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

Mark O'Carroll[1], John Huetsch[2], James Hamilton[2], Lindsey Moser[2], Sudar Alagarsamy[2], Matthias Salathe[3]

[1]Auckland City Hospital, Auckland, New Zealand

[2]Arrowhead Pharmaceuticals, Pasadena, USA

[3]University of Kansas Medical Center, Kansas City, USA

Conflict of interest disclosure

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RAGE Regulates Airway Inflammation in Asthma

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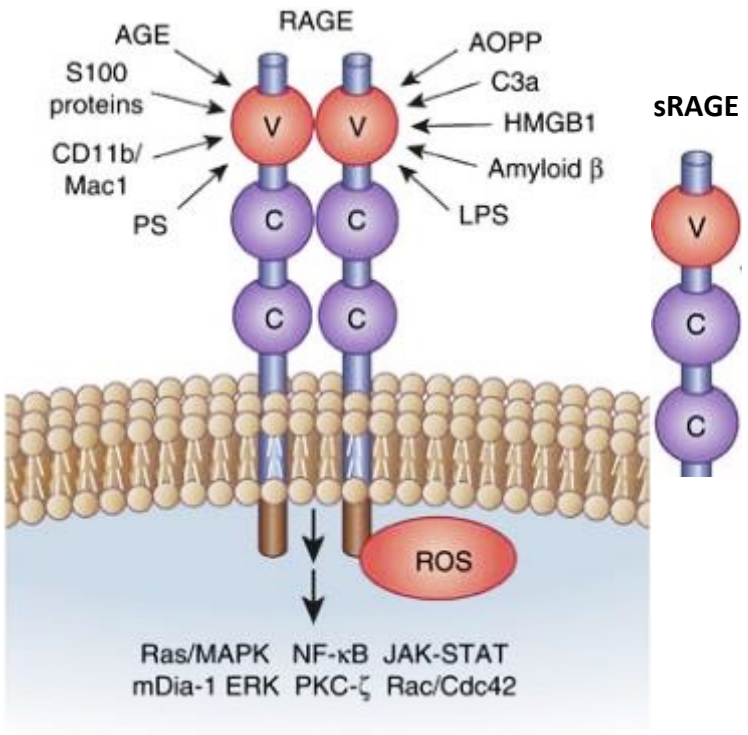
- The receptor for advanced glycation end-products (RAGE) is a pattern recognition receptor expressed abundantly in pulmonary epithelium, with low extrapulmonary expression.
- RAGE binds to a wide range of pro-inflammatory ligands, including HMGB1, S100 proteins, SAA, HSP70, and AGEs, resulting in activation of signalling pathways including NFκB and STAT6.[1]
- Animal models of asthma implicate RAGE as an upstream mediator of key Type-2 and non-Type-2 inflammatory cascades:
  - RAGE is required for allergen-induced release of IL-33, accumulation of ILC2s, and upregulation of IL-5 and IL-13.[2]
  - Models of severe steroid resistant neutrophilic airway disease indicate that inflammasome activation and neutrophil accumulation are RAGE-dependent.[3]
- RAGE can be cleaved to generate soluble RAGE (sRAGE), which is secreted into the airway and into serum.



1. Perkins TN et al. Allergy 2020.
2. Oczypok EA et al. J Allergy Clin Immunol 2015.
3. Killian KN et al. Front Immunol 2023.
4. Image: Yamamoto Y et al. Kidney Int 2012.

ARO-RAGE: siRNA Therapeutic Designed to Silence *AGER* mRNA in Pulmonary Epithelium

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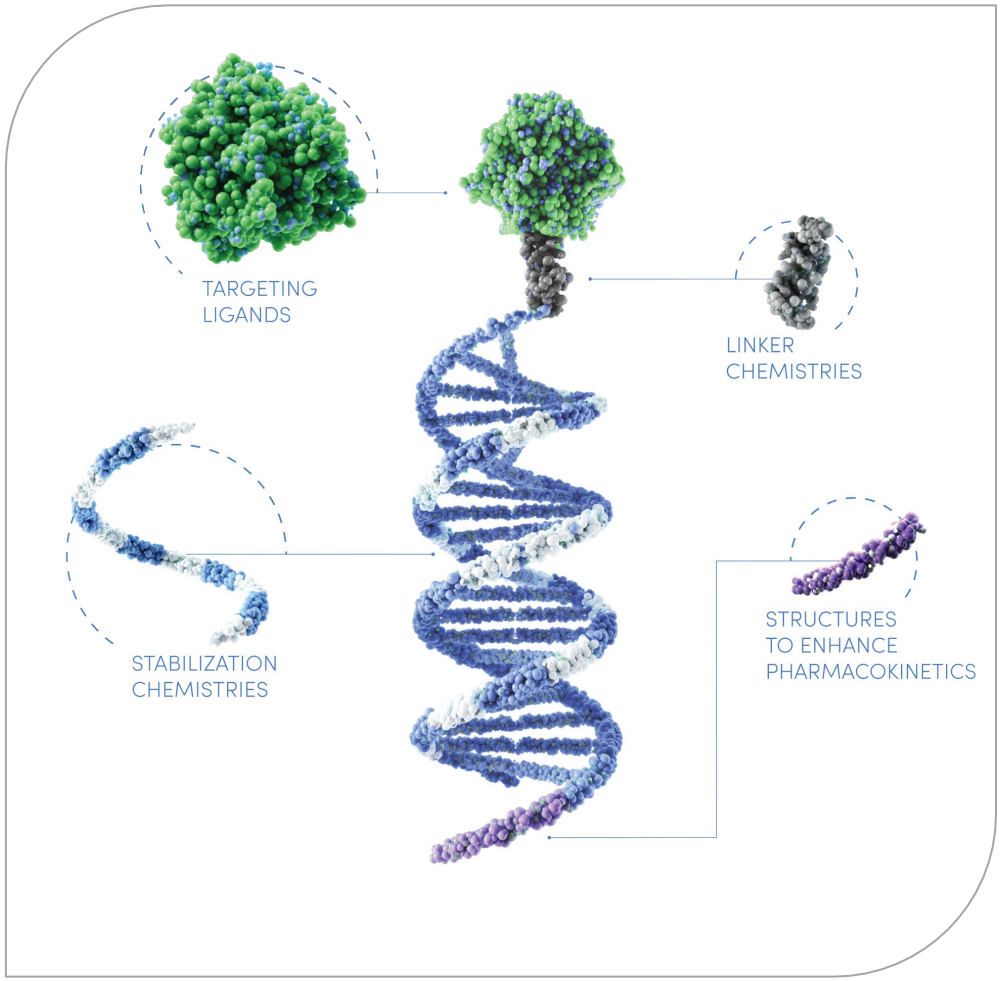

- ARO-RAGE is a RNAi-based, lung-targeted therapeutic designed to silence *AGER* mRNA within pulmonary epithelial cells, thereby decreasing RAGE protein expression.
- ARO-RAGE consists of a siRNA, which is designed to specifically silence RAGE expression, linked to an αvβ6 integrin targeting ligand, which drives pulmonary epithelial cell uptake.
- ARO-RAGE is delivered into the airway via an inhaled, nebulized solution.

AGER = gene encoding RAGE

ARO-RAGE First-in-Human Study Design

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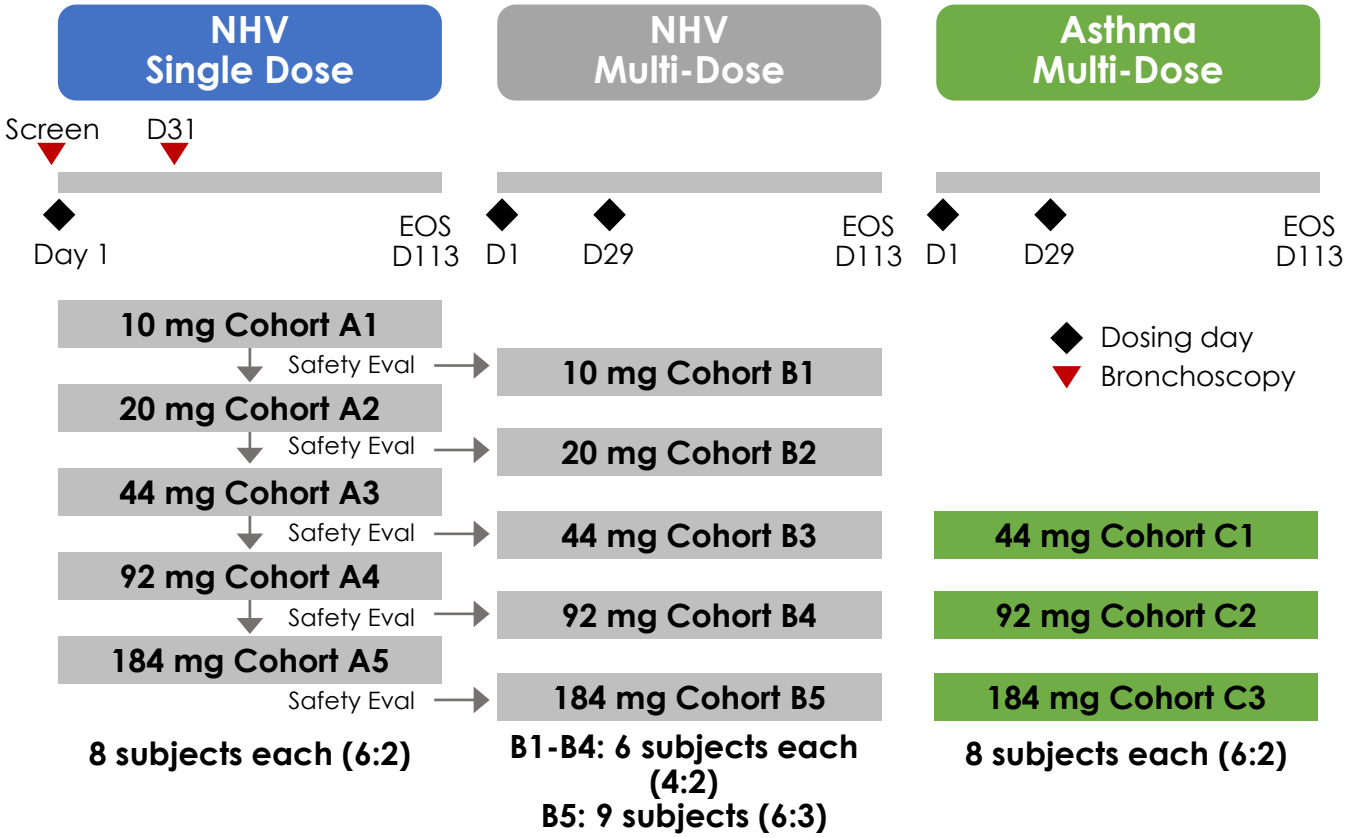
Study Design: ARORAGE-1001 (NCT05276570) is an ongoing, randomized, double-blind, placebo-controlled, phase 1/2a study of ARO-RAGE in healthy volunteers and subjects with asthma.

Subjects:
- Healthy volunteer cohorts: Age 18-55 years; no underlying lung disease; ppFEV$_1$ >80%; non-smoker
- Asthma cohorts: Age 18-60 years; mild-moderate asthma (GINA 1-4); ppFEV$_1$ ≥70%; BEC ≥200 cells/µl; non-smoker

Exposures:
- ARO-RAGE: ascending dose levels given on Day 1 (SAD) or Days 1 and 29 (MAD)
- Placebo: normal saline

Endpoints:
- Primary: TEAE incidence
- Target engagement (exploratory):
  - Serum sRAGE
  - BALF sRAGE



BEC = blood eosinophil count
EOS = end of study
MAD = multiple ascending dose
NHV = normal healthy volunteer

ppFEV$_1$ = percent-predicted forced expiratory volume in 1 second
SAD = single ascending dose
sRAGE = soluble RAGE
TEAE = treatment-emergent adverse event

ARORAGE-1001 Baseline Characteristics

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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)
White – no. (%)	41 (56.2)	8 (88.9)
BMI – kg/m^2	25.7 ± 3.6	26.0 ± 3.9
Prebronchodilator $ppFEV_1$ - %	96.3 ± 10.7	93.4 ± 10.1
ICS Dose – no. (%)		
None or Undetermined	---	3 (33.3)
Low	---	5 (55.6)
Medium	---	1 (11.1)
High	---	0 (0)
Blood eosinophil – cells/µl	---	256 ± 113
FeNO – ppb	---	37.8 ± 28.9
Serum total IgE – IU/ml	---	350 ± 257
Serum sRAGE – pg/ml	1167 ± 533	1280 ± 430
BALF sRAGE – pg/ml	2487 ± 1716	---

Data cut 17 July 2023

* mean ± SD.
^ N represents entire population (ARO-RAGE + placebo) randomized to date; ongoing study remains blinded.

BALF = bronchoalveolar lavage fluid
BMI = body-mass index
FeNO = fractional exhaled nitric oxide
ICS = inhaled corticosteroid
$ppFEV_1$ = percent-predicted forced expiratory volume in 1 second
sRAGE = soluble RAGE

Interim Blinded Safety Results: Summary of Treatment-Emergent Adverse Events

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Event	Healthy Volunteer SAD Cohorts (N=40)* n (%)	Healthy Volunteer MAD Cohorts (N=33)* n (%)	Asthma MAD 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)

*N represents entire population (ie ARO-RAGE + placebo) randomized to date, as the ongoing study remains blinded.
N = number of subjects in population; n = number of subjects reporting event; % = 100 x n/N.

MAD = multiple ascending dose
SAD = single ascending dose
TEAE = treatment-emergent adverse event
URTI = upper respiratory tract infection

Data cut 03 July 2023

Single Dose of ARO-RAGE Resulted in Dose-Dependent Decreases in BALF sRAGE at 1 Month

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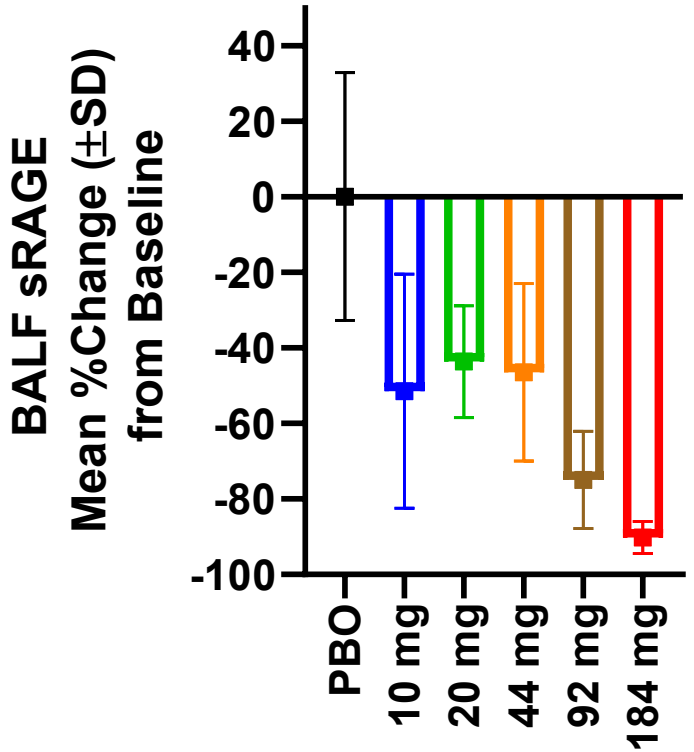
Healthy Volunteer SAD Cohorts
Change from Baseline at Day 31



Treatment	BALF sRAGE % Change from Baseline*
Placebo	0.1 ± 32.8
ARO-RAGE 10 mg	-51.5 ± 31.0
ARO-RAGE 20 mg	-43.6 ± 14.8
ARO-RAGE 44 mg	-46.4 ± 23.5
ARO-RAGE 92 mg	-74.9 ± 12.9
ARO-RAGE 184 mg	-90.2 ± 4.2

*mean ± SD.
N=10 placebo
N=6 per active treatment cohort

Data cut 18 July 2023

BALF = bronchoalveolar lavage fluid
PBO = placebo
SAD = single ascending dose
sRAGE = soluble RAGE

ARO-RAGE Resulted in Mean Maximum Serum sRAGE Reduction Up to 79% with Single Dose, Up to 80% with Multiple Doses

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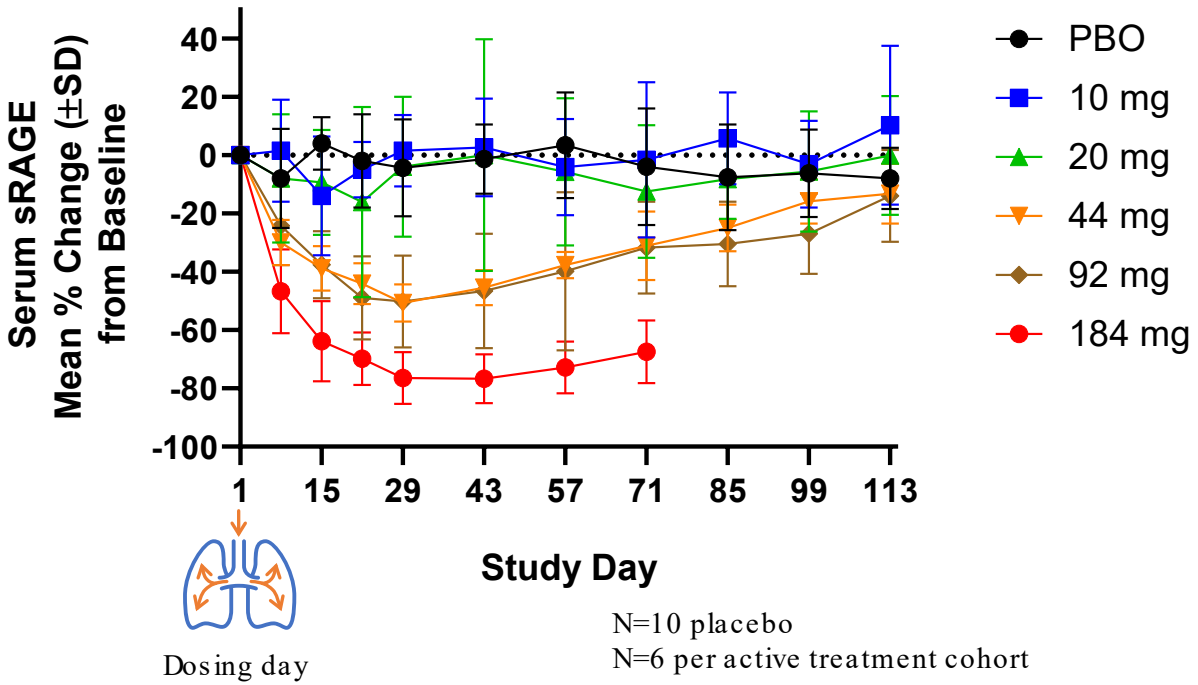
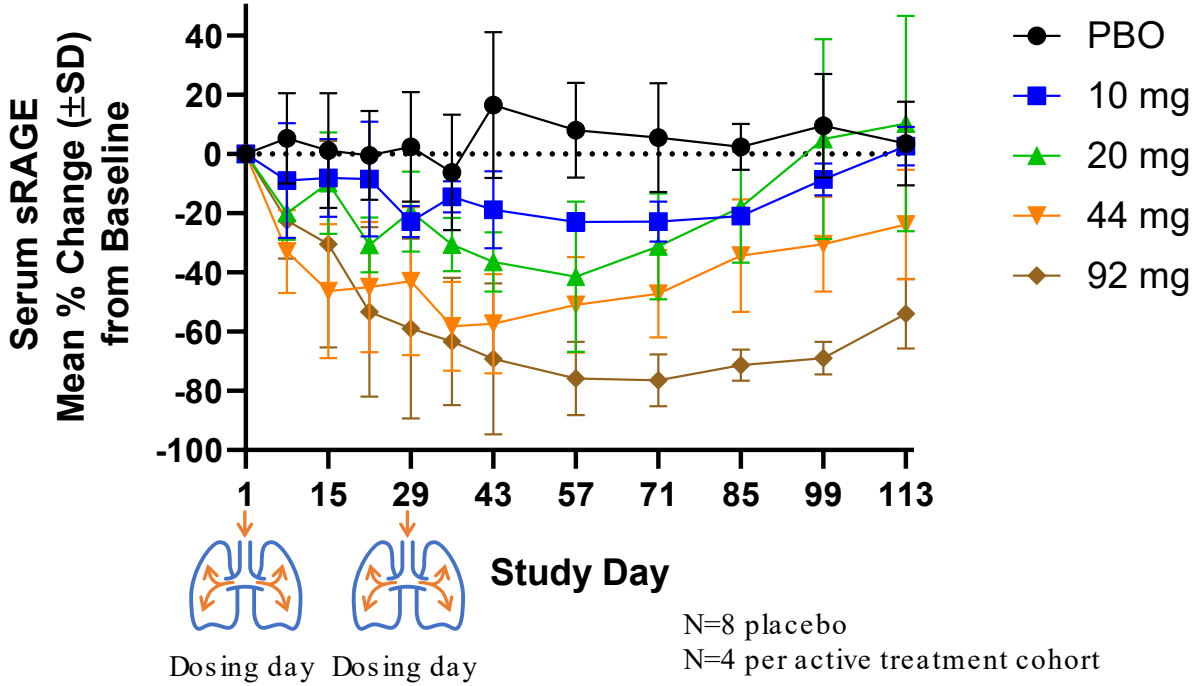
Healthy Volunteer SAD Cohorts



N=10 placebo
N=6 per active treatment cohort

Healthy Volunteer MAD Cohorts



N=8 placebo
N=4 per active treatment cohort

184 mg Dose Data Pending

PBO = placebo
SAD = single ascending dose
MAD = multiple ascending dose
sRAGE = soluble RAGE

Data cut 18 July 2023

ARO-RAGE Resulted in Comparable Serum sRAGE Reductions in Asthma and Healthy Subjects

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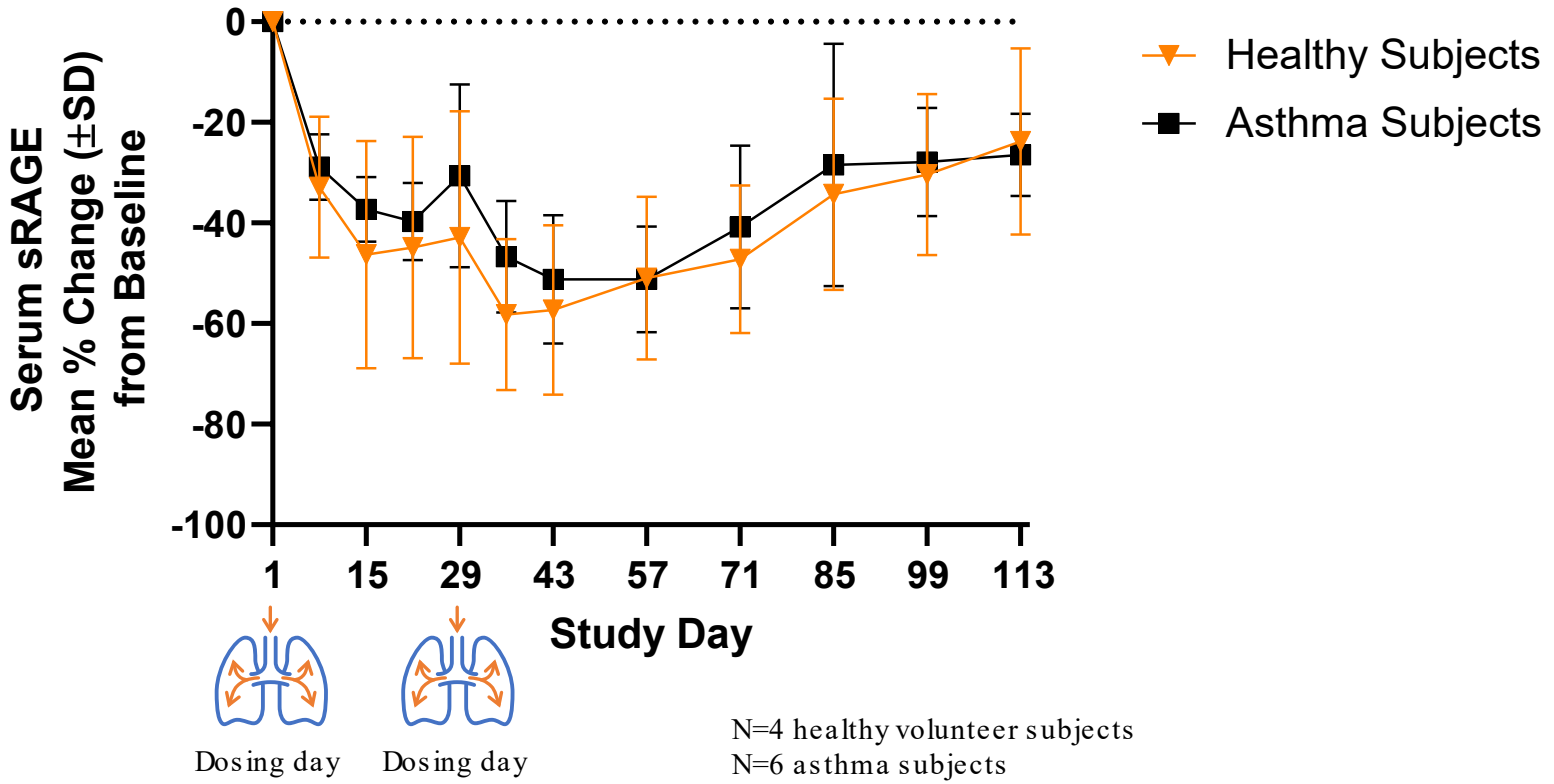
44 mg Multiple Dose Cohorts: Healthy vs. Asthma



N=4 healthy volunteer subjects
N=6 asthma subjects

Data cut 21 July 2023

Conclusions

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- ARO-RAGE has been well-tolerated to date in healthy volunteers and asthma patients.
- ARO-RAGE reduced sRAGE concentration in BALF and serum in a dose-dependent manner.
- Reduction of serum sRAGE by ARO-RAGE was similar in healthy volunteers and asthma patients at the 44 mg dose level. Asthma patient enrollment is ongoing at higher doses.

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4. Yamamoto Y, Yamamoto H. Interaction of receptor for advanced glycation end products with advanced oxidation protein products induces podocyte injury. 2012. 82:733-735.

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