A Phase I Study of Subcutaneous Administration of ARO-RAGE

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Background & Methods

Background

The receptor for advanced glycation end-products (RAGE) is a pulmonary epithelial pattern recognition receptor implicated as an upstream mediator of Type-2 and non-Type-2 inflammatory pathways contributing to asthma.[1,2,3]

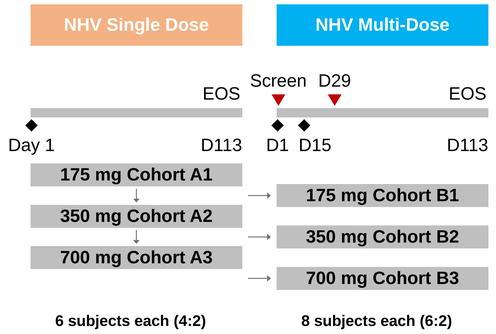
ARO-RAGE is an RNAi-based, lung-targeted therapeutic designed to silence *AGER* mRNA within pulmonary epithelial cells, thereby decreasing RAGE expression.

Inhalational administration of ARO-RAGE resulted in pulmonary silencing of RAGE expression in healthy subjects and patients with asthma.[4] This study is designed to assess the effects of subcutaneous (SC) administration of ARO-RAGE.

Study Design

ARORAGE-1002 is a randomized, double-blind, placebo-controlled phase 1 study, designed to assess the safety, PK, and pharmacodynamic effects of SC administered ARO-RAGE in healthy subjects. Subjects received ascending doses of ARO-RAGE or placebo (normal saline) via SC injection on Day 1 (SAD) or Days 1 and 15 (MAD).

- Primary Endpoint: TEAE incidence
- Other Endpoints: PK, BALF and serum sRAGE



Key Inclusion/ Exclusion Criteria

Age 18-55 years
Nonsmoker
No lung infection or disease
ppFEV$_1$ >80%

Abbreviations

AGER=gene encoding RAGE, BALF=bronchoalveolar lavage fluid, EOS=end-of-study; LLOQ=lower limit of quantification; MAD=multiple ascending dose, NHV=normal healthy volunteer, PBO=placebo, PK=pharmacokinetics, ppFEV$_1$=percent-predicted FEV$_1$, RNAi=RNA interference; SAD=single ascending dose, SC=subcutaneous; sRAGE=soluble RAGE, TEAE=treatment-emergent adverse event

References

1. Perkins TN. *Allergy* 2021;76:1350-66. 2. Oczypok EA. *JACI* 2015;136:747-56. 3. Killian KN. *Front Immunol* 2023;14:1039997. 4. O'Carroll MR. *AJRCCM* 2024;209:A1376.

Disclosures
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J. Hamilton, J. Huetsch, L. Moser, S. Alagarsamy, and A. Ta are employees of Arrowhead Pharmaceuticals.

Results

Baseline Characteristics

Characteristic	SAD		MAD	
	PBO (N=6)	ARO-RAGE (N=12)	PBO (N=6)	ARO-RAGE (N=19)
Age – yr ± SD	32.8 ± 12.5	38.8 ± 9.8	27.8 ± 9.4	28.8 ± 8.8
Male – no. (%)	5 (83.3)	6 (50.0)	5 (83.3)	9 (47.4)
BMI – kg/m^2 ± SD	26.3 ± 3.5	24.6 ± 2.7	25.4 ± 4.3	26.4 ± 4.5
Serum sRAGE – pg/ml ± SD	1069 ± 162	970 ± 314	1303 ± 617	1015 ± 379
BALF sRAGE – pg/ml ± SD	---	---	1581 ± 511	2482 ± 2195

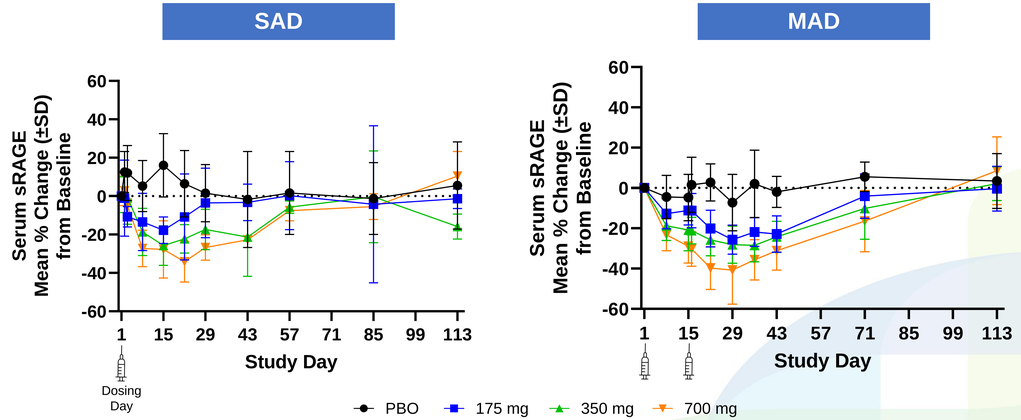
Summary of TEAEs

Event	SAD		MAD	
	PBO (N=6) n (%)	ARO-RAGE (N=12) n (%)	PBO (N=6) n (%)	ARO-RAGE (N=19) n (%)
≥1 TEAE	3 (50.0)	10 (83.3)	3 (50.0)	17 (89.5)
Mild	3 (50.0)	9 (75.0)	3 (50.0)	14 (73.7)
Moderate	0 (0)	1 (8.3)	0 (0)	3 (15.8)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
≥1 Serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)
≥1 TEAE leading to trial withdrawal or study drug discontinuation	0 (0)	0 (0)	0 (0)	0 (0)

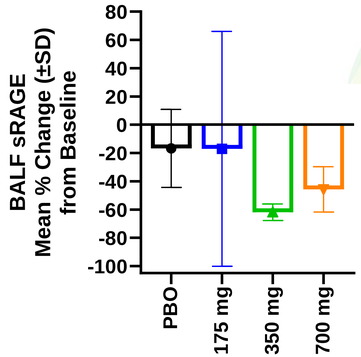
ARO-RAGE SC Demonstrated Favorable Safety Profile

- ARO-RAGE has not demonstrated any pattern of detrimental effect on FEV$_1$, FVC, or DLCO over time
- ARO-RAGE has not demonstrated any pattern of effect on systemic safety labs

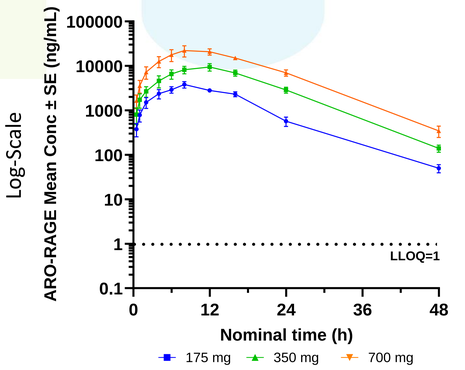
ARO-RAGE SC Resulted in Dose-Responsive Reductions in Serum sRAGE



Two Doses of ARO-RAGE SC Reduced BALF sRAGE



Dose-Dependent Plasma Exposure After Single Dose ARO-RAGE SC



Conclusions

- ARO-RAGE SC was well-tolerated, with subjects experiencing primarily mild TEAEs
- Systemic exposure to ARO-RAGE was dose-dependent, resulting in peak plasma concentration at median T$_{max}$ 8-12 hours, followed by rapid clearance
- ARO-RAGE SC reduced serum and BALF sRAGE, consistent with pulmonary target engagement