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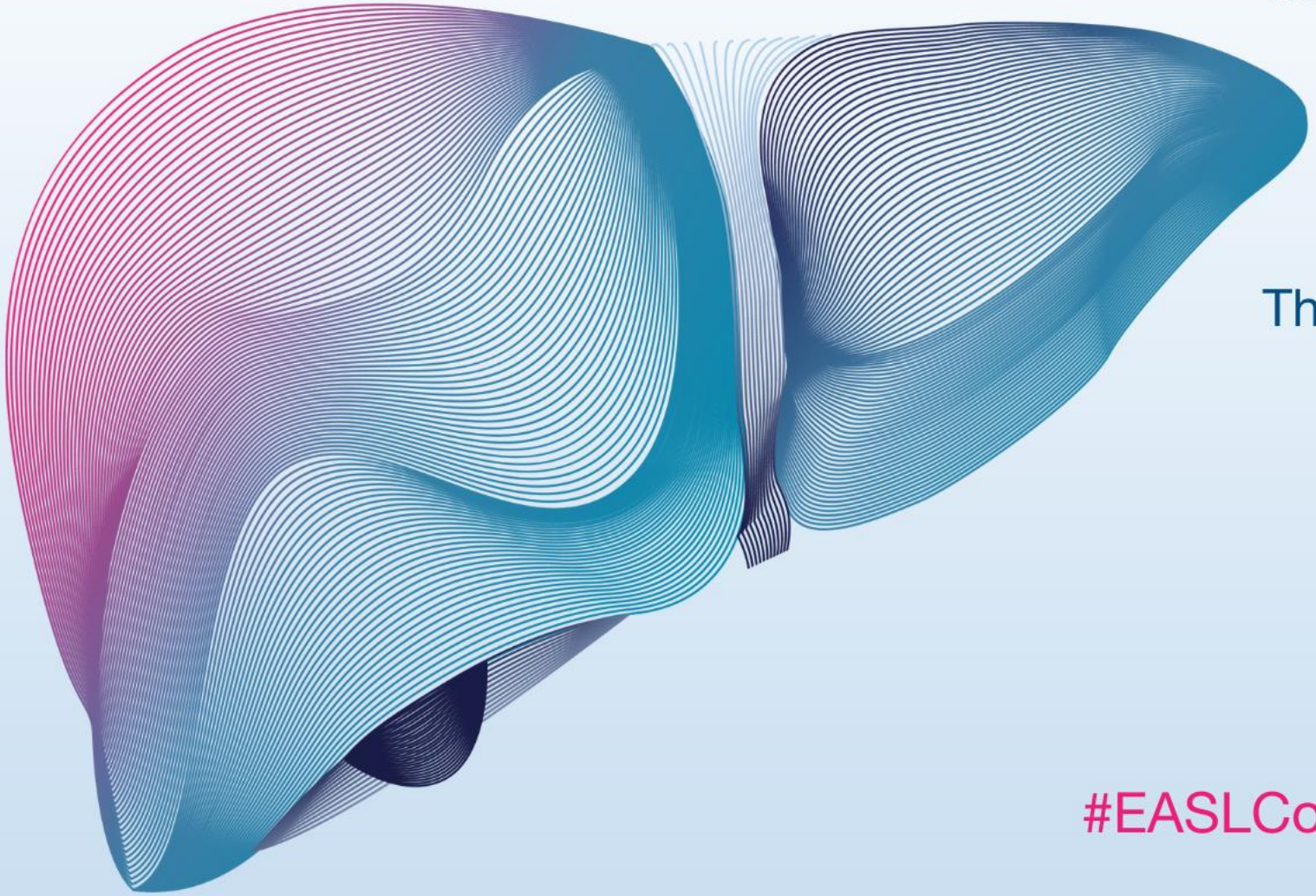

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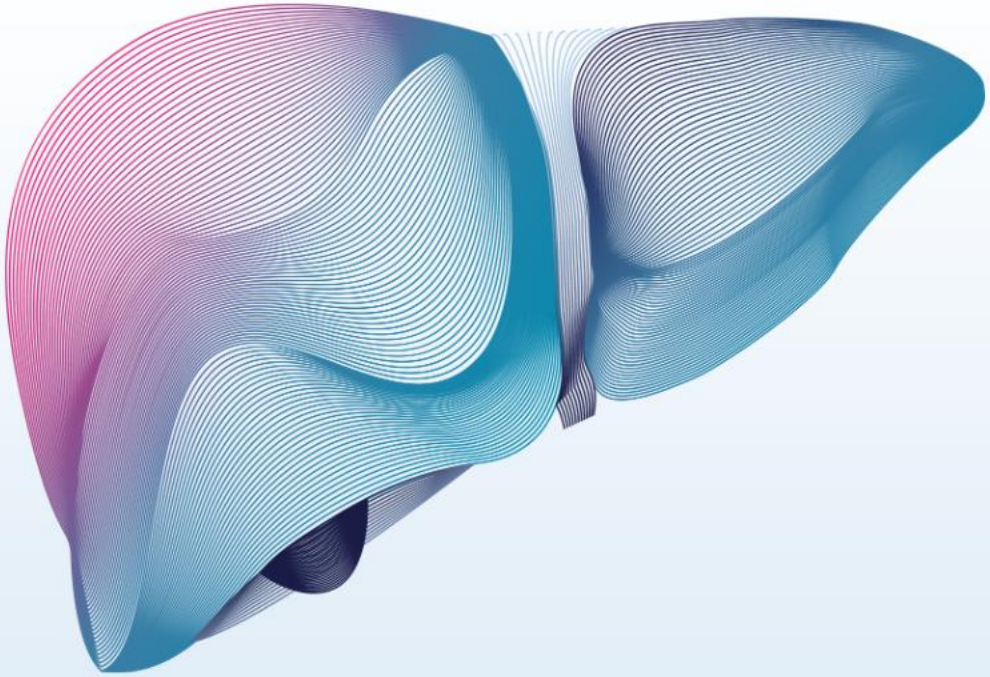

Fazirsiran reduces liver Z-alpha-1 antitrypsin synthesis, decreases globule burden and improves histological measures of liver disease in adults with alpha-1 antitrypsin deficiency: a randomized placebo-controlled phase 2 study

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Disclosures

- V Clark is a consultant and has received research grants from Takeda, Vertex and Novo Nordisk.
- C Strange has received research grants from Arrowhead and Vertex paid to Medical University of South Carolina, and consults for Takeda and Novo Nordisk A/S on AATD liver disease with monies donated to AlphaNet.
- P Strnad received research grants from Arrowhead, CSL Behring, Grifols Inc., Dicerna Pharmaceuticals and Vertex Pharmaceuticals, and consulting fees from CSL Behring, Grifols Inc., and Sanofi. He also has received meeting and travel funds from Biogen, CSL Behring, Gilead Pharmaceuticals and Takeda Pharmaceuticals, and served in leadership or fiduciary roles at the Alpha1 Deutschland and Alpha-1 Foundation.
- A Sanchez, AG Corsico and N Kappe have no financial disclosures.
- JM Vierling has no conflicts of interest or disclosures related to this topic.
- P Kwo is a consultant and/or stockholder for Abbvie, Aligos, Ambys, Antios, Drug Farm, Durect, Eisai, Enanta, Generon, Gilead, HepQuant, Inventiva, Mallinckrodt, Mirum and Surrozen, and has received research grants from Altimmune, Arrowhead, Assembly, Bristol-Myers Squibb, Eiger, Gilead, Novo Nordisk, Target Registries and Ultragenyx.
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- M Gray is a consultant for NovoNordisk, Takeda Pharmaceuticals and Theratechnologies.
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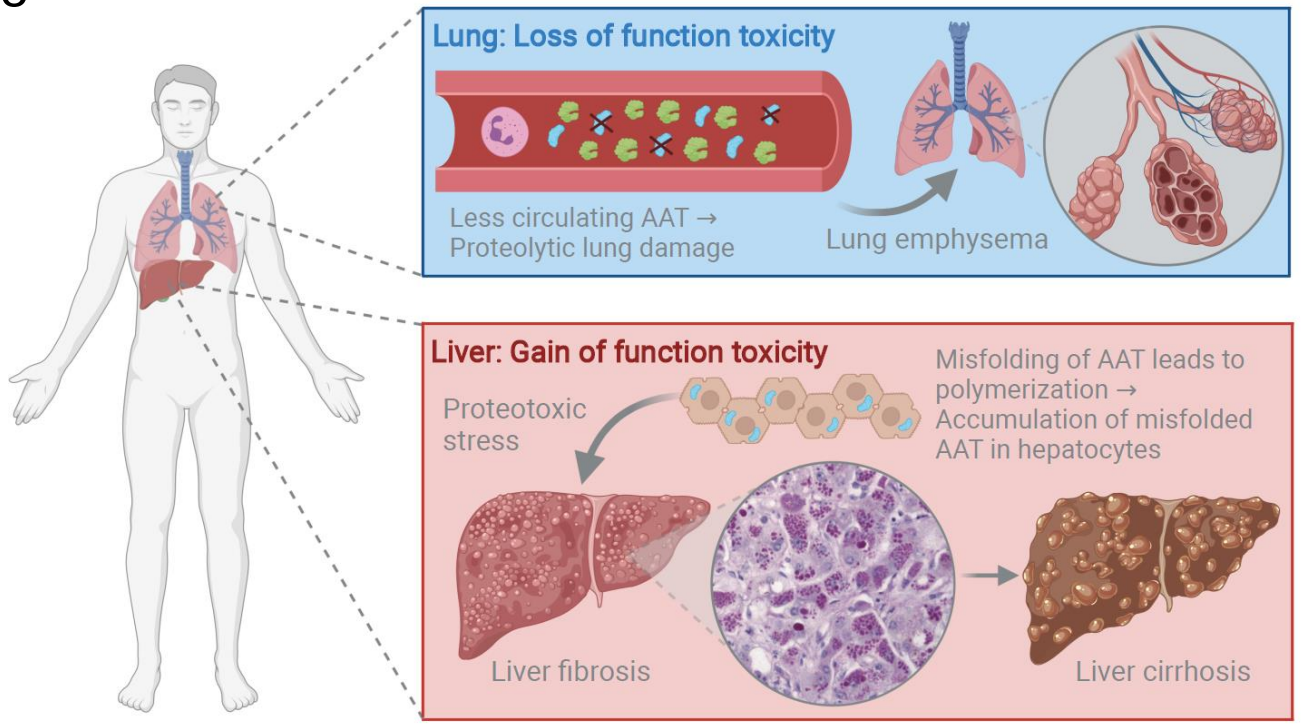
- R Vuppalanchi had received institutional funding from Arrowhead to conduct this study.
- M Brantly is a consultant for Takeda and Vertex.
- T Chang, T Schluep, R Zhou, J Hamilton and J San Martin are employees and stockholders of Arrowhead Pharmaceuticals, Inc.
- R Loomba serves as a consultant to Aardvark Therapeutics, Altimmune, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Gilead, Glympse Bio, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institution received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes, Takeda and Terns Pharmaceuticals. Co-founder of LipoNexus Inc.

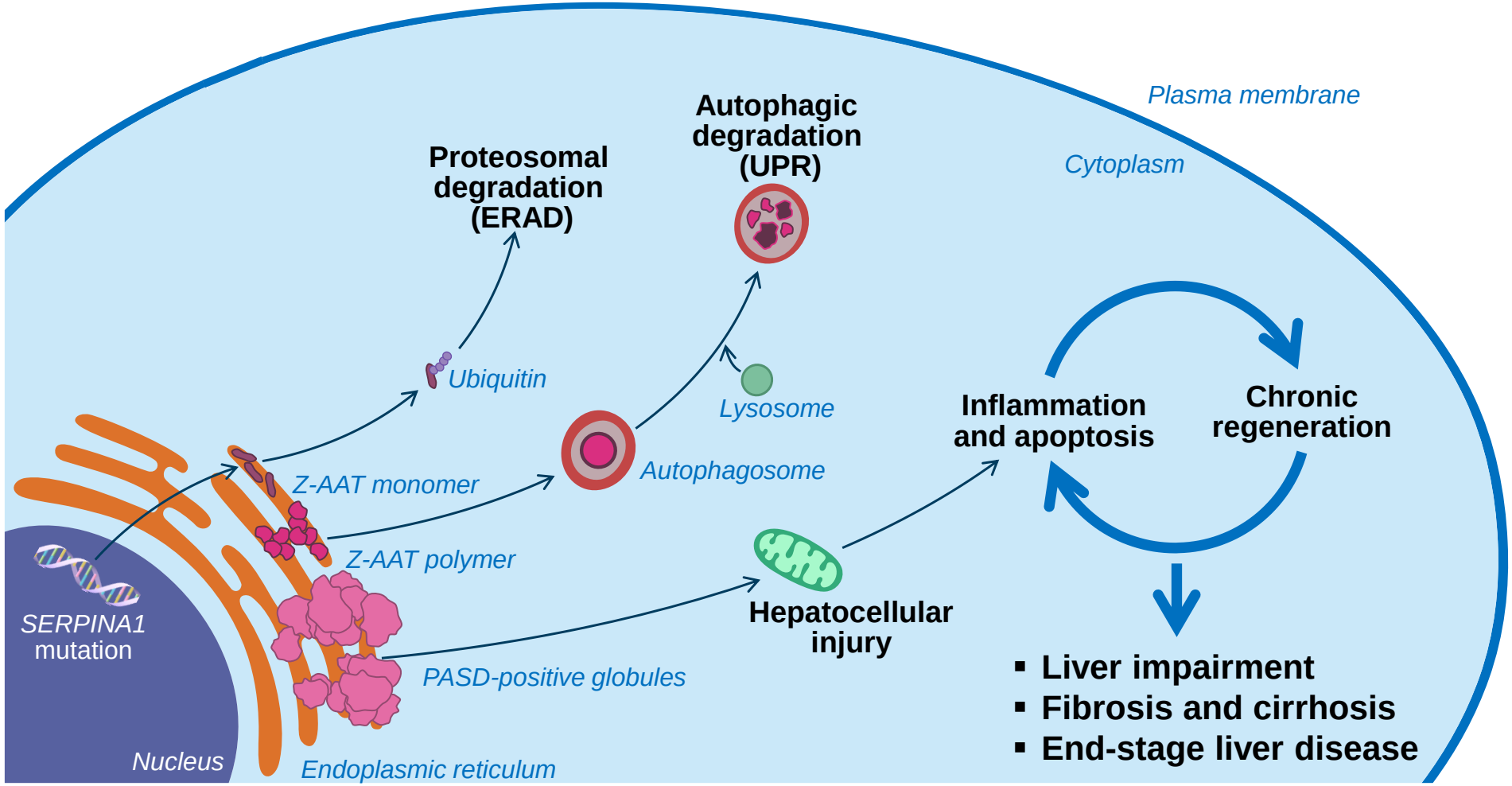
Background

- Alpha-1 antitrypsin (AAT) deficiency is caused by mutations in the *SERPINA1* gene leading to loss-of-function pulmonary disease and gain of-function liver disease.[1]
- 95% of severe cases are due to homozygous substitution of a single amino acid, Glu342Lys (Pi*ZZ genotype leading to production of Z-AAT).[1]
- Pi*ZZ homozygosity occurs in ~1 in 2500 to 3500 Caucasians.[1,2]
- A third of adults with Pi*ZZ may have clinically significant liver fibrosis.[2,3]



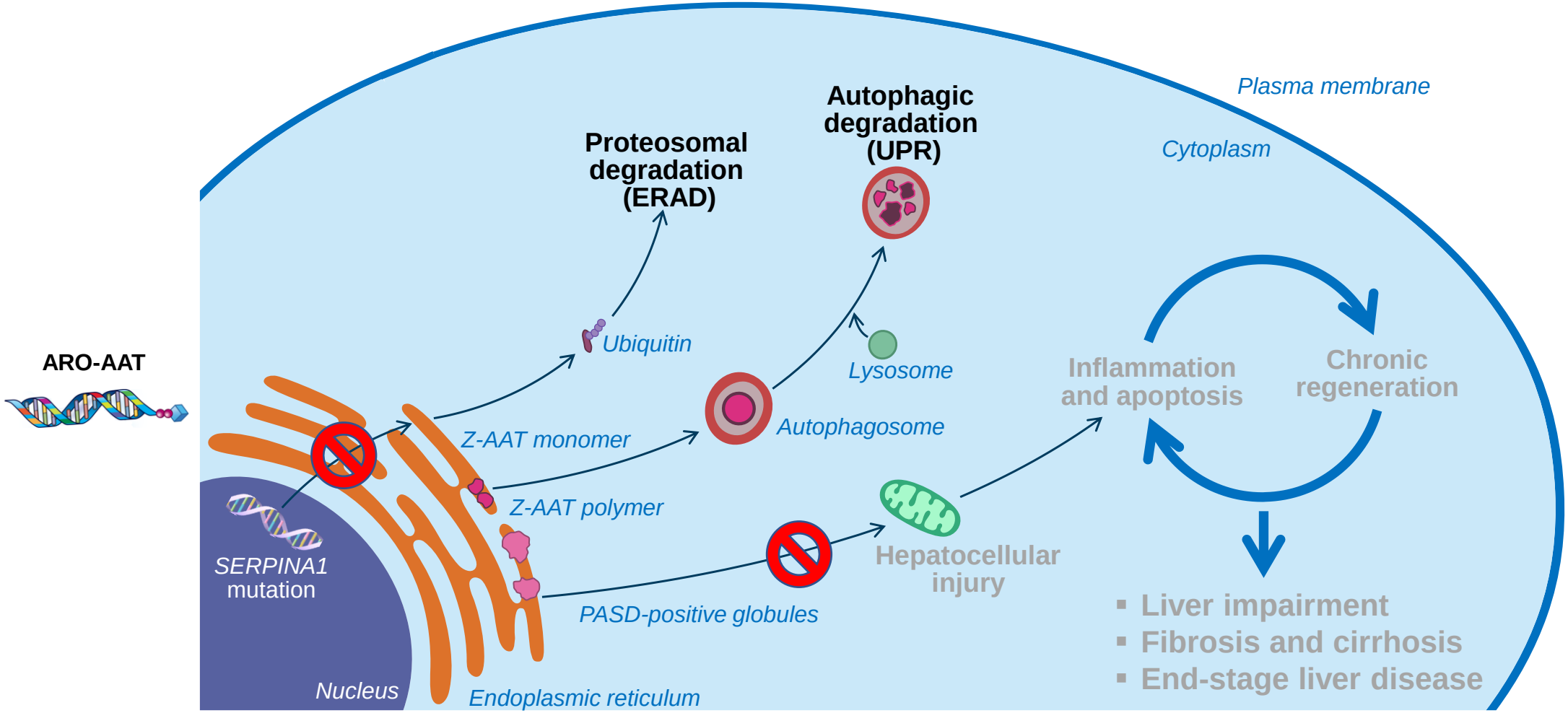
1. Strnad P, *et al. N Engl J Med* 2020;382:1443–55; 2. Alpha-1 Foundation: https://www.alpha1.org/Alpha1/wp-content/uploads/2019/09/HealthcareProvidersBrochure-1.pdf; 3. Clark VC, *et al. J Hepatol* 2018;69:1357–64.

Accumulation of hepatotoxic Z-AAT protein causes liver disease in alpha-1 antitrypsin deficiency (AATD)



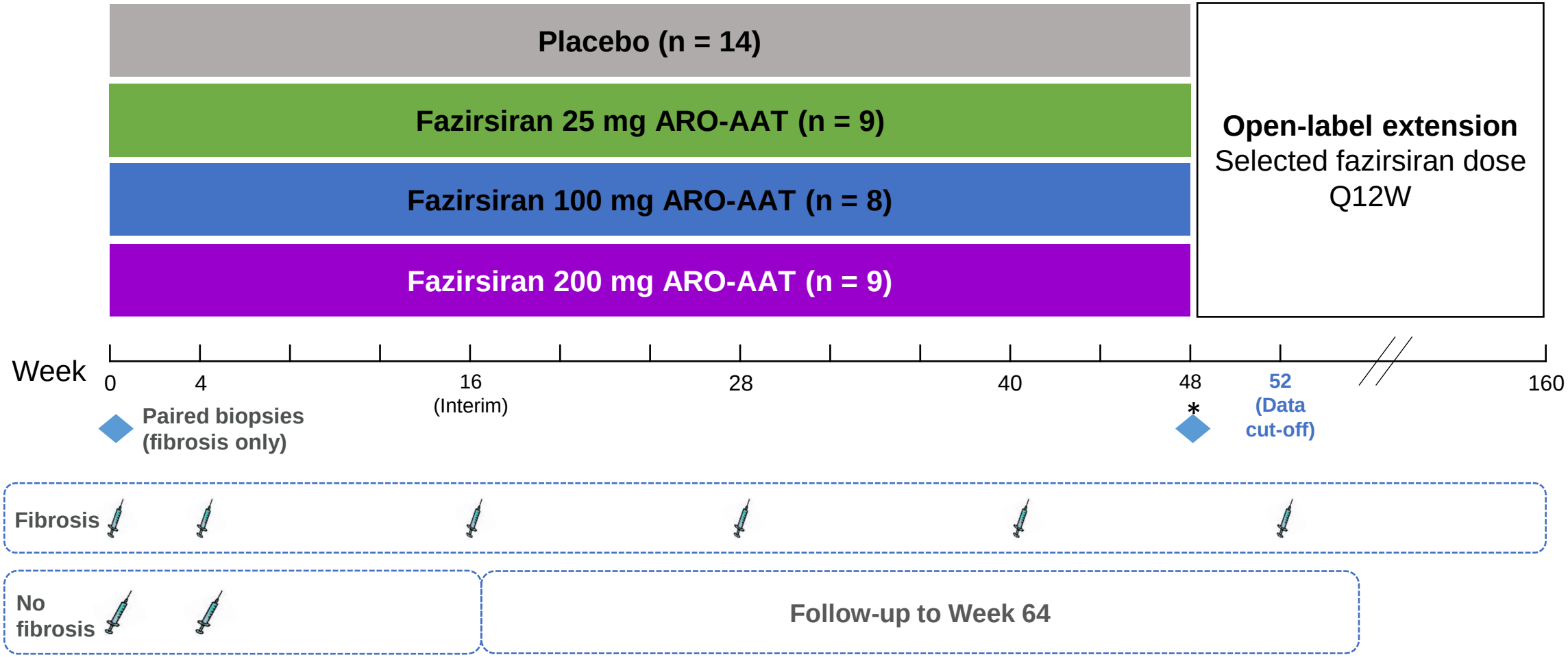
AAT, alpha-1 antitrypsin; ERAD, endoplasmic-reticulum-associated protein degradation; PASD, periodic acid Schiff plus diastase; UPR, unfolded protein response

Fazirsiran (ARO-AAT) is an RNA interference therapeutic that inhibits Z-AAT expression to allow clearance of polymers and globules and improvement in liver health



AAT, alpha-1 antitrypsin; ERAD, endoplasmic-reticulum-associated protein degradation; PASD, periodic acid Schiff plus diastase; UPR, unfolded protein response

AROAAT-2001 (SEQUOIA) study design



*Patients with fibrosis at screening will have a post-dose liver biopsy performed at Week 48. If a patient is beyond Week 48 at the time of IRB/EC approval of Protocol v4.0, then the post-dose biopsy will occur at Week 72 or Week 96.
EC, Ethics Committee; IRB, Institutional Review Board; Q12W, every 12 weeks

Endpoints and analyses

Primary endpoint

- Serum Z-AAT levels at Week 16

Secondary endpoints

- Liver Z-AAT levels
- Serum liver enzyme levels
- METAVIR fibrosis stage*
- Treatment-emergent AEs, SAEs

Other histological endpoints*

- Total PASD-positive globules (score 0–9)
- Portal inflammation (score 0–3)
- Interface hepatitis (score 0–3)
- Hepatocyte cell death (score 0–2)
- Lobular inflammation (score 0–3)

Statistics

- Primary efficacy analysis
  - Mixed model repeated measures was used to analyze the percent change of serum Z-AAT levels from baseline to Week 16
  - The difference in least-squares mean percent change from baseline (with 95% confidence intervals) at Week 16 was estimated between each pair of active dose group and placebo

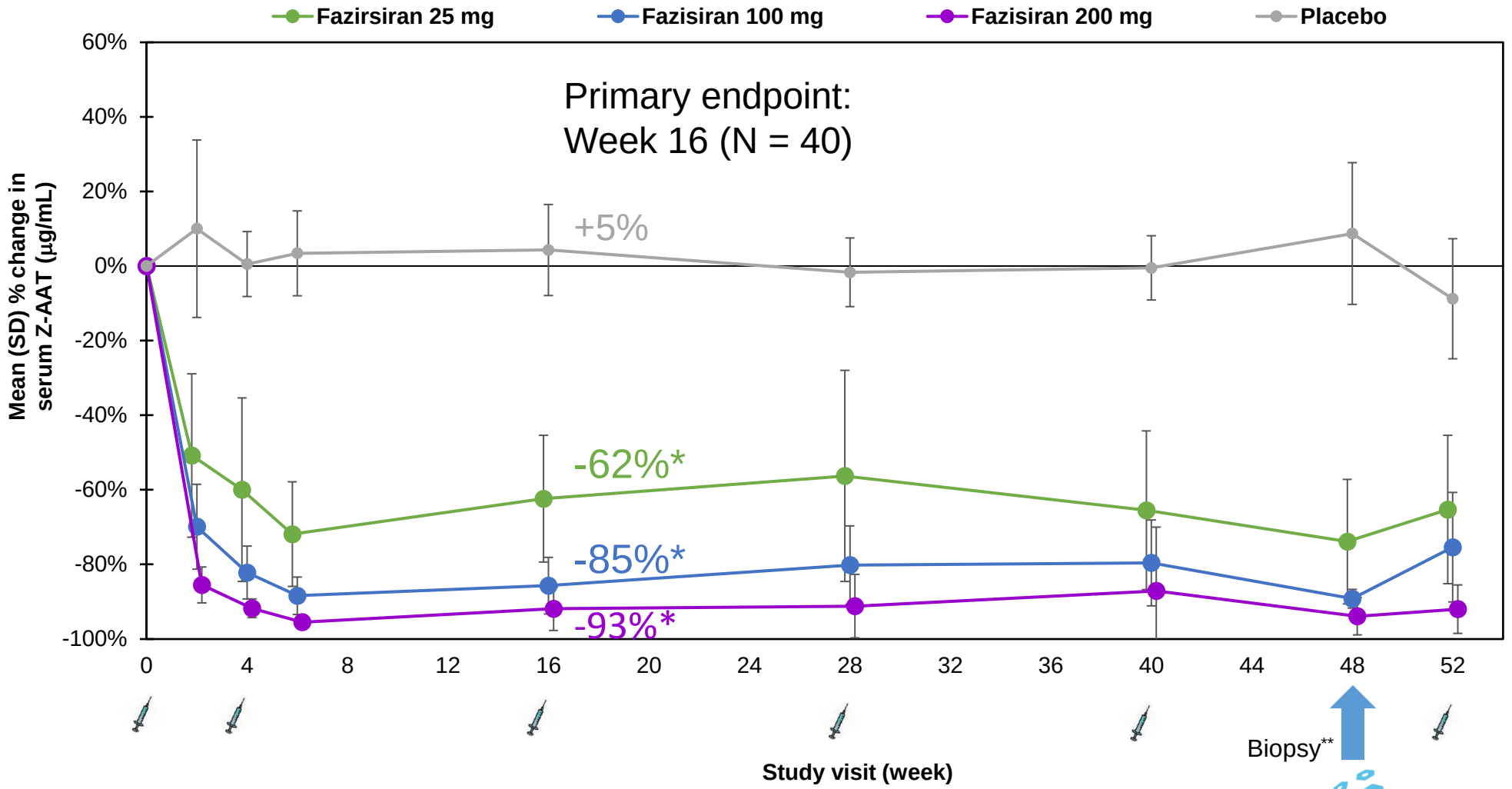
*All histological endpoints were centrally read and adjudicated by three pathologists.
AE, adverse event; PASD, periodic acid Schiff plus diastase; SAE, serious adverse event

Baseline characteristics

	Placebo (n = 14)	Fazirsiran 25 mg (n = 9)	Fazirsiran 100 mg (n = 8)	Fazirsiran 200 mg (n = 9)
Mean age (SD), years Min, Max	57 (9) 45, 72	53 (18) 20, 72	48 (12) 28, 64	52 (9) 37, 64
Male, n (%)	9 (64%)	4 (44%)	2 (25%)	3 (33%)
Mean weight (SD), kg	94 (20)	84 (18)	87 (27)	81 (19)
Mean BMI (SD), kg/m^2	29.9 (7.2)	26.8 (5.5)	30.1 (8.1)	27.7 (6.8)
Fibrosis at screening (locally read) No Yes	 5 (36%) 9 (64%)	 5 (56%) 4 (44%)	 3 (38%) 5 (63%)	 2 (22%) 7 (78%)
Adjudicated fibrosis stage (centrally read) F0 F1 F2 F3 F4	N = 8/9 1 (11%) 3 (33%) 5 (56%) 0 (0%) 0 (0%)	N = 3/4 1 (25%) 0 (0%) 3 (75%) 0 (0%) 0 (0%)	N = 5/5 0 (0%) 3 (60%) 1 (20%) 1 (20%) 0 (0%)	N = 6/7 1 (14%) 3 (43%) 2 (29%) 1 (14%) 0 (0%)
Mean FEV_1 % predicted (SD) – post bronchodilation	91 (11)	96 (12)	98 (6)	95 (18)
On AAT augmentation therapy	4 (29%)	3 (33%)	0 (0%)	3 (33%)

AAT, alpha-1 antitrypsin; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; SD, standard deviation

Fazirsiran reduced serum Z-AAT concentration in a dose-dependent manner (n = 40 to Week 16, n = 25 with fibrosis to Week 52)



Week 48 (n = 25)

+9%

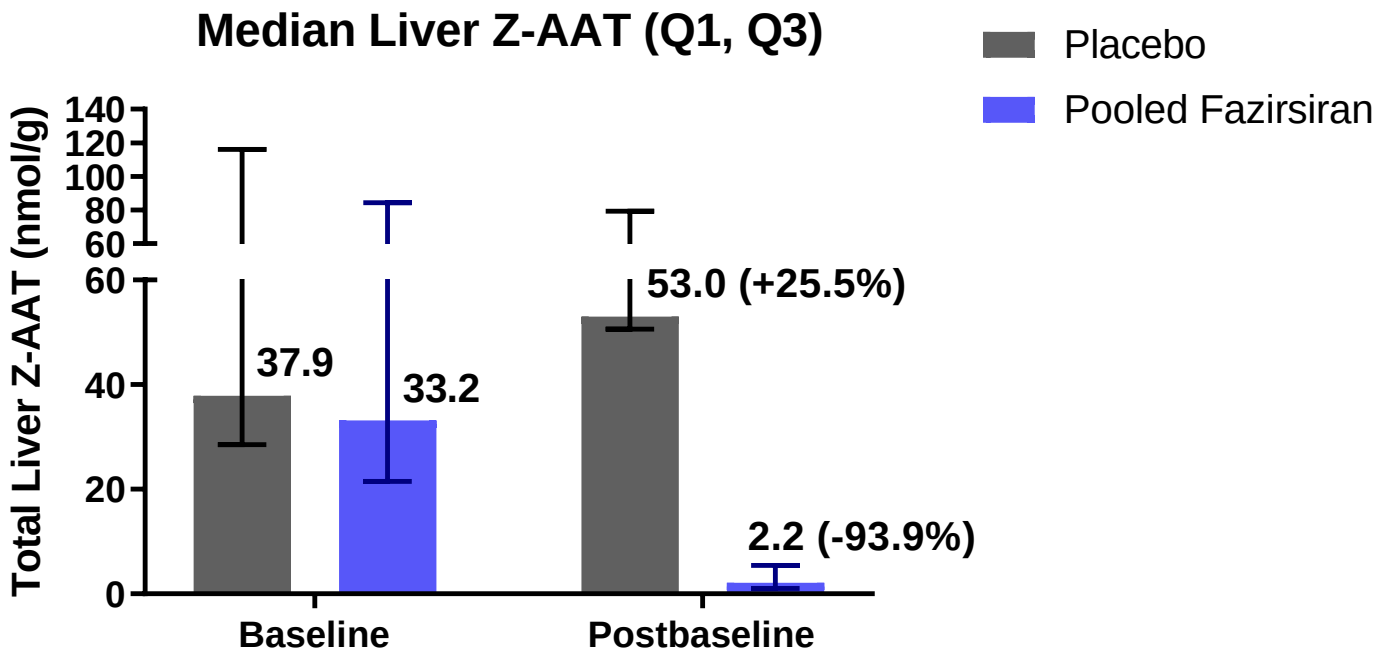
-74%

-89%

-94%

*$p < 0.001$ vs placebo ** Post-dose biopsies were collected at week 48, 72, or 96

Fazirsiran significantly reduced liver Z-AAT

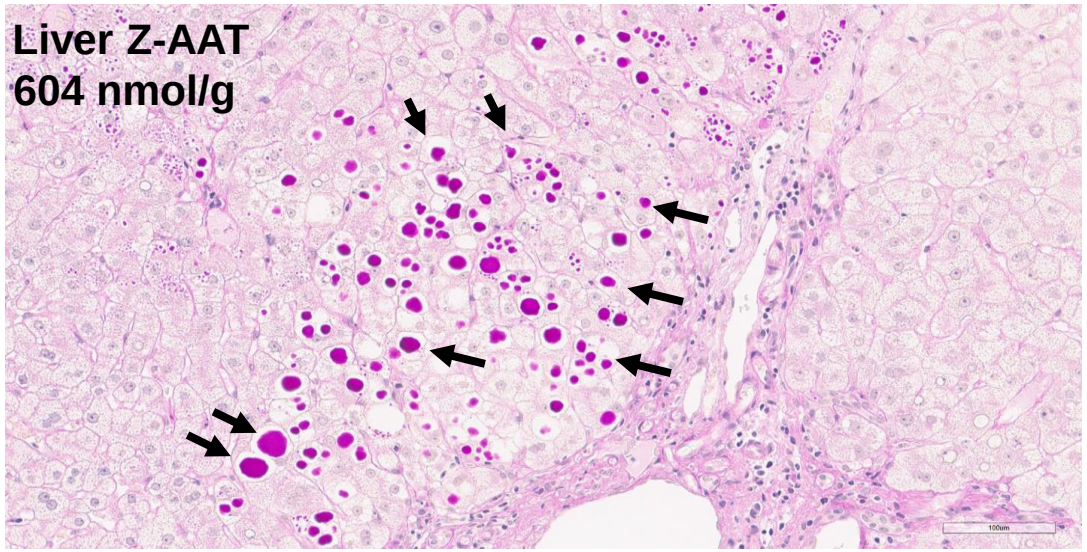


Liver Z-AAT	Placebo	Fazirsiran 25 mg	Fazirsiran 100 mg	Fazirsiran 200 mg
Median (Q1, Q3) baseline, nmol/g protein	37.9 (28.5, 116.2)	58.7 (41.8, 169.4)	319.4 (24.2, 628.0)	22.4 (18.7, 33.2)
Least-squares mean % difference (95% CI) vs placebo at post-dose biopsy		**-135%** (-224%, -46%) ***p* = 0.0054**	**-116%** (-212%, -20%) ***p* = 0.0203**	**-141%** (-210%, -72.7%) ***p* = 0.0004**

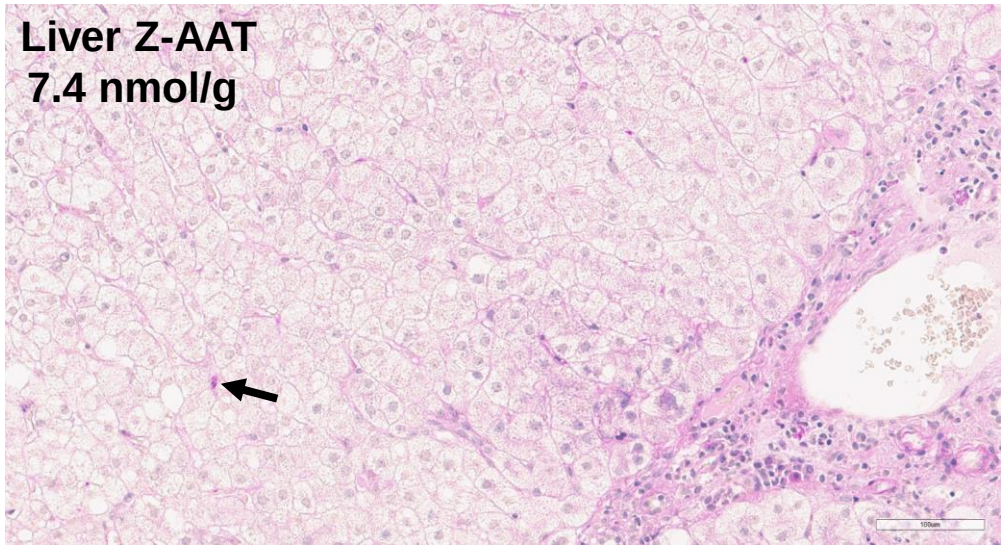
AAT, alpha-1 antitrypsin; CI, confidence interval

Fazirsiran consistently reduced hepatic globule burden

Screening



Post-dose biopsy



Mean (SD) PASD-positive globule burden

	Placebo (n = 9)	Pooled fazirsiran (n = 16)
Baseline	6.9 (1.76)	5.9 (2.24)
Post-baseline	6.6 (2.13)	2.3 (2.24)
Median % change	**-3%**	**-68%**

Patients with change in PASD-positive globule burden

PASD-positive globule burden	Placebo (n = 9)	Pooled fazirsiran (n = 16)
≥ 1-point improvement*	4/9 (44%)	**16/16 (100%)**
No change	1/9 (11%)	0/16 (0%)
≥ 1-point worsening**	4/9 (44%)	**0/14 (0%)**

*A baseline minimum severity score of 0, as assessed by the central read, was ineligible for assessment of improvement.
**A baseline maximum severity score, as assessed by the central read, was ineligible for assessment of worsening.

Fazirsiran treatment reduced histological signs of hepatic inflammation

	Placebo (n = 9)	Pooled fazirsiran (n = 16)
Portal inflammation (score 0–3)		
≥ 1-point improvement*	**0/8 (0%)**	**5/12 (42%)**
No change	5/9 (56%)	10/16 (63%)
≥ 1-point worsening**	4/9 (44%)	1/15 (7%)
Interface hepatitis (score 0–3)		
≥ 1-point improvement*	**0/8 (0%)**	**8/12 (67%)**
No change	7/9 (78%)	7/16 (44%)
≥ 1-point worsening**	2/9 (22%)	1/15 (7%)
Hepatocyte cell death (score 0–2)		
≥ 1-point improvement*	3/5 (60%)	7/11 (64%)
No change	4/9 (44%)	7/16 (44%)
≥ 1-point worsening**	2/9 (22%)	2/13 (15%)
Lobular inflammation (score 0–3)		
≥ 1-point improvement*	2/9 (22%)	2/14 (14%)
No change	7/9 (78%)	12/16 (75%)
≥ 1-point worsening**	0/9 (0%)	2/16 (13%)

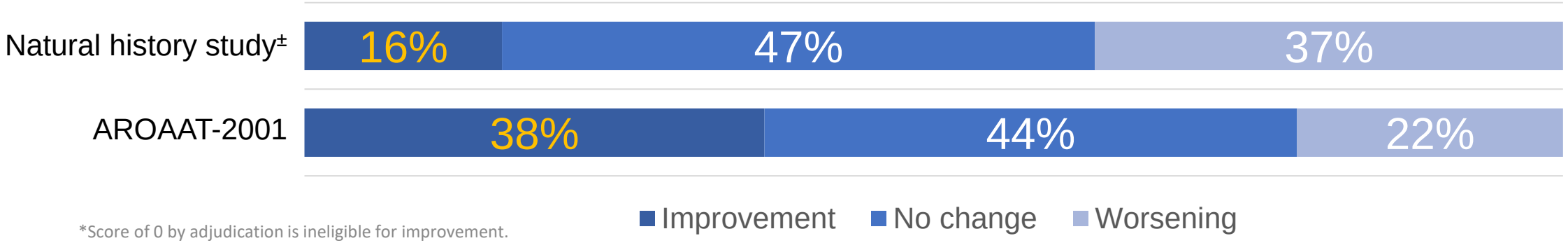
- Median serum liver enzymes (ALT/AST/GGT) were within the normal range at baseline and remained stable throughout the study across all groups.

*A baseline minimum severity score of 0, as assessed by the central read, was ineligible for assessment of improvement.
**A baseline maximum severity score, as assessed by the central read, was ineligible for assessment of worsening.

Of fazirsiran-treated participants, 50% showed improvements in liver fibrosis

METAVIR fibrosis	Placebo (n = 9)	Pooled fazirsiran (n = 16)
≥ 1-point improvement*	3/8 (38%)	**7/14 (50%)**
No change	4/9 (44%)	5/16 (31%)
≥ 1-point worsening**	2/9 (22%)	4/16 (25%)

- Rate of improvement in fibrosis in the placebo group was almost double that expected based on results from a large 3-year natural history study (38% vs 16%)



*Score of 0 by adjudication is ineligible for improvement.
**Score of 4 (fibrosis) by adjudication is ineligible for worsening.
± Clark, V. C., Marek III, G., Liu Liu, X., Miao, G., Lou, X.-Y. and Brantly, M. 2021. Progression of fibrosis in alpha-1 antitrypsin deficiency: a prospective liver biopsy study. Abstract No. 35. Hepatology, 74(1), 25A.

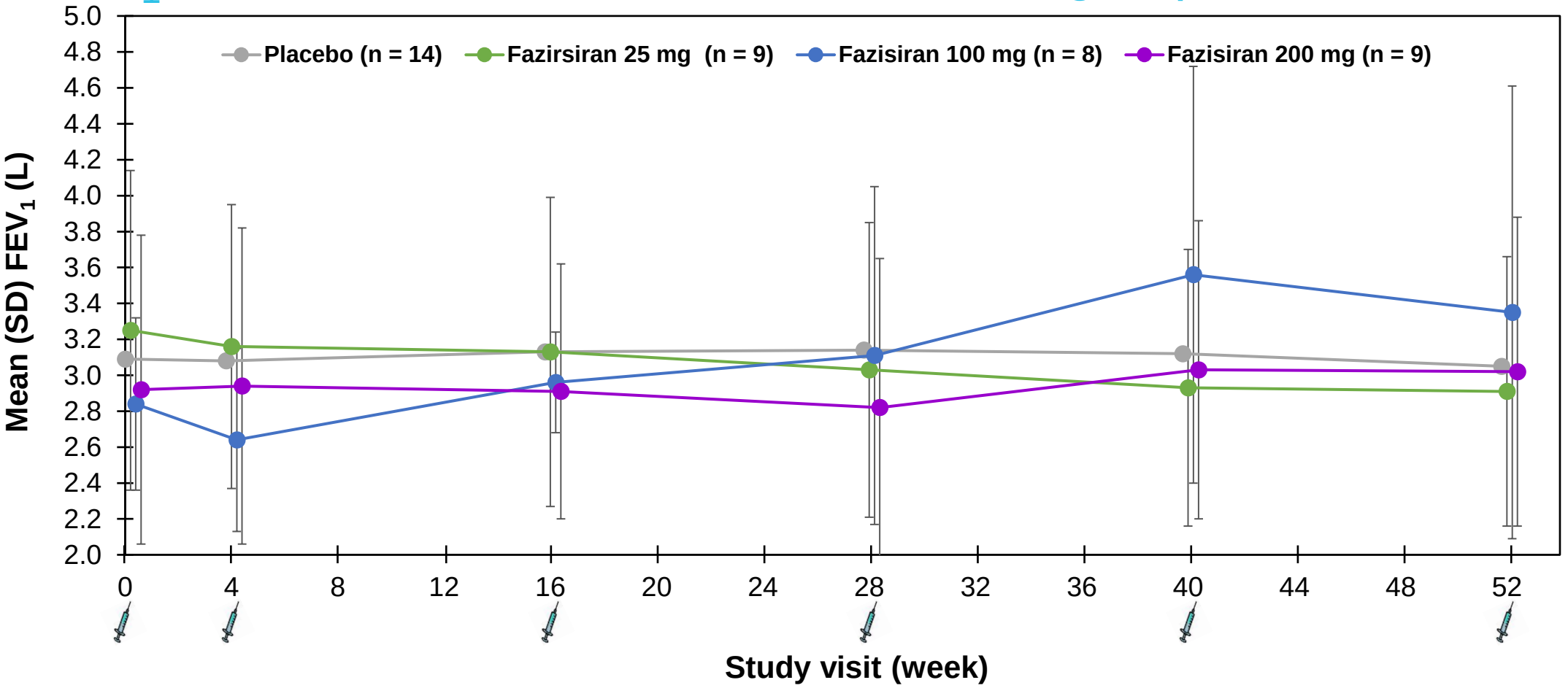
Summary of safety and adverse events

Subject Incidence, n (%)	Placebo (n = 14)	Fazirsiran 25 mg (n = 9)	Fazirsiran 100 mg (n = 8)	Fazirsiran 200 mg (n = 9)
TEAEs	13 (92.9%)	9 (100%)	8 (100%)	9 (100%)
TEAEs in 4 or more subjects				
COVID-19	2 (14%)	0 (0%)	2 (25%)	6 (67%)
Headache	3 (21%)	4 (44%)	1 (13%)	2 (22%)
Procedural pain	3 (21%)	1 (11%)	0 (0%)	4 (44%)
Arthralgia	3 (21%)	2 (22%)	2 (25%)	0 (0%)
Diarrhea	2 (14%)	2 (22%)	1 (13%)	0 (0%)
Nausea	3 (21%)	1 (11%)	0 (0%)	1 (11%)
Back pain	0 (0%)	1 (11%)	1 (13%)	2 (22%)
Fatigue	2 (14%)	1 (11%)	1 (13%)	0 (0%)
Treatment-related TEAEs	8 (57%)	2 (22%)	4 (50%)	4 (44%)
Serious TEAEs	3 (21%)	0 (0%)	0 (0%)	2 (22%)
TEAEs leading to drug discontinuation, dose interruptions or study withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TEAEs causing deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- No TEAE-related study drug discontinuation, dose interruptions or premature study withdrawals
- Two SAEs in the fazirsiran 200 mg group: both infective exacerbations of bronchiectasis in 2 participants with history of pulmonary disease who were receiving AATD augmentation therapy
- SAEs in placebo group
  - 1 patient with acute pancreatitis, influenza and staphylococcal wound infection
  - 1 patient with decreased pulmonary function test and hypertensive crisis who was on AAT augmentation therapy
  - 1 patient with presyncope

AATD, alpha-1 antitrypsin deficiency; SAE, serious adverse event; TEAE, treatment-emergent adverse event

FEV_1 remained stable over time across all groups



- Pulmonary function test results (FEV_1 and DLCO) for both fazirsiran and placebo were stable over time with no apparent dose-dependent effects

DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s; SD, standard deviation

Summary and conclusions

- Fazirsiran reduced serum Z-AAT in a dose dependent manner and was well tolerated
- Liver concentrations of Z-AAT were reduced compared to placebo at all dose levels
- PASD-positive globule burden, portal inflammation, interface hepatitis, and fibrosis were improved
- This is the second phase 2 study in which 50% of participants showed an improvement in liver fibrosis[1]
- Improvement in liver fibrosis at one year in the placebo group highlights challenges with this end point in a small sample size
- These results are consistent with findings from an open-label, phase 2 study (AROAAT-2002)[1] and support further development of fazirsiran in larger phase 3 studies

1. Strnad P *et al*., Fazirsiran for liver disease associated with alpha1-antitrypsin deficiency. *N Engl J Med* 2022; 387:514–24.

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