rest of the doses were taken at home (at-home dosing)
  - Subjects were called 1 week after each dose escalation visit to assess for dosing adherence and dose reactions
  - Daily diaries were used by subjects to document doses taken, reasons for missed or partial doses, and any dose related symptoms during the up-dosing phase to assess at-home adherence
- Subjects were given at-home, dosing instructions to take their daily dose by mixing the capsules' content in non-allergenic food and consuming the entire serving
- Subjects were educated on potential reactions (eg, skin, respiratory, and/or gastrointestinal [GI]) and symptoms were recorded per subject assessment
- If adverse events (AEs) occurred, investigators could withhold doses, down-dose, split doses in half for twice-daily dosing, stay longer at the same dose, or discontinue the study early
- Appropriate treatment for AEs was dependent on the type and the severity of symptoms (eg, mild, moderate, or severe)
- Protocol-defined dosing modifications and stopping rules included:
  - Considering missed doses to be a safety issue that could warrant study discontinuation
  - Halting up-dosing and re-starting with a reduced dose if >3 days of dosing were missed
  - Halting further up-dosing attempts and maintaining at the previously achieved level if ≥2 doses of epinephrine were given or if there was failure to accomplish up-dosing after 3 attempts
  - Removal from the study if ≥7 days of missed dosing occurred, or if there was a significant number of episodes of missed dosing (ie, ≥3 days on at least 3 occasions)

Figure 1. ARC001 Study Design



DBPCFC, double blind PBO-controlled food challenge.
*"Tolerate" is defined as dose being tolerated with no dose-limiting symptoms.
†Reflects cumulative dose in the DBPCFC.

RESULTS

- 55 subjects (65% male; median age 8.8 years, range 4 to 26 years) were randomly assigned to receive AR101 (n=29) or PBO (n=26)
- The median time to completion of the study was 22 weeks for both groups[3]

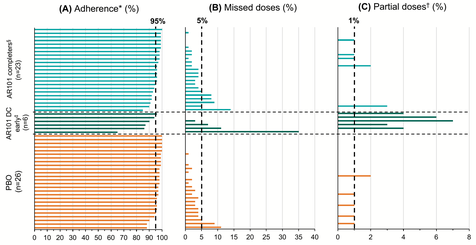
Table 1. Summary of At-Home Dosing Adherence and Symptoms

Type of Dose	AR101 (n=29)	PBO (n=26)
Days with planned at-home dosing,* mean (SD)	134.3 (51.4)	146.0 (13.7)
% Days with any at-home dose,† mean (SD)	94.7 (6.8)	96.9 (3.4)
% Days with full doses, mean (SD)	93.6 (6.9)	96.7 (3.4)
% Days with partial doses, mean (SD)	1.1 (1.9)	0.2 (0.5)
% Days with missed doses, mean (SD)	4.7 (6.8)	2.4 (2.8)
% Days with dosing symptoms, mean (SD)	9.8 (11.4)	2.5 (5.6)

*Defined as days on study minus days of in-clinic dosing.
†Defined as either a full or partial dose.

- Overall adherence, or full doses consumed at-home, was 95% **(Table 1)**
- Mean percentage of days with missed or partial doses was higher in the AR101 group compared with the PBO group **(Table 1)**

Figure 2. Adherence, Missed Doses, and Partial Doses for Individual Subjects



DC, discontinued.
*Defined as the percentage of at-home planned doses that were fully consumed.
†Defined as the percentage of at-home planned doses in which at least half a dose was consumed.
‡Subjects who discontinued treatment prior to completion of up-dosing.
§Subjects who successfully completed up-dosing and underwent an exit DBPCFC.

- 6 AR101-treated subjects (21%) discontinued early due to recurrent GI AEs or a combination of GI AEs and adherence issues; all symptoms resolved within 1-3 weeks of discontinuation of AR101[3]
- In the 6 subjects who discontinued early, the number of missed and partial doses was higher compared with AR101 completers (n=23) and the PBO group (n=26) where no subjects discontinued early **(Figure 2)**
- The highest achieved doses for the 6 subjects who discontinued early were: 6 mg for 1 subject, 12 mg for 2 subjects, and 80 mg for 3 subjects

Table 2. Reasons for At-Home Missed and Partial Doses

	AR101	PBO
Missed doses, n	**144**	**91**
Medical†, n	41*	12
Non-medical‡, n	99	71
Unknown§, n	4	8
Partial doses, n	**28**	**8**
Medical†, n	15	5
Non-medical‡, n	13	3
Unknown§, n	0	0

*Includes 1 instance of "broken elbow" per subject notation.
†Examples per subject notation: physician instructions, stomach virus, vomiting, nausea, asthma exacerbation, diarrhea.
‡Examples per subject notation: forgot, traveling, home too late, spillage.
§Examples per description: dosed missed but reason left blank or inability to confirm dose given or missed.

- The majority of missed doses in AR101-treated (69% [99/144]) and PBO subjects (78% [71/91]) occurred for non-medical reasons **(Table 2)**
- The percentage of missed doses due to any medical reason was higher in the AR101-treated subjects (28% [41/144]) compared with the PBO subjects (13% [12/91]) **(Table 2)**
- A total of 28 partial doses were consumed by subjects for AR101, and 8 partial doses given were consumed by PBO subjects **(Table 2)**

Figure 3. Percentage of At-Home Missed Doses for Each Treatment Level

- The percentage of missed doses was higher in AR101-treated subjects compared with PBO subjects across all treatment dose levels **(Figure 3)**
- The number of missed doses did not appear to be associated with dose levels for AR101-treated subjects or PBO subjects **(Figure 3)**

CONCLUSIONS

- Limitations to this analysis were
  - Small number of subjects
  - All the data presented in this poster were collected exclusively from the subjects' daily diaries; therefore, subject reporting bias cannot be ruled out
- In ARC001, which lasted 22 weeks, the overall at-home dosing adherence for AR101 and PBO was 95%
- The majority of missed doses were due to non-medical reasons (eg, forgetting, schedule conflicts)
- Subjects appeared to be highly motivated, and were compliant with their physician's instructions, such as skipping a dose or taking a partial dose when needed
- Adherence with at-home dosing of AR101 is being further investigated in ARC002, an extension-phase study of ARC001, and will also be investigated in all future and ongoing Phase 3 studies[4,5]

REFERENCES

1. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133(2):291-307.
2. Sampson HA. Food allergy – accurately identifying clinical reactivity. *Allergy*. 2005;60(Suppl 79):19-24.
3. Bird JA, Spergel JM, Jones SM, et al. A novel characterized peanut allergen formulation (AR101) for oral immunotherapy (OIT) induces desensitization in peanut-allergic subjects: a Phase 2 clinical safety and efficacy study. Presented at: EAACI 2015; June 6, 2015; Barcelona, Spain. Abstract 104805.
4. Bird JA, Spergel JM, Jones SM, et al. The efficacy of AR101, a peanut-derived pharmaceutical for oral immunotherapy (OIT), is maintained and tolerability is increased with low-dose maintenance therapy. Presented at: AAAAI 2016; March 6, 2016; Los Angeles, CA. Abstract L60.
5. ClinicalTrials.gov. NCT02635776. www.clinicaltrials.gov. Accessed January 20, 2017.

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