A First-in-Human Study of ARO-RAGE, a Novel Inhaled RNA-Interference Therapy for Asthma

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Background & Methods

Background

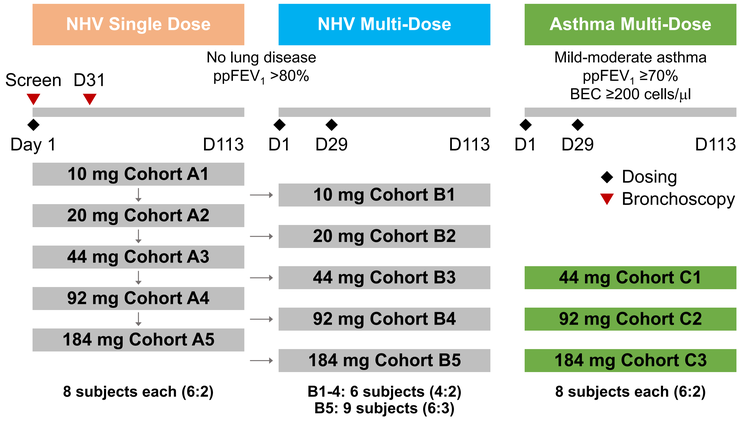
The receptor for advanced glycation end-products (RAGE) is a pulmonary epithelial pattern recognition receptor, which is implicated as an upstream mediator of Type-2 and non-Type-2 inflammatory cascades in asthma.[1,2,3]

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

Study Design

ARORAGE-1001 is an ongoing, randomized, double-blind, placebo-controlled, phase 1/2a study, designed to assess the safety, tolerability, PK, and pharmaco-dynamic effects of ARO-RAGE. Subjects received ascending doses of ARO-RAGE (active) or normal saline (PBO) via nebulizer on Day 1 (SAD) or Days 1 and 29 (MAD).

- Primary Endpoint: TEAE incidence
- Secondary & Exploratory Endpoints: PK; BALF and serum sRAGE



Abbreviations

AGER=gene encoding RAGE, BALF=bronchoalveolar lavage fluid, BEC=blood eosinophil count, MAD=multiple ascending dose, NHV=normal healthy volunteer, PBO=placebo, PK=pharmacokinetics, $ppFEV_1$=percent-predicted FEV_1, preBD=prebronchodilator, RNAi=RNA interference; SAD=single ascending dose, 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.

Disclosures
This research has been funded by Arrowhead Pharmaceuticals.
M. O'Carroll and M. Salathe have received consultation fees from Arrowhead Pharmaceuticals.
J. Huetsch, J. Hamilton, A. Ta, L. Moser, and S. Alagarsamy are employees of Arrowhead Pharmaceuticals.

Results

Baseline Characteristics

Characteristic	Healthy Volunteer (N=73)*	Asthma (N=25)*
Age – yr ± SD	34.7 ± 9.5	36.0 ± 11.2
Male – no. (%)	21 (28.8)	8 (32.0)
PreBD $ppFEV_1$ - %	96.3 ± 10.7	92.5 ± 10.9
BEC – cells/µl	139 ± 95	278 ± 190
Serum sRAGE – pg/ml	1139 ± 502	1106 ± 373
BALF sRAGE – pg/ml	2301 ± 1627	---

Blinded Summary of TEAEs

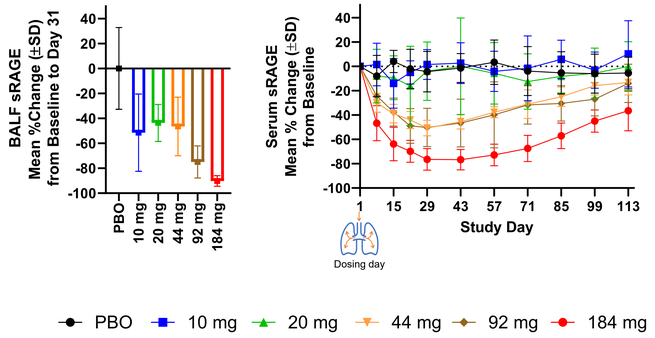
Event	NHV SAD Cohorts (N=40)* n (%)	NHV MAD Cohorts (N=33)* n (%)	Asthma Cohorts (N=25)* n (%)
≥1 TEAE	32 (80.0)	23 (69.7)	21 (84.0)
≥1 Serious TEAE	0 (0)	1 (3.0)#	0 (0)
≥1 TEAE leading to trial withdrawal or study drug discontinuation	0 (0)	0 (0)	0 (0)

*Pooled population (ARO-RAGE & PBO) in ongoing, blinded study.
#Not related to study treatment per investigator.

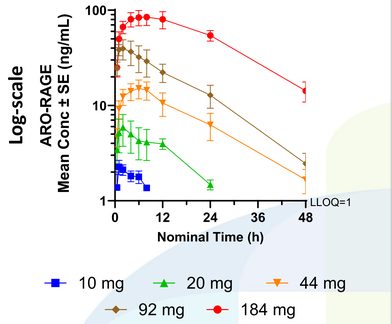
ARO-RAGE Has Demonstrated a Favorable Safety Profile

- 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

Single Dose of ARO-RAGE Reduced BALF and Serum sRAGE in NHVs

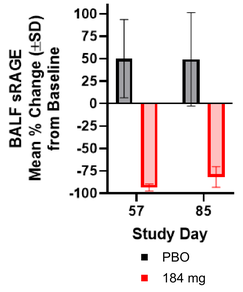


ARO-RAGE Plasma Exposure Following Single ARO-RAGE Dose

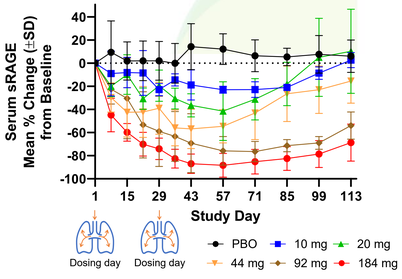


Multiple Doses of ARO-RAGE Reduced BALF & Serum sRAGE in NHVs and Asthma Patients

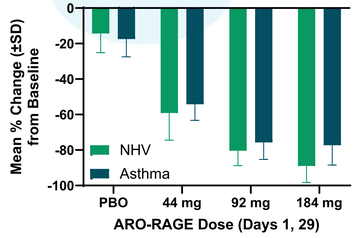
BALF sRAGE Following 2 Doses of ARO-RAGE in NHVs



Serum sRAGE Following 2 Doses of ARO-RAGE in NHVs



Mean Maximum Serum sRAGE Reduction Following 2 Doses of ARO-RAGE



Data cut 05 Apr 2024 from an ongoing study.

Conclusions

- ARO-RAGE has been well-tolerated to date, without any serious adverse effects related to study drug
- Systemic exposure to inhaled ARO-RAGE is of limited quantity and duration
- ARO-RAGE reduced sRAGE in BALF and serum in a dose-responsive manner, with similar reductions in NHVs and asthma patients