A First-in-Human Study of ARO-RAGE, an RNAi Therapy Designed to Silence Pulmonary RAGE Expression

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Background & Methods

Background

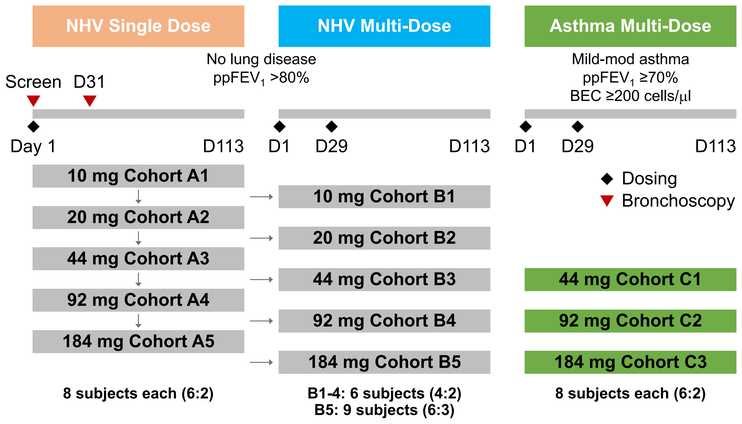
The receptor for advanced glycation end-products (RAGE) is a pulmonary epithelial pattern recognition receptor, which is implicated as an upstream mediator of Type-2 and non-Type-2 inflammatory cascades in asthma.[1,2,3]

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, and pharmaco-dynamic effects of ARO-RAGE.

- Primary Endpoint: TEAE incidence
- Exploratory: BALF and serum soluble RAGE (sRAGE) as target engagement biomarkers



AGER=gene encoding RAGE, BALF=bronchoalveolar lavage fluid, BEC=blood eosinophil count, MAD=multiple ascending dose, NHV=normal healthy volunteer, PBO=placebo, SAD=single ascending dose, TEAE=treatment-emergent adverse event

Exposures

Active treatment	**Placebo**
ARO-RAGE, ascending doses on Day 1 (SAD) or Days 1 and 29 (MAD)	Normal saline

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.

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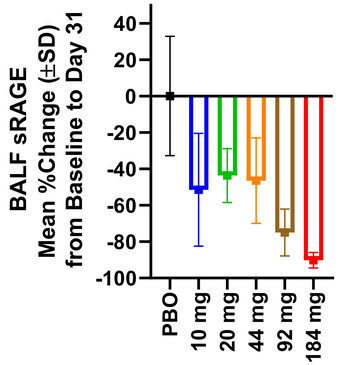
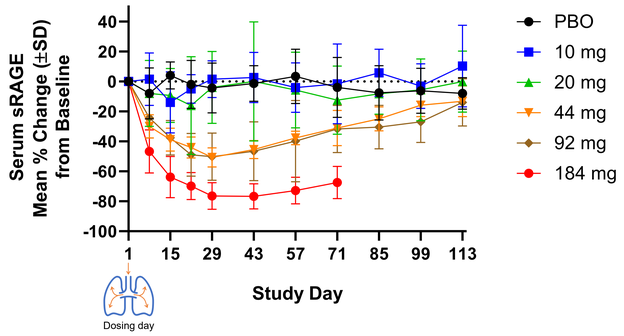
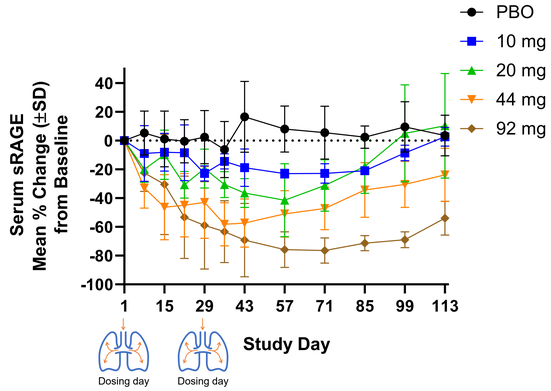
Results

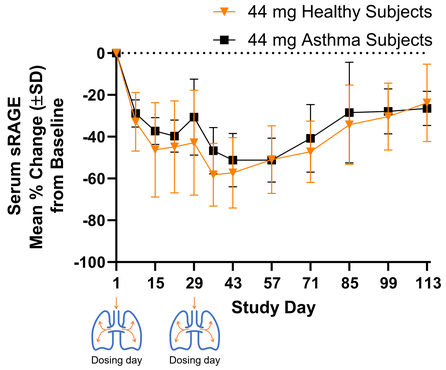
Single Dose of ARO-RAGE Reduced BALF and Serum sRAGE in Healthy Subjects





Multiple Doses of ARO-RAGE Reduced Serum sRAGE in Healthy and Asthma Subjects





Data cut 21 July 2023 from an ongoing study.

Baseline Characteristics

Characteristic	Healthy Volunteer (N=73)*	Asthma (N=9)*
Age – yr	34.7 ± 9.5	37.7 ± 11.9
Male – no. (%)	21 (28.8)	3 (33.3)
PreBD ppFEV$_1$ - %	96.3 ± 10.7	93.4 ± 10.1
BEC – cells/µl	---	256 ± 113
Serum sRAGE – pg/ml	1167 ± 533	1280 ± 430
BALF sRAGE – pg/ml	2487 ± 1716	---

BEC=blood eosinophil count, preBD=prebronchodilator, sRAGE=soluble RAGE

Blinded Summary of TEAEs

Event	NHV SAD Cohorts (N=40)* n (%)	NHV MAD Cohorts (N=33)* n (%)	Asthma Cohorts (N=9)* n (%)
≥1 TEAE	29 (72.5)	20 (60.6)	8 (88.9)
≥1 Serious TEAE	0 (0)	0 (0)	0 (0)
≥1 TEAE leading to trial withdrawal or study drug discontinuation	0 (0)	0 (0)	0 (0)
Most common TEAEs			
Headache	10 (25.0)	4 (12.1)	3 (33.3)
URTI	6 (15.0)	5 (15.2)	2 (22.2)
COVID-19	5 (12.5)	6 (18.2)	0 (0)
Oropharyngeal pain	3 (7.5)	6 (18.2)	0 (0)

URTI=upper respiratory tract infection
*Pooled population (ARO-RAGE & PBO) in ongoing, blinded study.

Conclusions

- ARO-RAGE has been well-tolerated to date
- ARO-RAGE reduced sRAGE concentration in BALF and serum in a dose-dependent manner
- Reduction of serum sRAGE was similar in healthy and asthma subjects at the 44 mg dose level

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