ARO-AAT for Liver Disease in Alpha-1 Antitrypsin Deficiency

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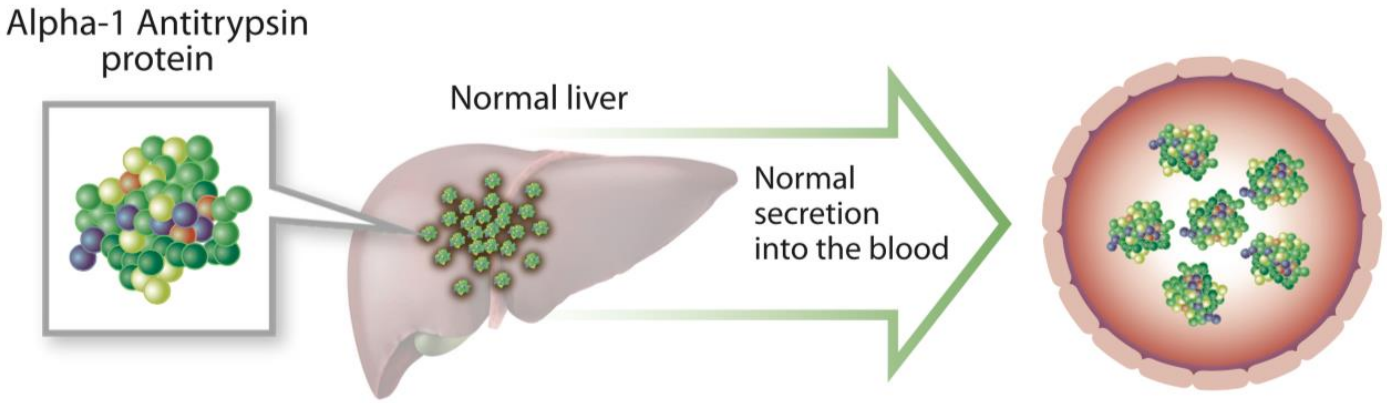
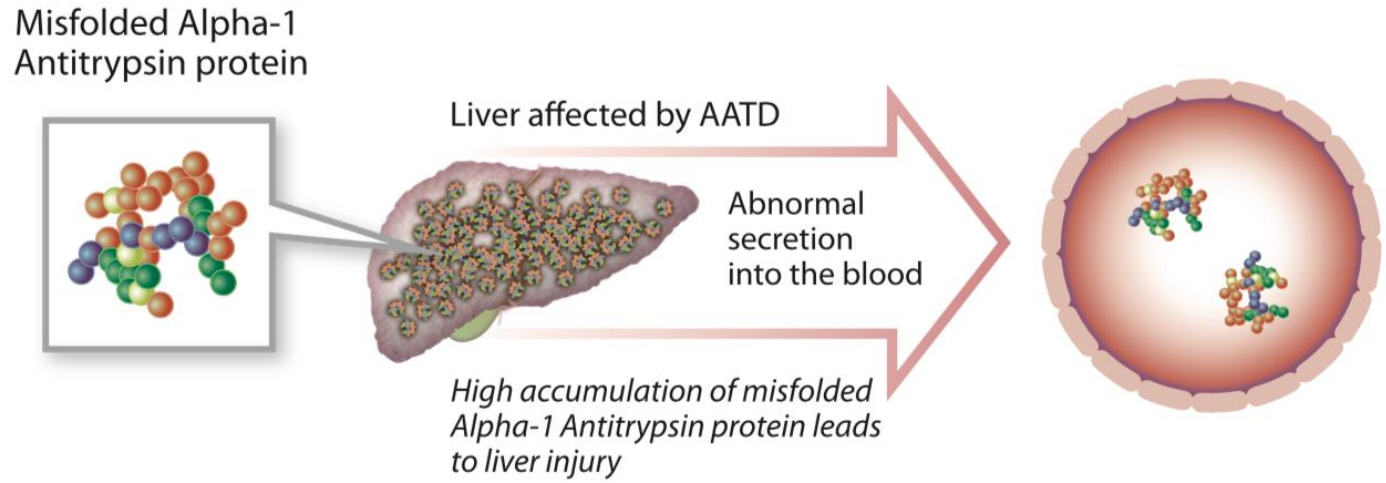
Alpha-1 Antitrypsin Deficiency

Normal AAT



Normal blood levels of normal protein protect lungs, no liver accumulation

Abnormal AAT (Z-AAT)



Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection, accumulated protein injures liver

No current treatment

Treated with AAT protein replacement therapy today

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Fibrosis is related to Z-AAT accumulation

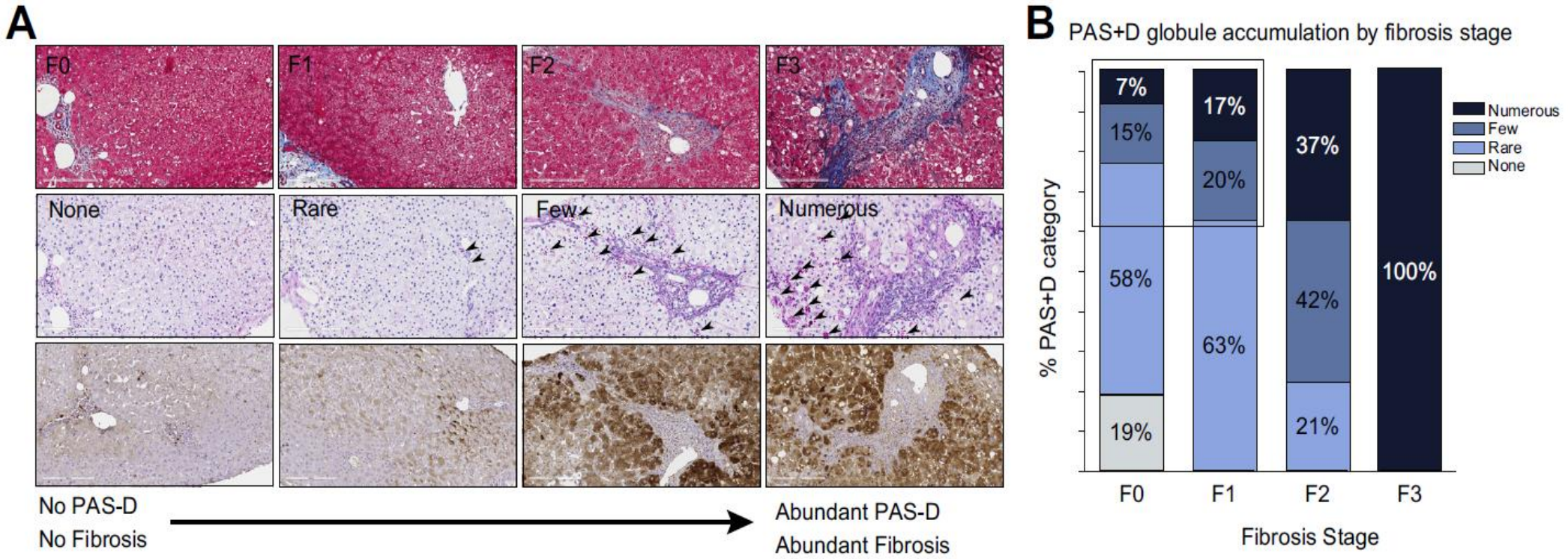
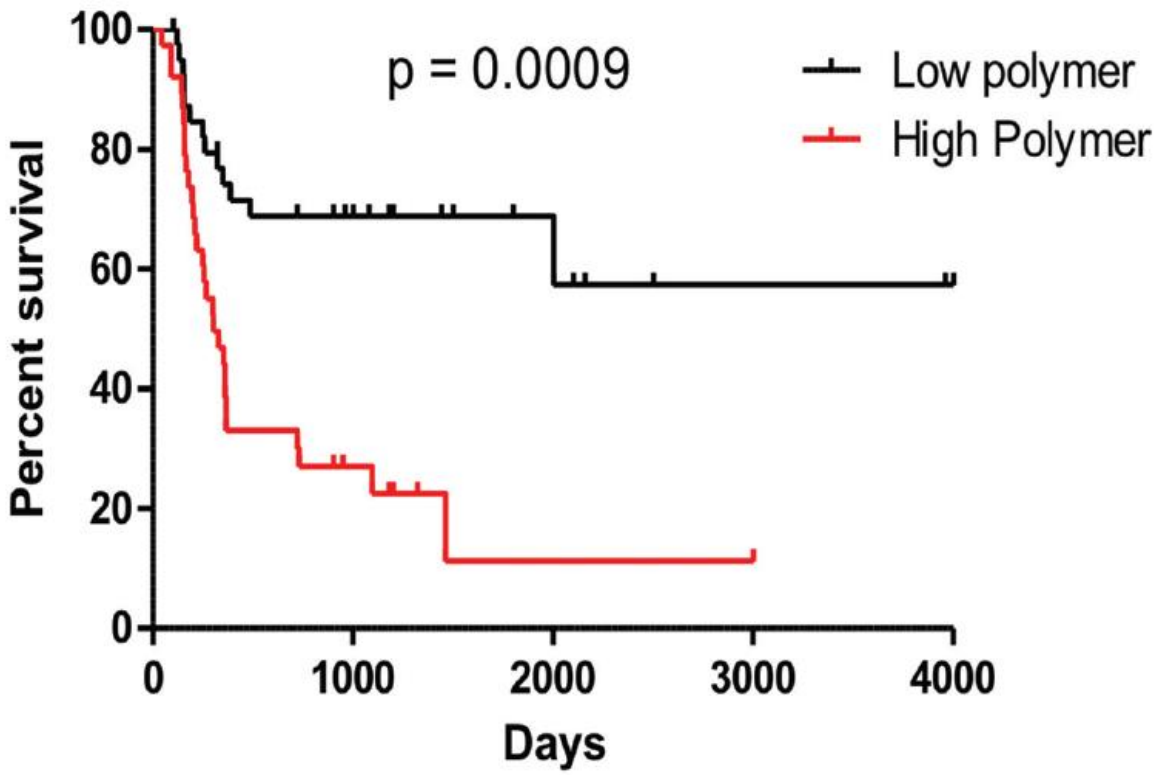


Fig. 3. Fibrosis is related to ATZ accumulation in hepatocytes. (A) Representative liver biopsies show increasing fibrosis stage, PAS + D globule grade, and total ATZ accumulation. Top (Masson Trichome), middle (PAS-D), bottom (Total AAT IHC). Black arrows highlight cells with PAS-D globules. Scale bar represents 200 μm. (B) At higher fibrosis stages, the proportion of biopsies with numerous PAS + D globules increases. This observation supports the concept of a "toxic gain of function" whereby retention of ATZ within hepatocytes is responsible for liver disease. Furthermore, individuals with PAS + D accumulation but low fibrosis scores (box) may represent an "at risk" population. AAT, alpha-1 antitrypsin; ATZ, AAT Z form; PAS + D, PAS-positive, diastase-resistant.

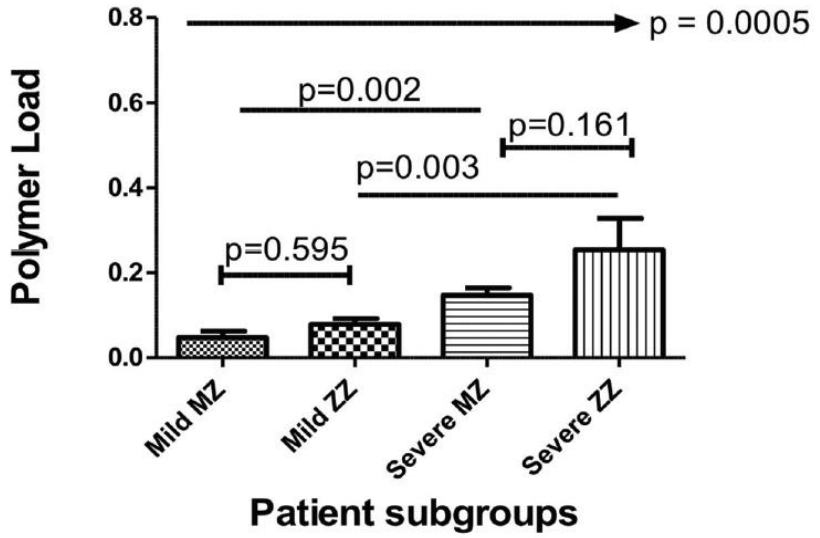
Clark et al, 2018

Polymer load influences survival



Mela et al., 2020

Patients with polymer load above the median (high polymer) have an **increased risk of liver-related mortality** compared to those with Z-AAT polymer load below the median (low polymer)



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What is the Risk of Developing Liver Disease?

Clinically significant fibrosis is as high as **1/3 of all ZZ Alphas**

	Year	Fibrosis Stage ≥2	Fibrosis Stage ≥ 3
Hamesch* (n=554)	2019	23.6%	13.6%
Clark (n=94)	2018	35.1%	6.4%
Morer (n=23)	2017	26%	8.6%
Dawwas (n= 22)	2013	37.4%	NA

*determined by transient elastography

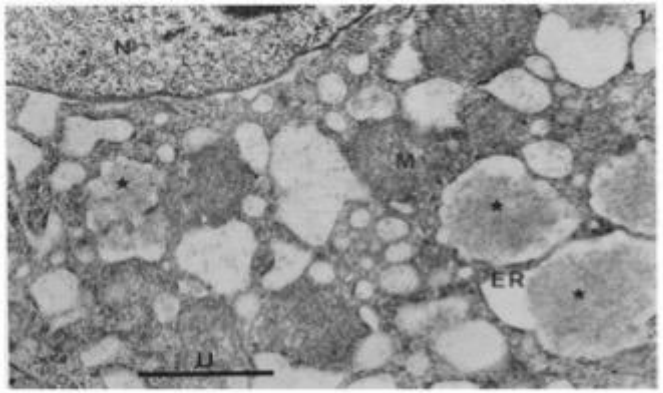
1. *Teckman 2019*
2. *Hamesch 2019*
3. *Clark 2018*
4. *Morer 2017*
5. *Dawwas 2013*

ARO-AAT: therapeutic rationale

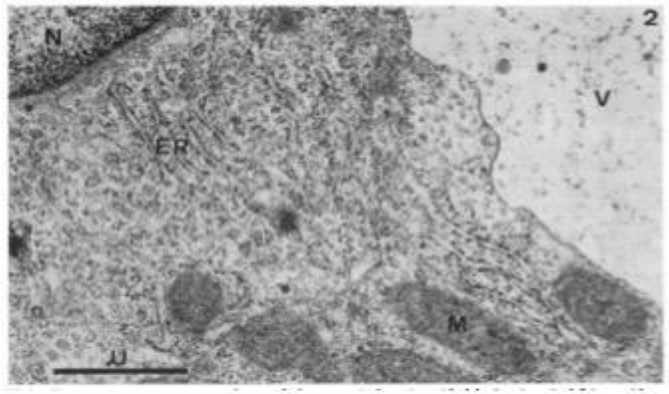
ARO-AAT designed to stop Z-AAT production by silencing AAT gene expression to:

- Prevent liver accumulation of Z-AAT
- Allow clearance of accumulated Z-AAT protein
- Prevent cycles of cellular damage
- Prevent/Reverse progression of liver fibrosis

PiZZ phenotype (diseased)



Pi null phenotype (normal liver)

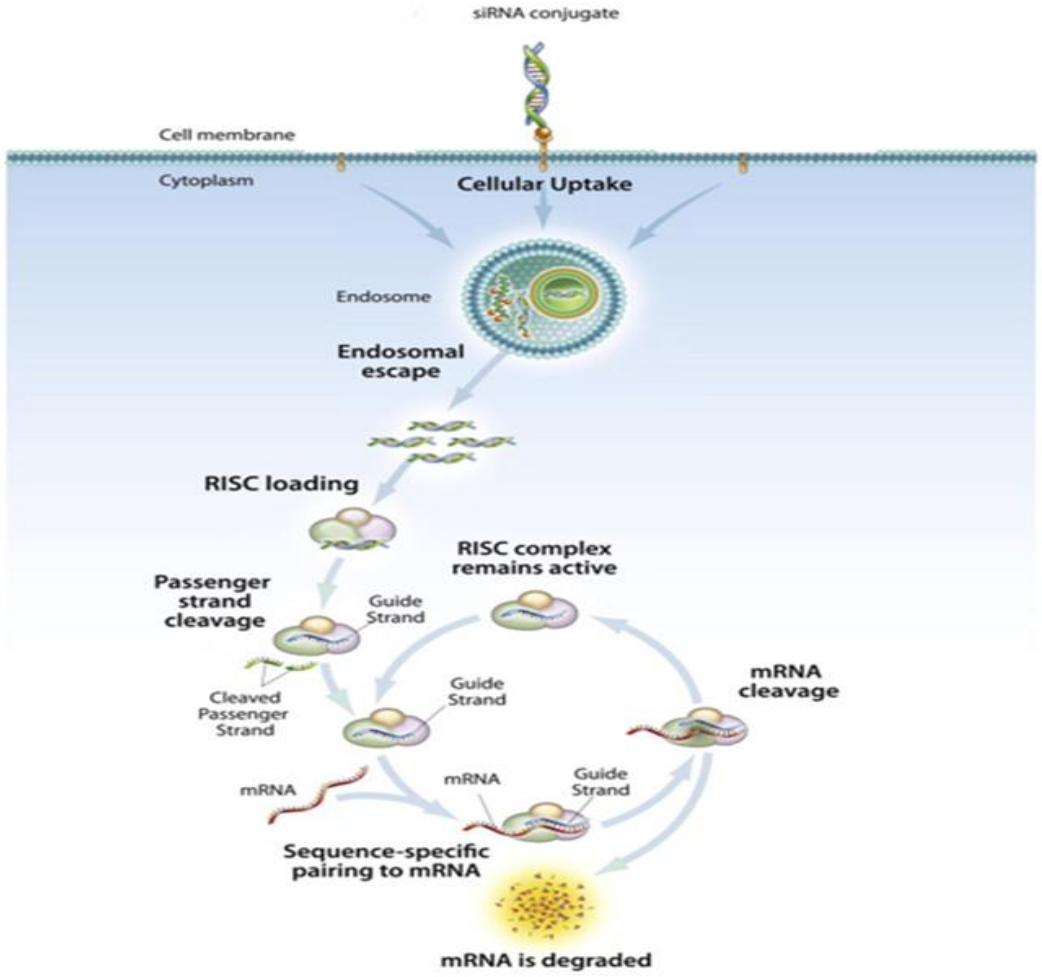


Feldmann G et al., *Gut* 1975

ARO-AAT is a Liver Targeted RNAi therapeutic

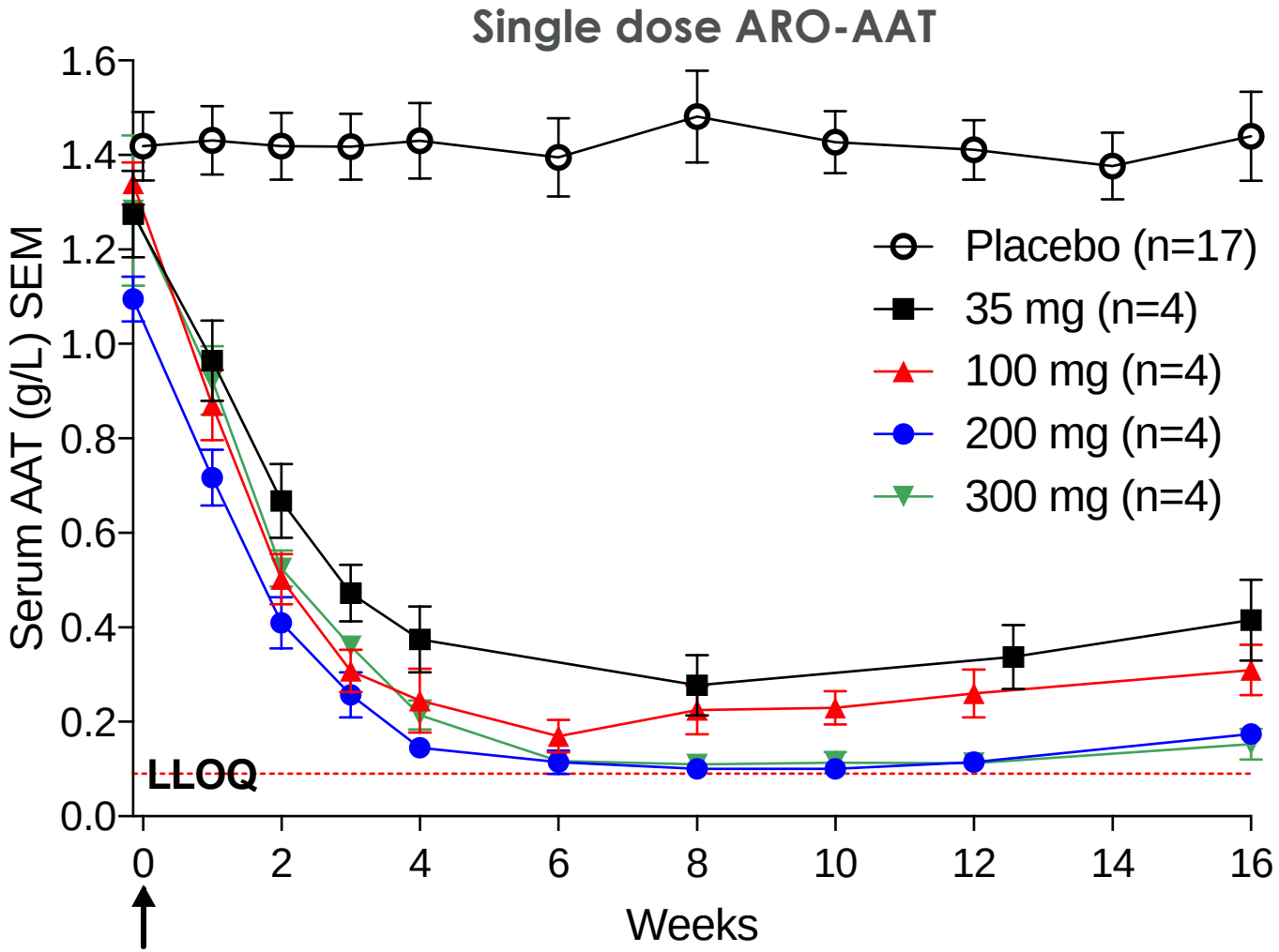
Advantages of RNAi:

- Undruggable targets
- Potency
- Duration
- Safety



Therapeutic gene silencing with **RNA interference** is highly precise and efficient

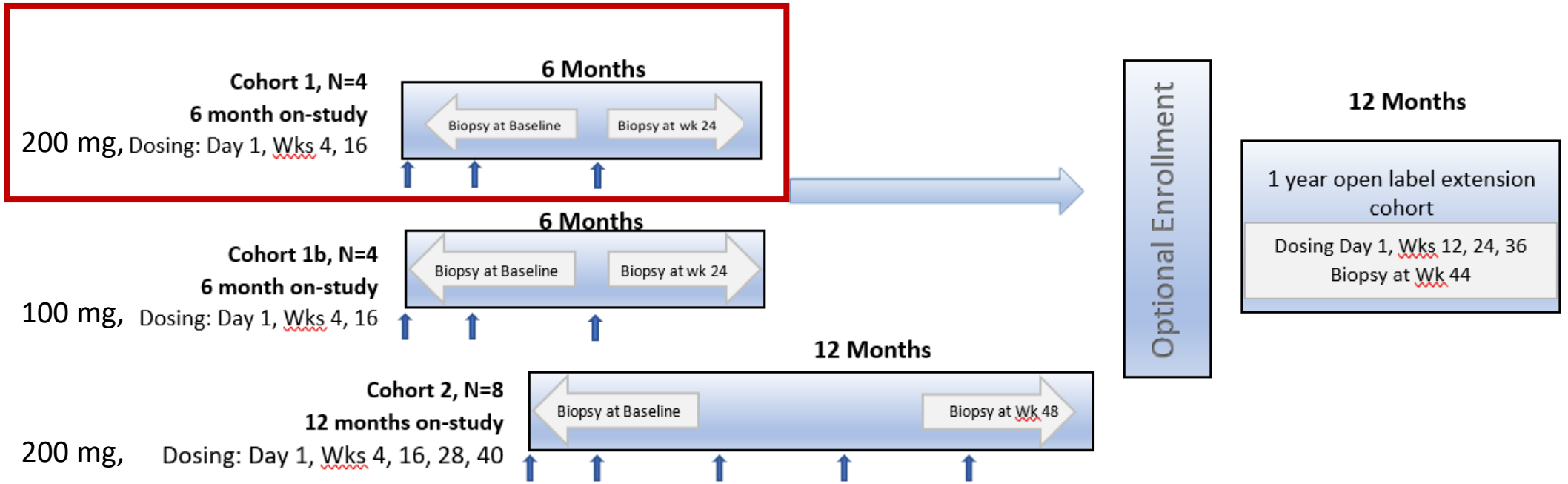
ARO-AAT Phase 1: Single doses of ARO-AAT show reductions in serum AAT in Healthy Volunteers



Wooddell et al., 2020

AROAAT2002: First Results in PiZZ Patients

- Open label (All received ARO-AAT)
- Countries: Germany, UK, Austria
- Study is fully enrolled



Strnad et al., AASLD 2020

Cohort 1 Baseline Characteristics

	Subject (all Male)			
	450-001	450-003	450-004	450-005
Age (years)	46	20	56	56
BMI (kg/m2)	24.6	23.5	26.3	30.7
Liver Fibrosis (Biopsy)*	F3	F2	F2	F3
FEV1 % predicted	56%	87%	106%	106%
AAT Augmentation (Y/N)	Y	N	N	N

*Screening assessment

Strnad et al., AASLD 2020

AROAAT2002 Cohort 1 Summary Safety

- Single SAE of EBV related myocarditis
- No AEs secondary to adverse changes in markers of liver function, renal function or platelets
- No treatment emergent AEs related to change in pulmonary status or pulmonary function were reported
- No clinically meaningful changes in ppFEV1 from baseline to Week 24 were observed

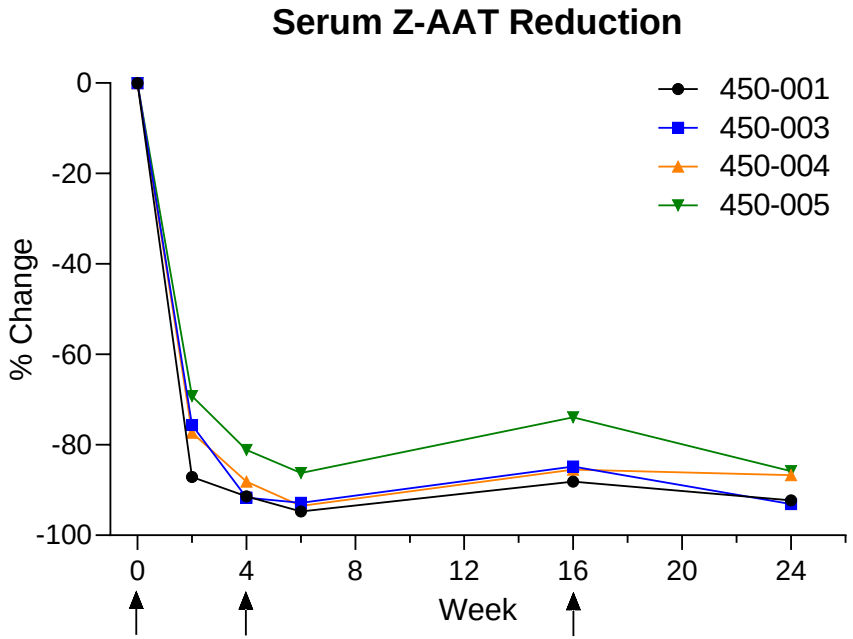
Cohort 1: Changes in ppFEV1

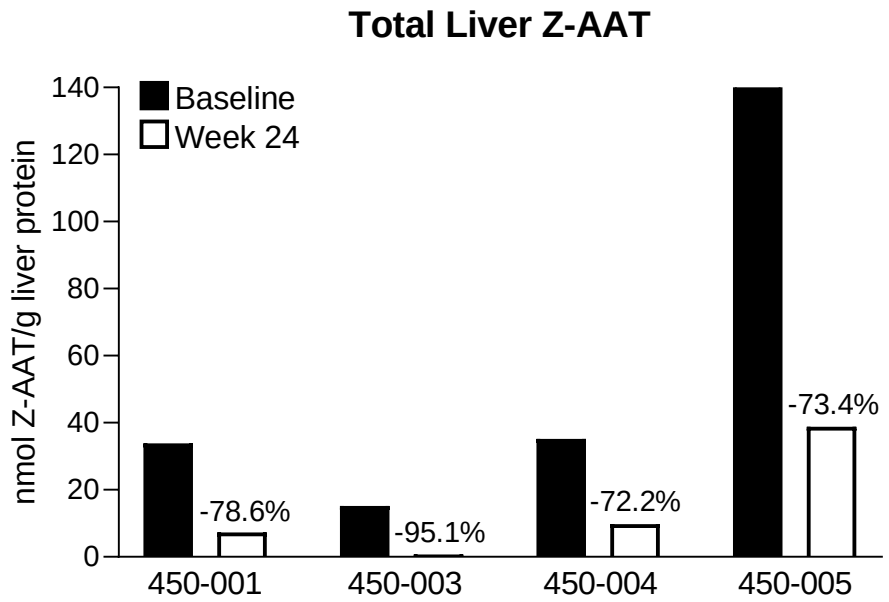
Subject	Baseline	Wk4	Wk16	Wk24
450-001	56.0	51.0	55.0	52.0
450-003	87.0	83.0	84.0	78.0
450-004	106.0	106.0	107.0	108.0
450-005	106.0	98.0	101.0	104.0

Data cut through Week 24

Strnad et al., AASLD 2020

Serum Z-AAT reductions correlates with intra-hepatic reductions





- Week 24 serum Z-AAT reductions of **85.8% to 93.1%**
- Week 24 liver Z-AAT reductions of **72.2% to 95.1%**

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Strnad et al., AASLD 2020

Both Z-AAT monomer and polymer levels reduced

Pharmacodynamic Response at Week 24 Relative to Baseline

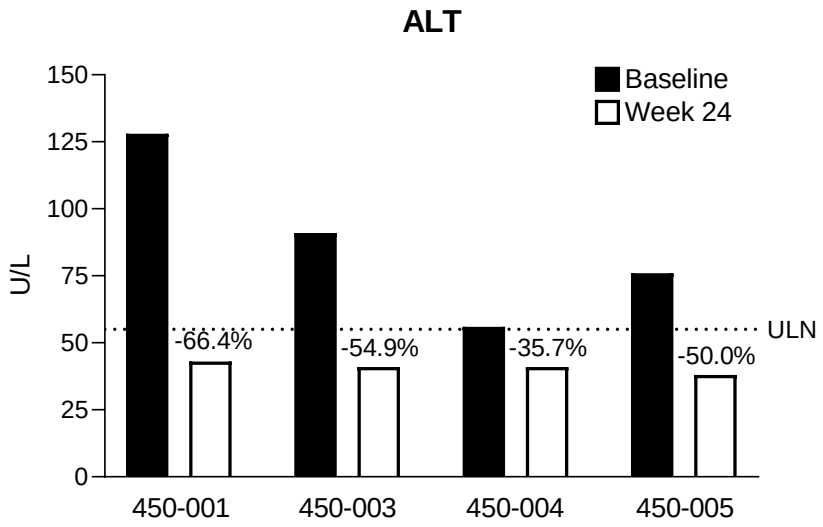
	Subject			
	450-001	450-003	450-004	450-005
Serum Z-AAT, Δ %	-92.3%	-93.1%	-86.7%	-85.8%
Total liver Z-AAT*, baseline	33.9	15.2	35.2	146
Week 24	7.25	0.751	9.77	38.8
Δ %	-78.6%	-95.1%	-72.2%	-73.4%
Soluble liver Z-AAT* baseline	16.8	13.6	33.3	33.5
Week 24	1.71	0.697	4.38	6.3
Δ %	-89.8%	-94.9%	-86.8%	-81.2%
Insoluble liver Z-AAT* baseline	17.1	1.6	1.9	112.5
Week 24	5.54	0.054	5.39	32.5
Δ %	-67.6%	-96.6%	183.7%	-71.1%
ALT, U/L, baseline	128	91	56	76
Week 24	43	41	36	38
Δ %	-66.4%	-54.9%	-35.7%	-50.0%
GGT, U/L, baseline	68	37	97	777
Week 24	39	21	41	347
Δ %	-42.6%	-43.2%	-57.7%	-55.3%
FibroScan®, kPa, baseline	8.9	6.7	12.7	22.5
Week 24	6.6	5.2	12.6	17.8
Δ %	-25.8%	-22.4%	-0.8%	-20.9%
Pro-C3, ng/mL, baseline	38.3	16.4	22.3	23.6
Week 24	18.6	17.3	15.4	15.2
Δ %	-51.4%	5.5%	-30.9%	-35.6%

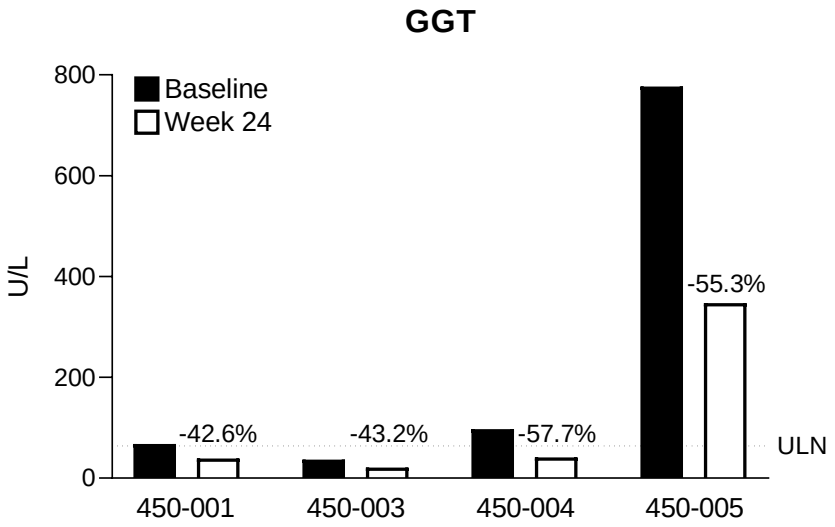
*nmol/g liver protein

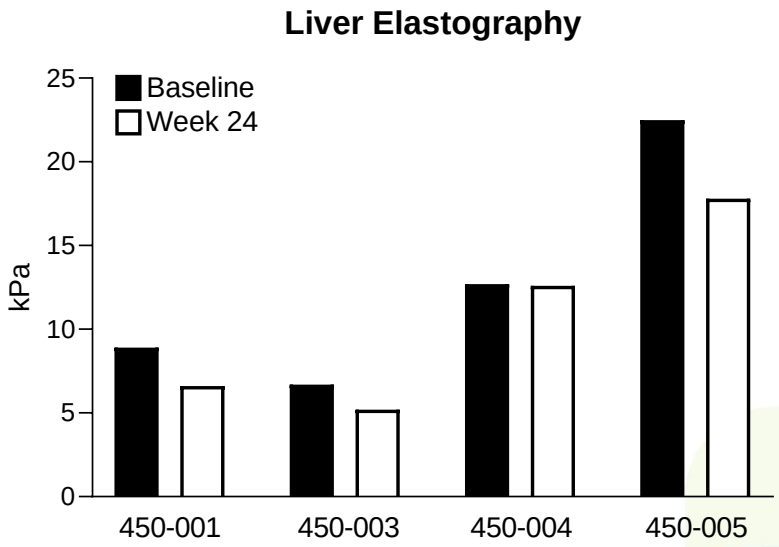
- All subjects demonstrated Week 24 liver monomer Z-AAT reductions ranging from **81.2% to 94.9%**
- 3 of 4 subjects demonstrated Week 24 liver polymer Z-AAT reductions ranging from **71.1% to 96.6%**

Strnad et al., AASLD 2020

Z-AAT reductions correspond to improvements in clinically relevant biomarkers







- Week 24 ALT reductions of **35.7% to 66.4%**
- Week 24 GGT reductions of **42.6% to 57.7%**
- FibroScan reductions of up to **25.8%**

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Strnad et al., AASLD 2020

In conclusion

- ARO-AAT is the first therapeutic to address synthesis of Z-AAT which is the underlying cause of liver disease in alpha-1 antitrypsin deficiency
- ARO-AAT has been well tolerated in healthy volunteers and PiZZ subjects
- In a small cohort of PiZZ patients, ARO-AAT treatment has demonstrated consistent reductions in serum and liver Z-AAT levels
- Reductions in liver Z-AAT levels correspond to improvements in clinically relevant biomarkers including ALT, GGT, FibroScan

Thank you from the Arrowhead team!

Thank you to all the sites, investigators, study coordinators and alpha-1 patients for your commitment to this important clinical research !

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