

CO-8195, a novel orally active small-molecule corrector for Alpha-1 Antitrypsin Deficiency (AATD), increases functional secreted Z-A1AT and reduces polymerized Z-A1AT in cellular assays and in the PiZ mouse model

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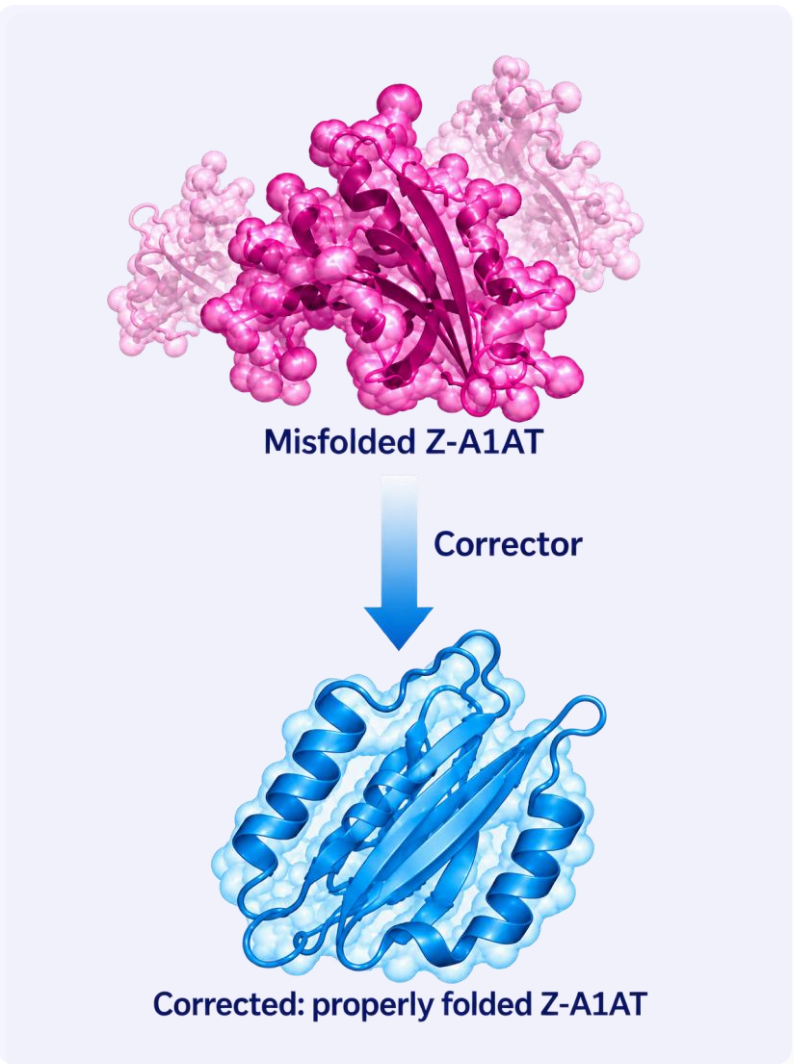
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Goal, discovery and mechanism of action

Congruence goal

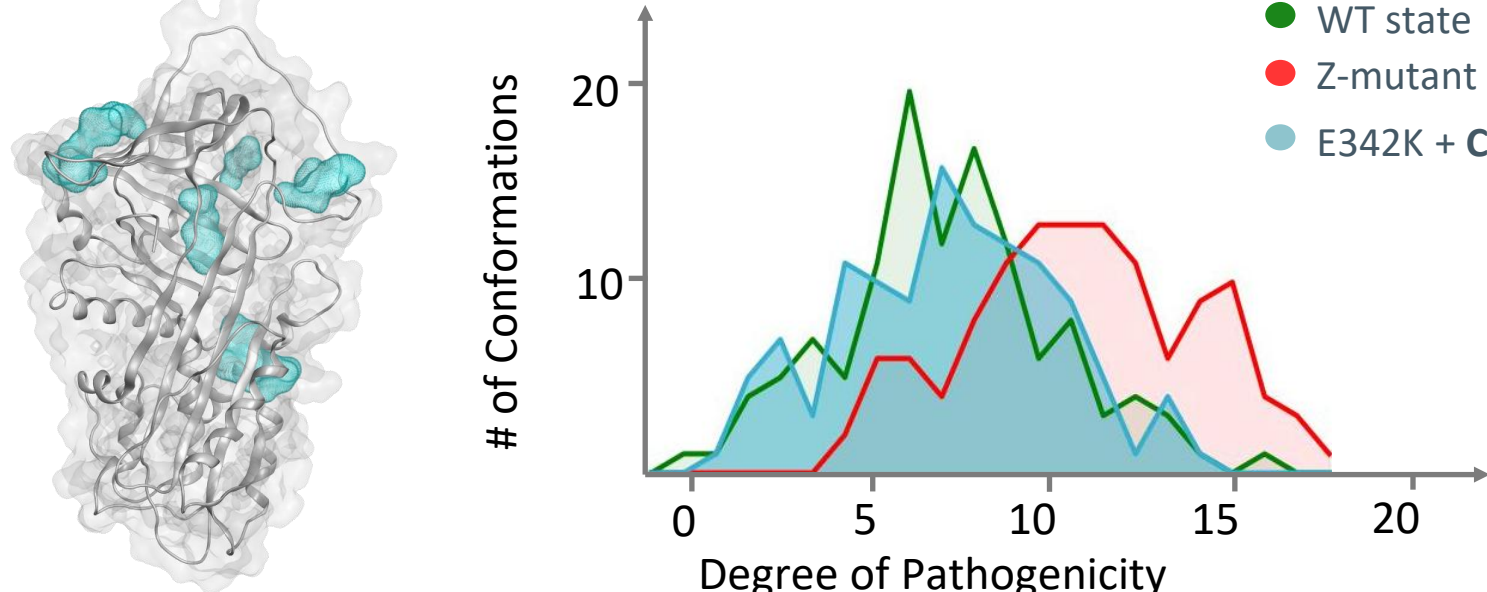
- To develop a *differentiated, optimized oral small-molecule corrector*
- with the potential to restore **protective levels of functional A1AT**
- liver-targeted:** achieving optimal hepatic exposure and effectively **reduce Z-A1AT polymer burden**
- To address **both lung and liver disease**

Small-molecule Corrector

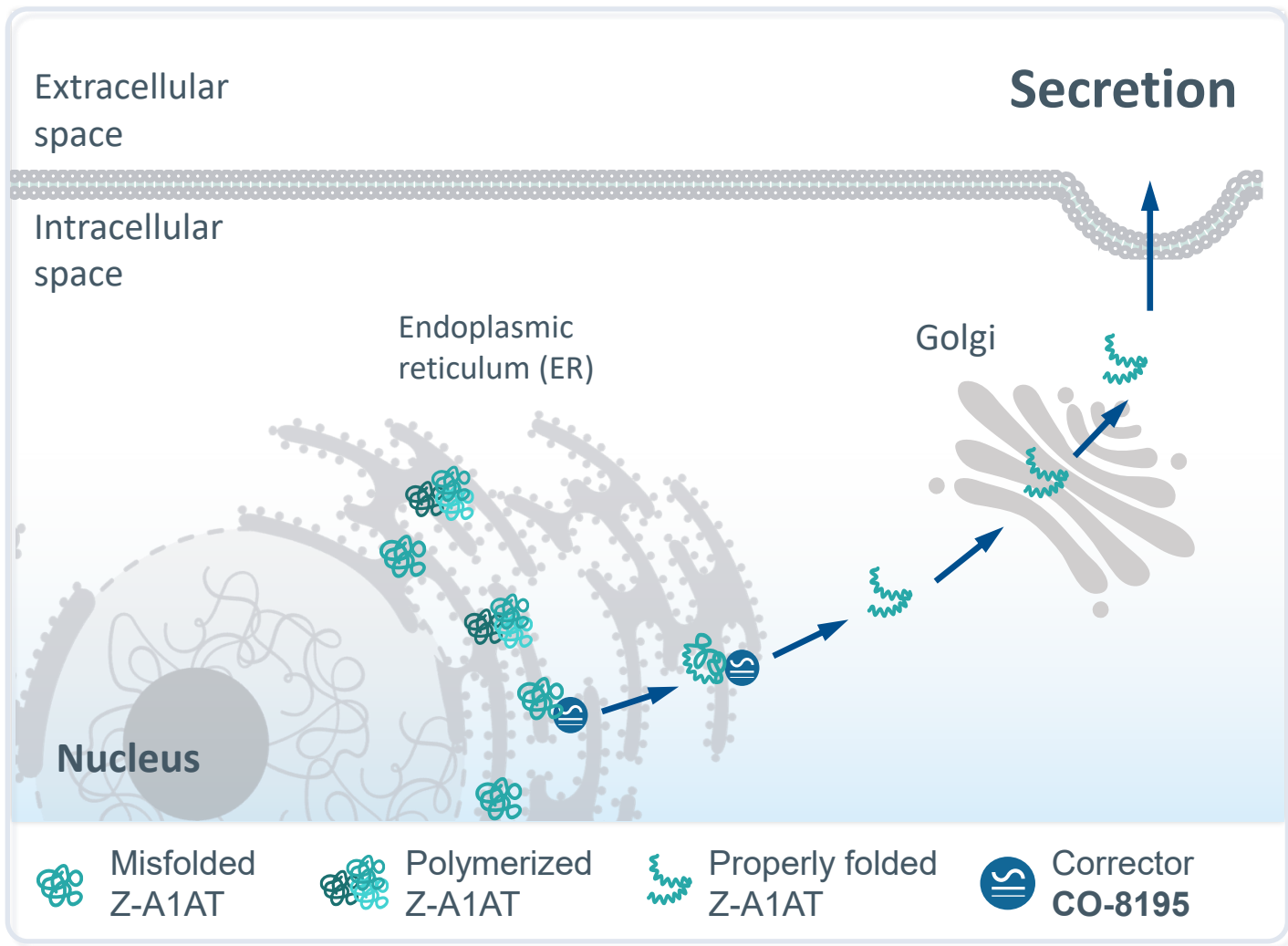


Revenir™ engine

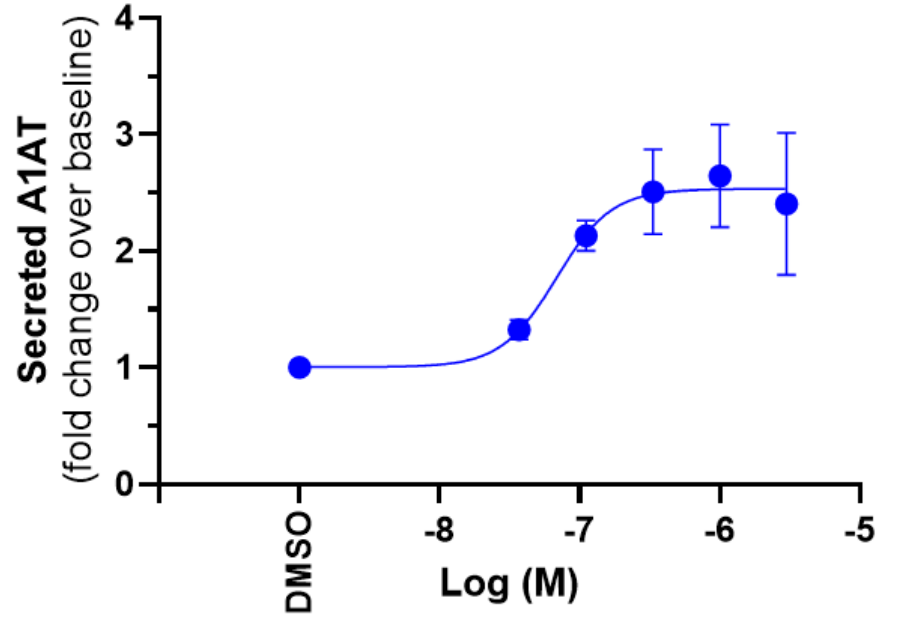
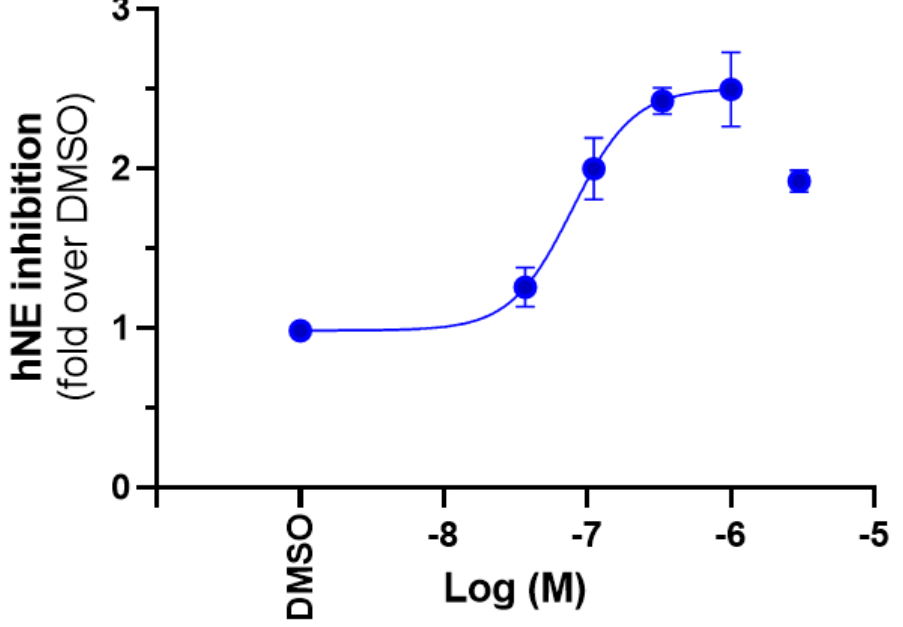
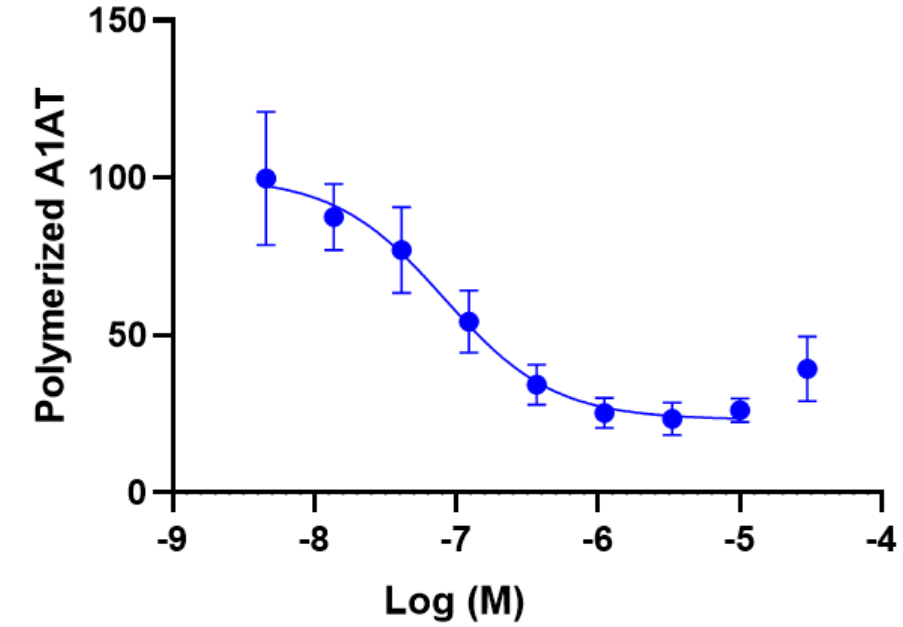
- The Revenir™ computational engine identifies pockets where small molecules may restore protein function and predicts small-molecule hits
- CO-8195** reverses conformational landscape from Z-mutant → wild-type (WT) state



CO-8195 Mechanism of Action



In Vitro Characterization of CO-8195 Effects

Concentration-dependent ↑ Z-A1AT secretion, ↓ Z-A1AT polymer levels and Z-A1AT hNE inhibition function restauration			
Assay	Z-A1AT Secretion	Z-A1AT Function	Z-A1AT Polymer Reduction
Method	ELISA	Enzymatic	In-cell Western
Sample type	Cell supernatant	Cell supernatant	Fixed cells
Parameter analyzed	Z-A1AT in cell supernatant (A1AT antibody)	Activity of hNE in presence of hNE substrate	Z-A1AT polymer (2C1 antibody)
Evaluated in target-relevant, human liver-derived HepG2 cells homozygous for E342K (Z-allele)			
	EC ₅₀ (95% CI, nM) / E _{max} (±SD)		
	68 nM (4.0-116.8) / 2.6-fold (±0.44)	79 nM (60.3-102.3)/ 2.5-fold (±0.23)	82 nM (18.4-152.5)

ADMET and in Vivo Evaluation

Excellent ADME properties

Orally bioavailable with preferential liver distribution

- ✓ High oral bioavailability (%F)
- ✓ Low-to-moderate clearance (CL)
- ✓ High liver-to-plasma ratio (Kp ~ 7) in preclinical species and PiZ mice

Liver Distribution (Kp) assessment			
Setting	Tissue	Species	Kp
In vitro	Hepatocytes	mouse	7.5
		human	3.6
In vivo	Liver	WT mouse	6.8
		PiZ mouse	7.7

Non mutagenic (AMES test negative)

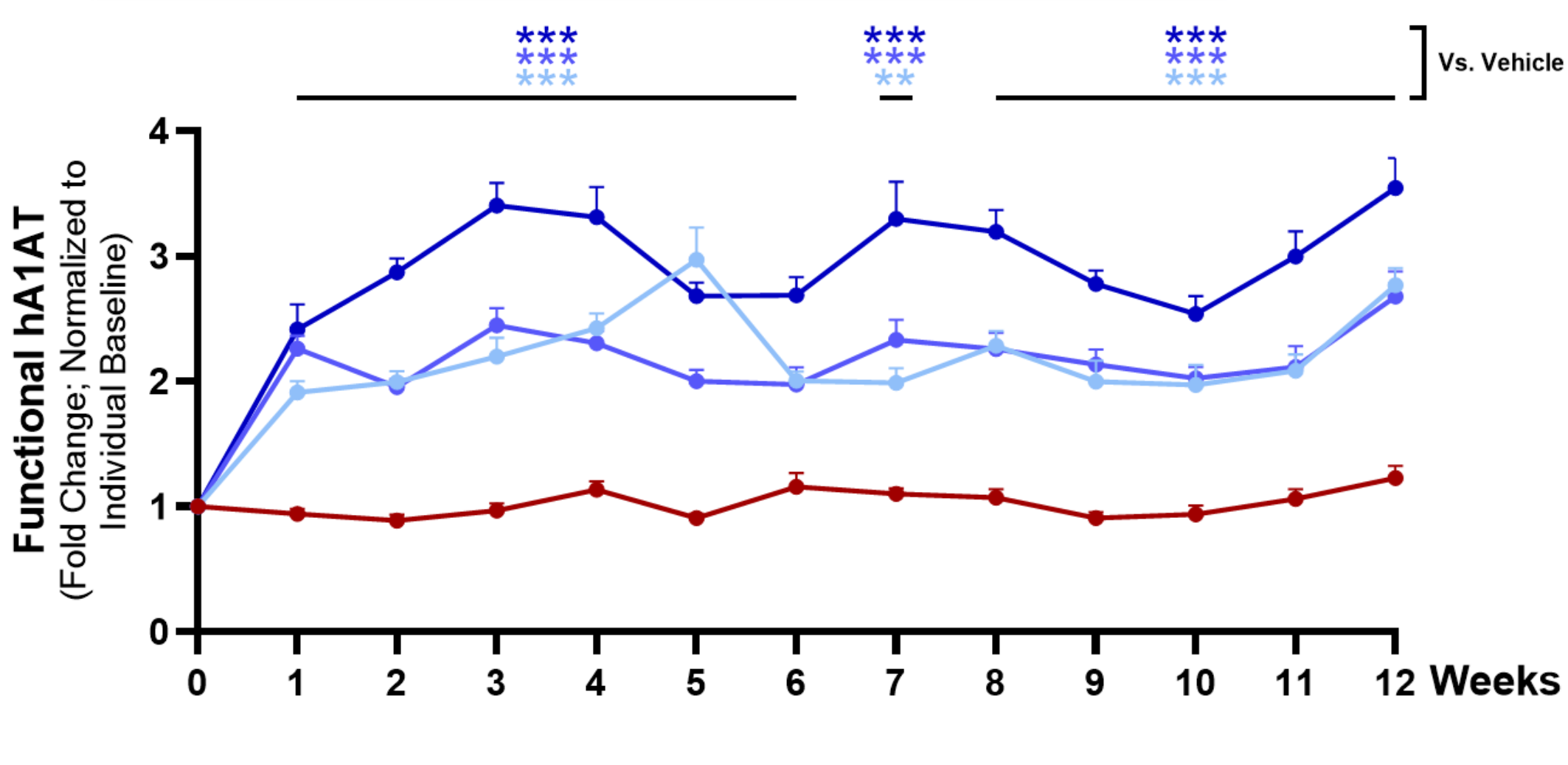
Favorable hERG profile

12-Week Oral Therapy in PiZ Mice: CO-8195 Produces Durable Efficacy

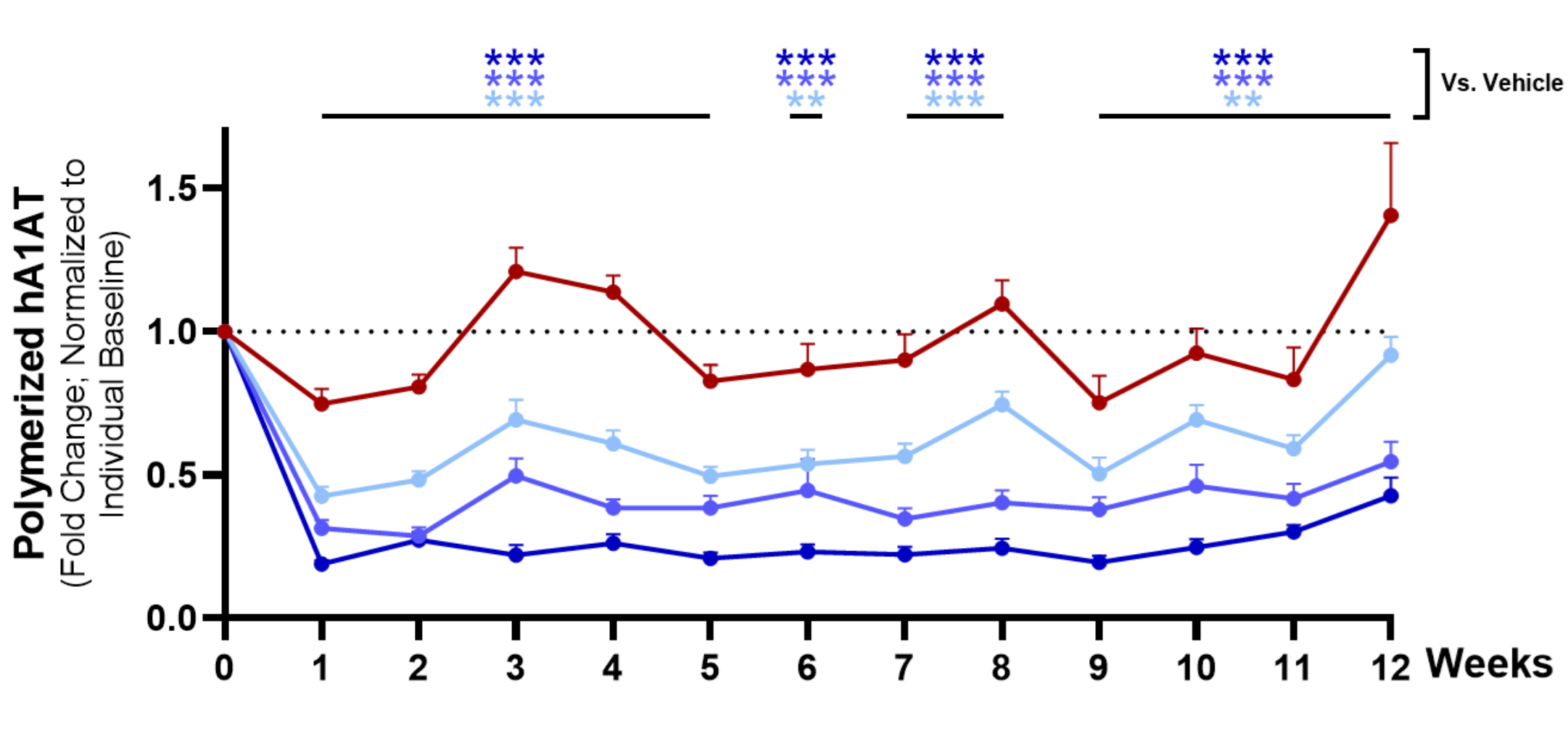
PiZ mouse model

- Strain #035411 (JAX)
- Carries ~16 human Z-A1AT copies
- Age at study start: 5-8 weeks, ♂
- Pharmacodynamic endpoints:**
 - Restoration of plasma Z-A1AT function (binding to neutrophil elastase)
 - Reduction of systemic Z-A1AT polymers in plasma
 - Reduction of liver Z-A1AT polymers (by ELISA, histology)

Functional Z-A1AT in plasma



Polymer Z-A1AT in plasma

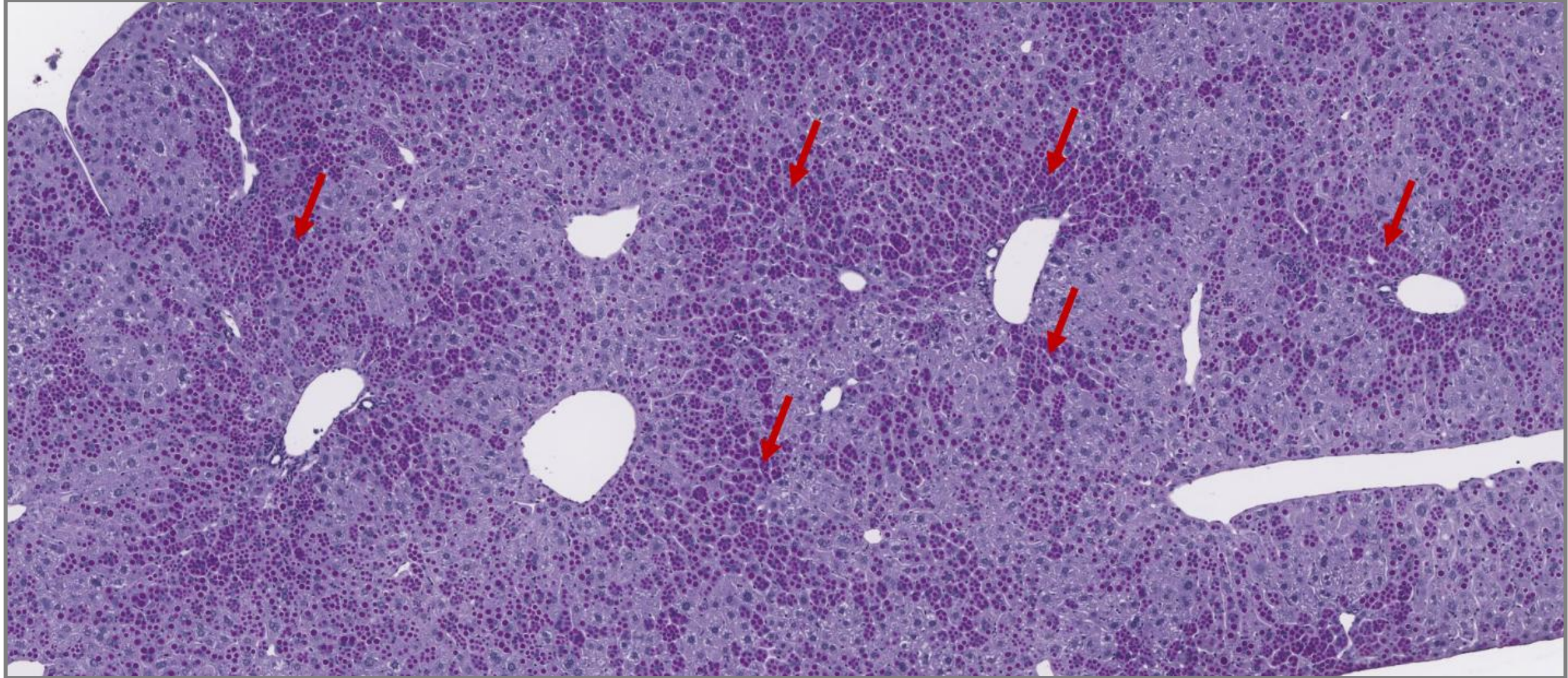
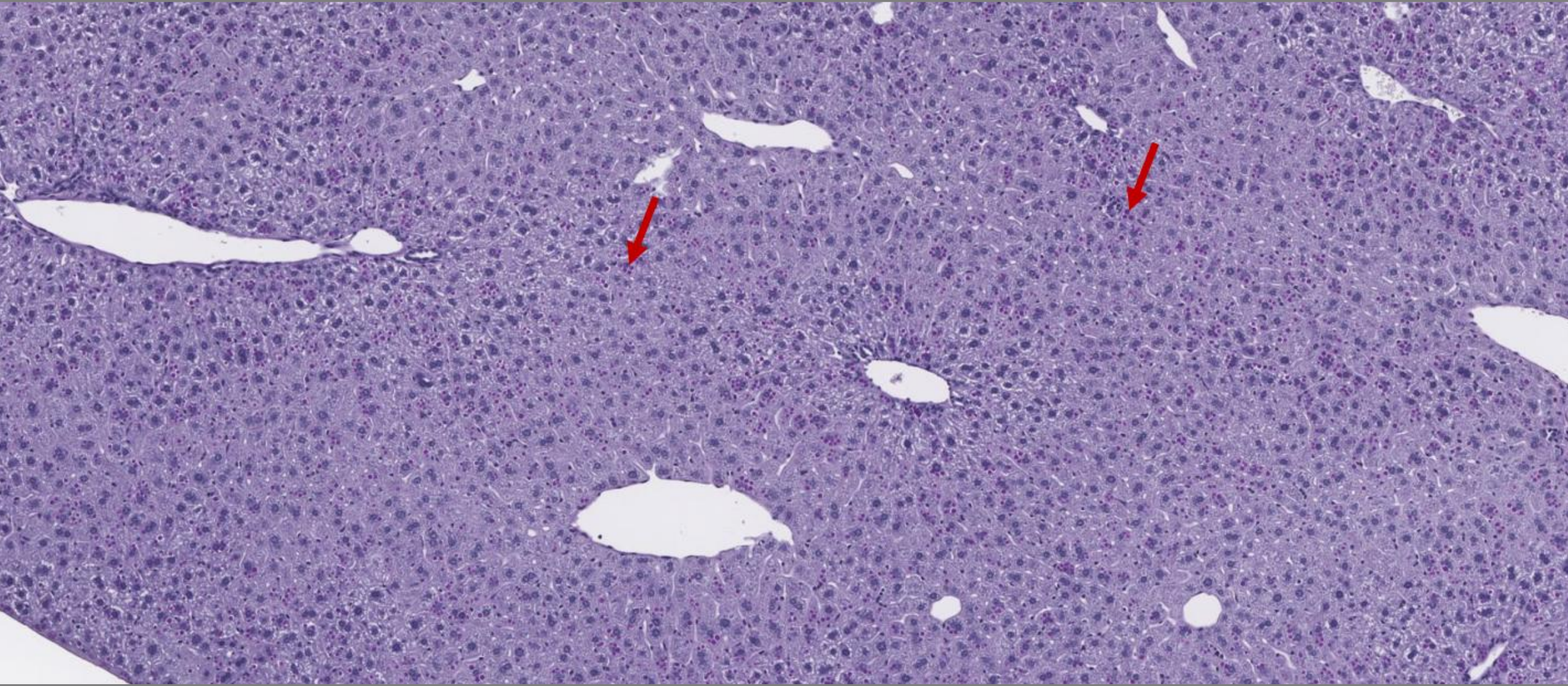


Vehicle (red); CO-8195: 30, 60, 120 mg/kg PO QD (light to dark blue).

Liver efficacy in PiZ Mice after 12-Week Oral Therapy: CO-8195 Induces Liver Polymer Clearance

Vehicle-treated

CO-8195-treated



CO-8195 Dose (mg/kg)	Liver polymers reduction	
	ELISA	PAS-D positivity
30	↓ 9%	↓ 43%
60	↓ 52%	↓ 59%
120	↓ 72%	↓ 72%

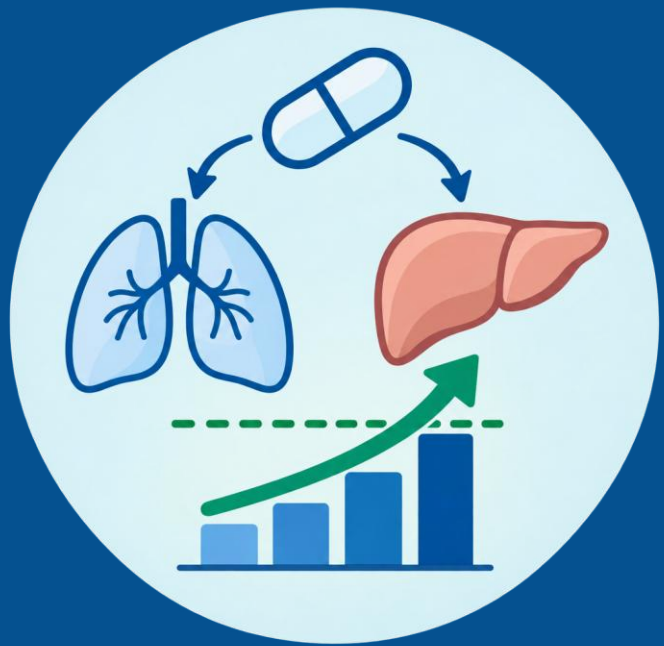
PAS-D positivity quantifies stained pixels in the liver section.

Conclusions

- CO-8195 is a novel orally active small-molecule Z-A1AT corrector
- CO-8195 increases secretion of functional Z-A1AT and reduces Z-A1AT polymers *in vitro* and *in vivo*, supporting its potential to address both lung and liver diseases in AATD
- IND-enabling safety studies ongoing. Phase 1 initiation targeted for H1 2027

Acknowledgments: Congruence Therapeutics Team, ERS Conference Organizers
Disclosure: A.K. is an employee of Congruence Therapeutics Inc. and holds stock options

Z-A1AT, Z-alpha-1 antitrypsin; hNE, human neutrophil elastase; ELISA, enzyme-linked immunosorbent assay; PiZ mouse, transgenic mouse expresses human SERPINA1 (Z-A1AT)



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