Reduction of Intra-hepatic Z-AAT Synthesis by Fazirsiran Decreases Globule Burden and Improves Histological Measures of Liver Disease in Adults with Alpha-1 Antitrypsin Deficiency

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ORIGINAL ARTICLE

Fazirsiran for Liver Disease Associated with Alpha$_1$-Antitrypsin Deficiency

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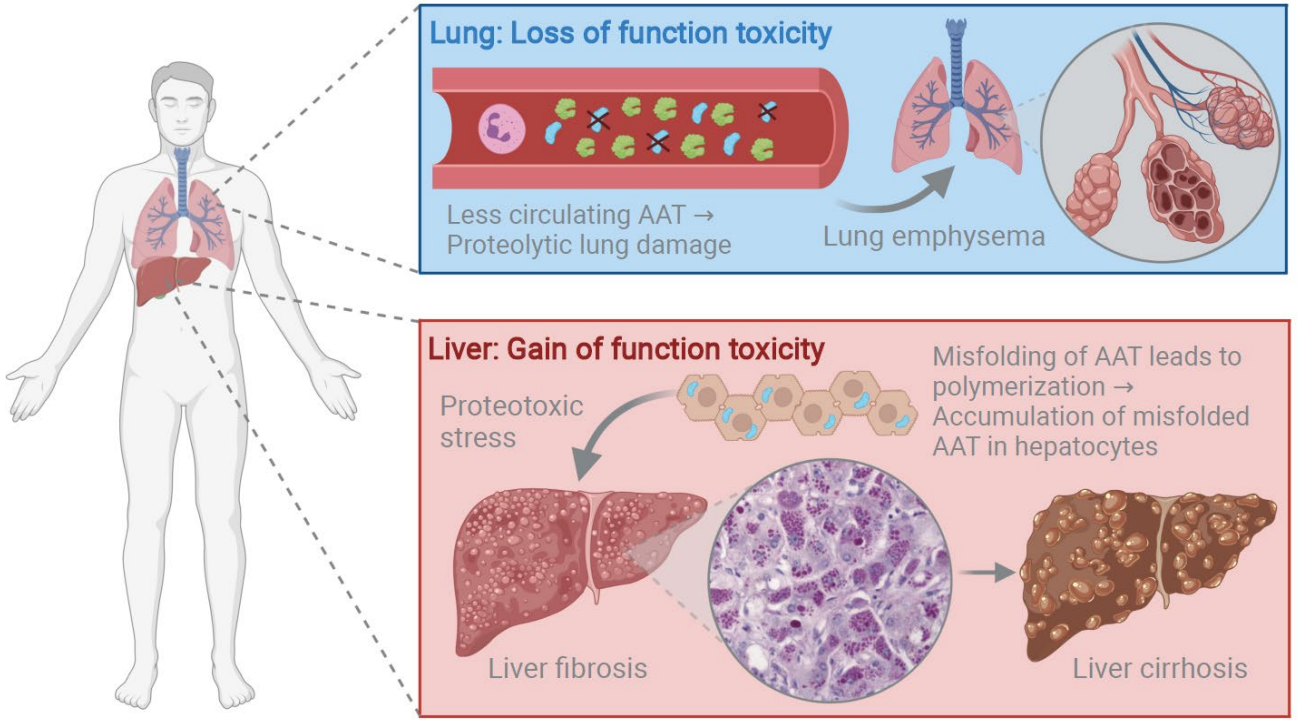
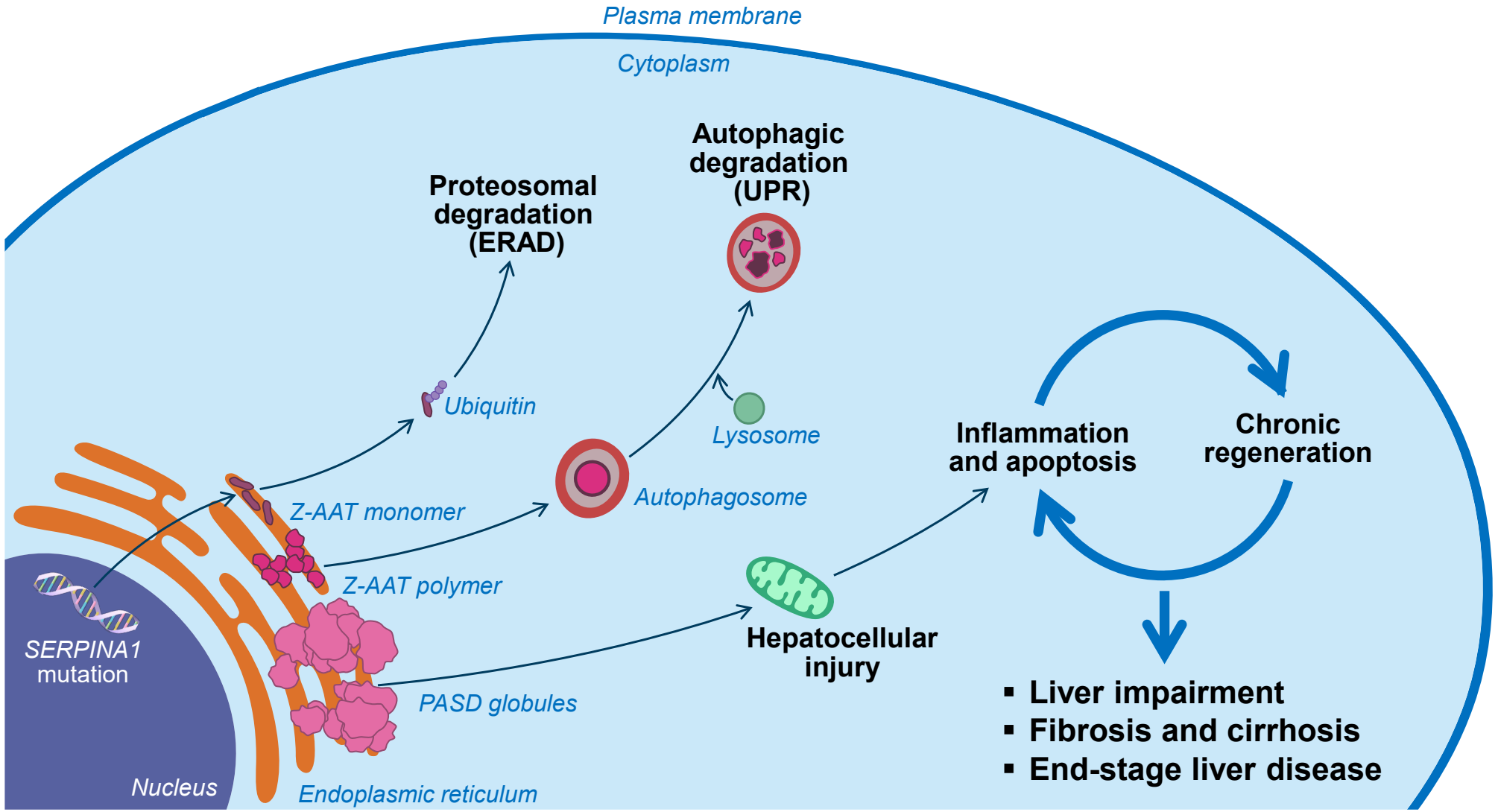
Background

- 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 (PIZZ).[1]
- PiZZ homozygosity occurs in ~1 in 2,500 to 3,500 of Caucasians.[1,2]
- A third of adults with PIZZ may have clinically significant liver fibrosis.[2,3]

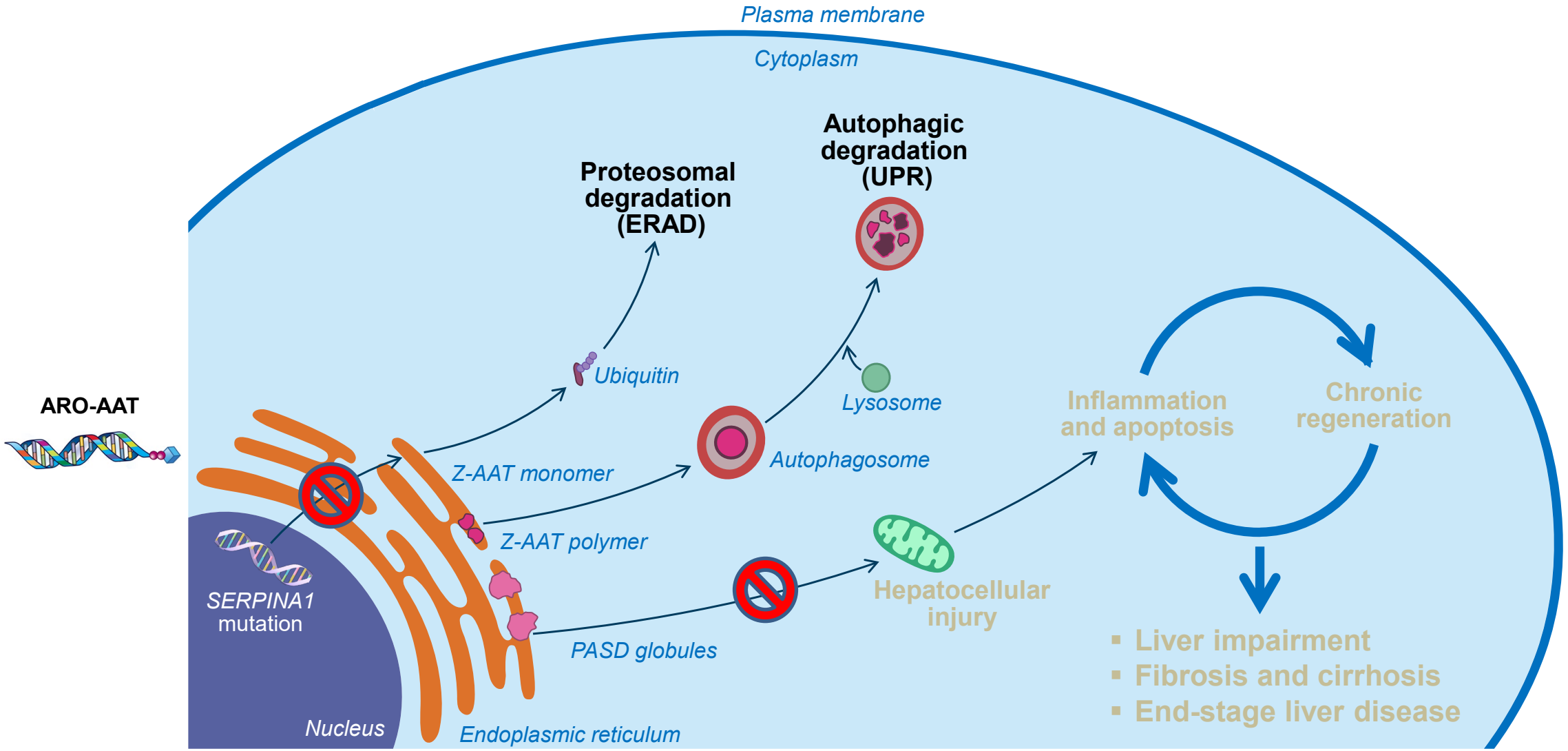


[1] Strnad P, et al. N Engl J Med 2020;382:1443-55; [2] Alpha-1 Foundation: https://www.alpha1.org/Alpha1/wp-content/uploads/2019/09/HealthcareProvidersBrochure-1.pdf; 3 Clark VC, et al. J Hepatol 2018;69:1357-64.

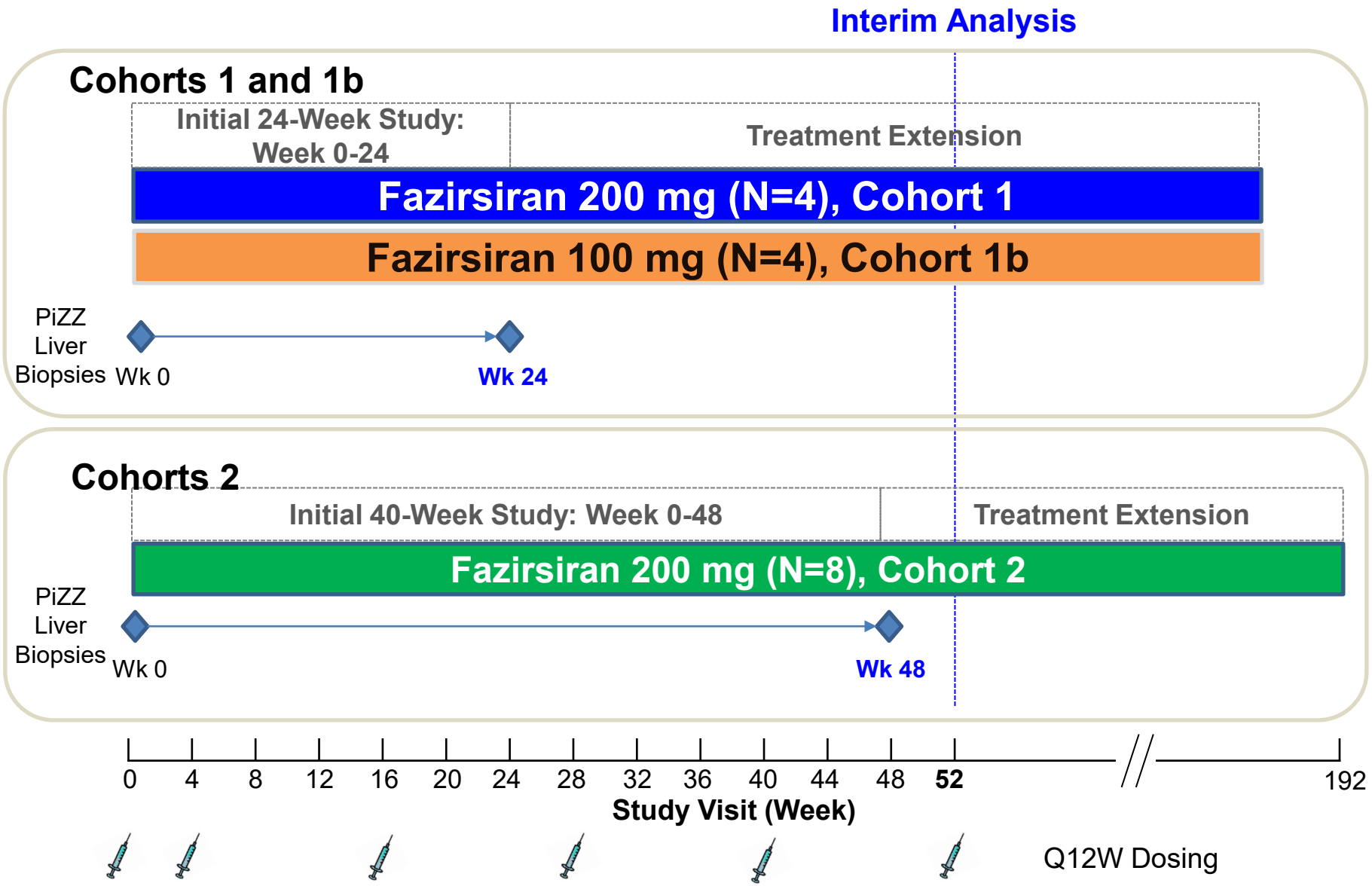
Accumulation of Hepatotoxic Z-AAT Protein Causes Liver Disease in Alpha-1 Antitrypsin Deficiency (AATD)



Fazirsiran (ARO-AAT) Inhibits Z-AAT Expression to Allow Clearance of Polymers and Globules and Improvement in Liver Health



AROAAT-2002 Study Design



Interim Analysis

- Laboratory: up to 52 wks
- Biopsy: 24 or 48 wks
- Safety: up to 1.5 years

Endpoints

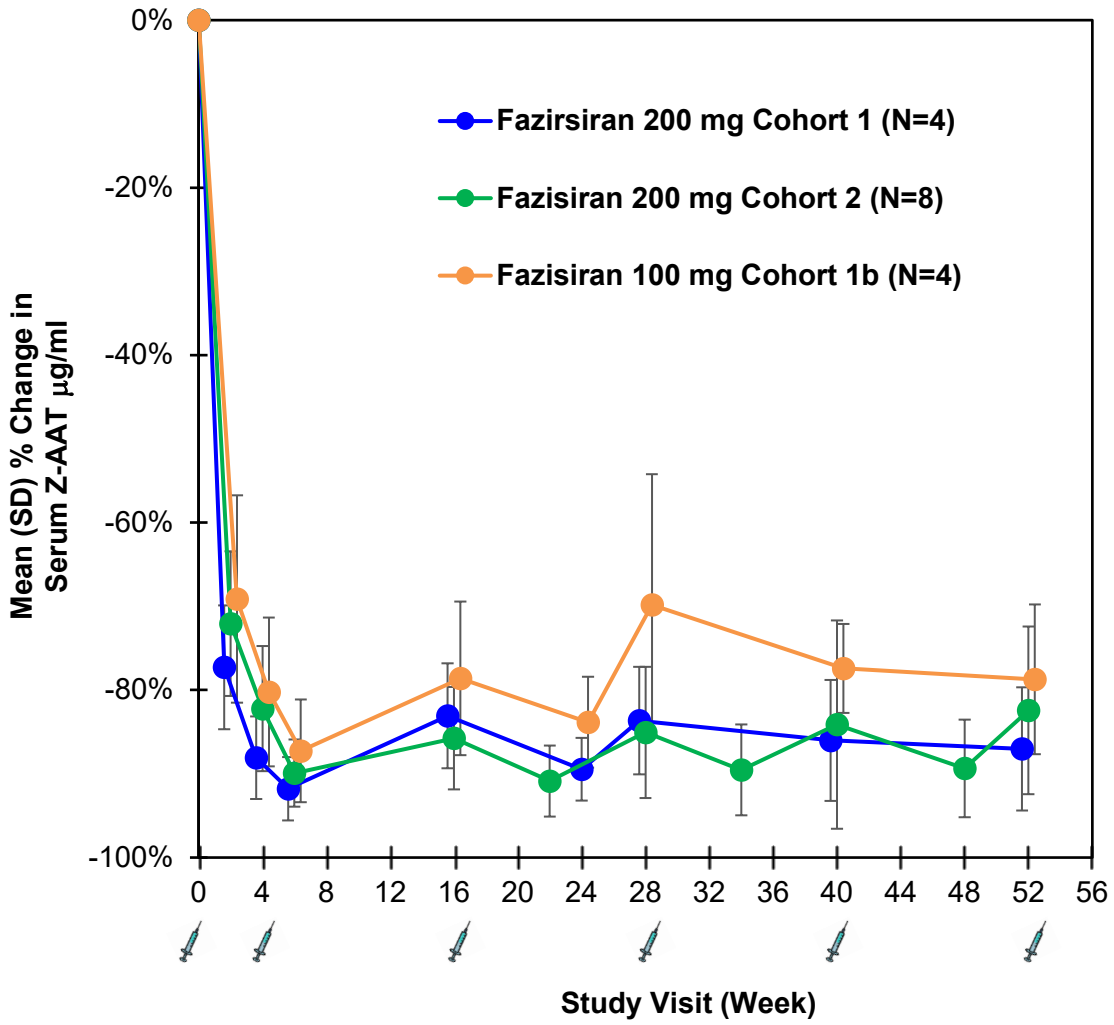
- Serum Z-AAT and total liver Z-AAT
- Adjudicated histology by 3 pathologists
  - Total PAS+D Globules (score 0-9)
  - METAVIR fibrosis stage
- Liver enzymes, liver stiffness, Pro-C3
- Treatment-emergent AEs (TEAEs), SAEs

Baseline Characteristics

	Fazirsiran 200 mg Cohort 1 (N=4)	Fazirsiran 200 mg Cohort 2 (N=8)	Fazirsiran 100 mg Cohort 1b (N=4)	Total (N=16)
Mean age (SD), years Min, Max	45 (17) 20, 56	55 (14) 24, 66	55 (10) 41, 65	52 (14) 20, 66
Male, n (%)	4 (100%)	7 (88%)	3 (75%)	14 (88%)
Mean weight (SD), kg	87 (14)	77 (14)	83 (17)	81 (14)
Mean BMI (SD), kg/m^2	26.3 (3.2)	24.1 (4.7)	27.5 (4.1)	25.5 (4.2)
Genotype (PiZZ-positive)	4 (100%)	8 (100%)	4 (100%)	16 (100%)
Fibrosis Stage F0 F1 F2 F3 F4 Not evaluable	 0 (0%) 0 (0%) 1 (25%) 1 (25%) 2 (50%) 0 (0%)	 0 (0%) 1 (13%) 4 (50%) 3 (38%) 0 (0%) 0 (0%)	 1 (25%) 1 (25%) 1 (25%) 0 (0%) 0 (0%) 1 (25%)	 1 (6%) 2 (13%) 6 (38%) 4 (25%) 2 (13%) 1 (6%)
On AAT Augmentation Therapy	1 (25%)	4 (50%)	1 (25%)	6 (38%)

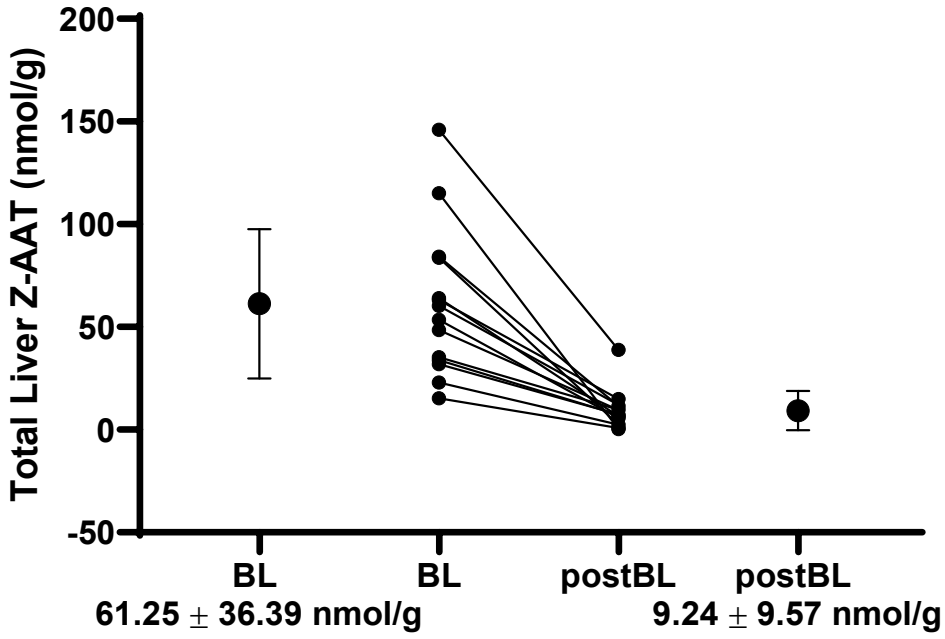
Fazirsiran Reduced Serum and Intra-hepatic Z-AAT Concentration

Serum Z-AAT



Intra-hepatic Z-AAT

Absolute Δ: -52.0±31.6 nmol/g; P=0.0001
Relative Δ: -84.6±8.97%

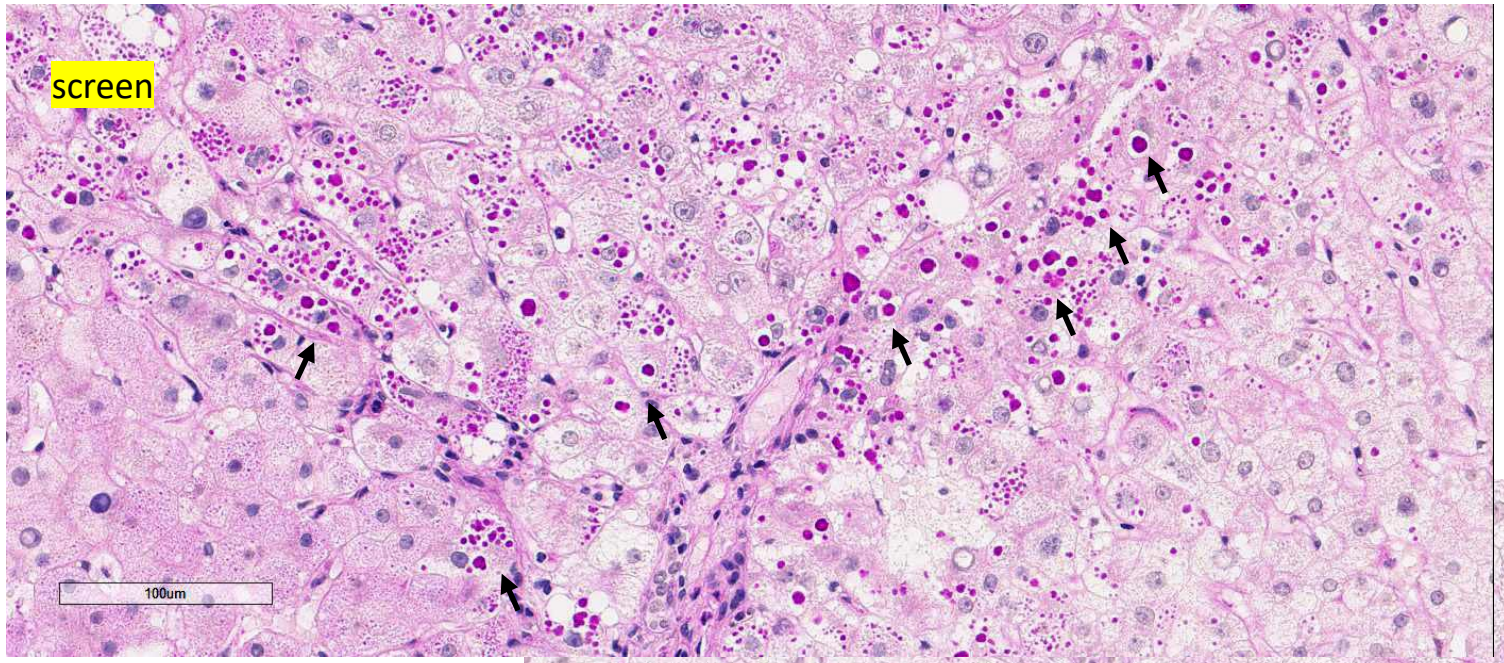


Two patients in Cohort 2 had insufficient liver biopsy samples for LC-MS/MS analysis.

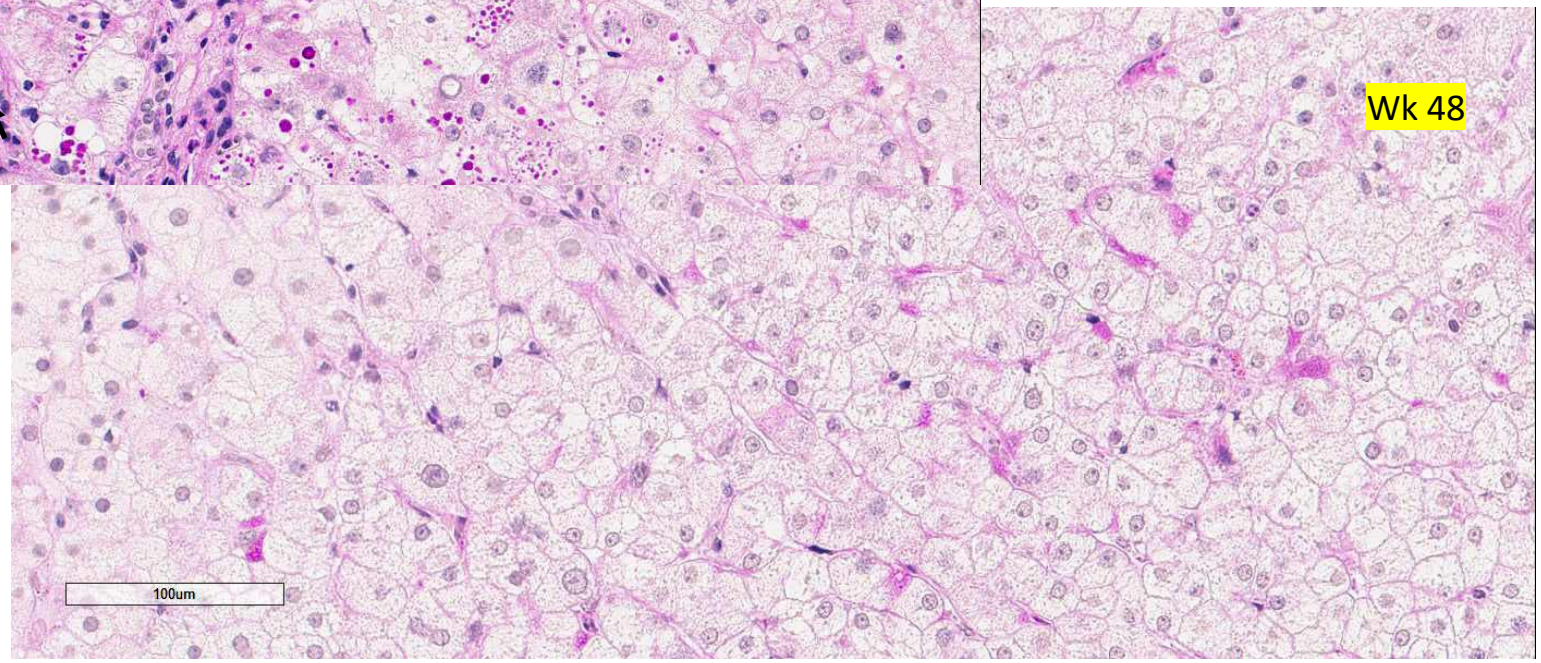
BL denotes baseline, postBL postbaseline at Week 24 or 48
Z-AAT = alpha-1 antitrypsin Z-mutant protein

Fazirsiran Treatment Reduced Histological Globule Burden

All Patients Had Reduced Globule Burden: Mean Score 7.4 at Baseline vs. 2.3 Postbaseline



	Total Liver Z-AAT (nmol/g)	PAS+D Total Globule Score
Baseline	83.7	8
Week 48	2.48	3



Cohort 2 (200 mg)

62 yo white female

63 kg, 24.6 BMI

Augmentation Therapy: No

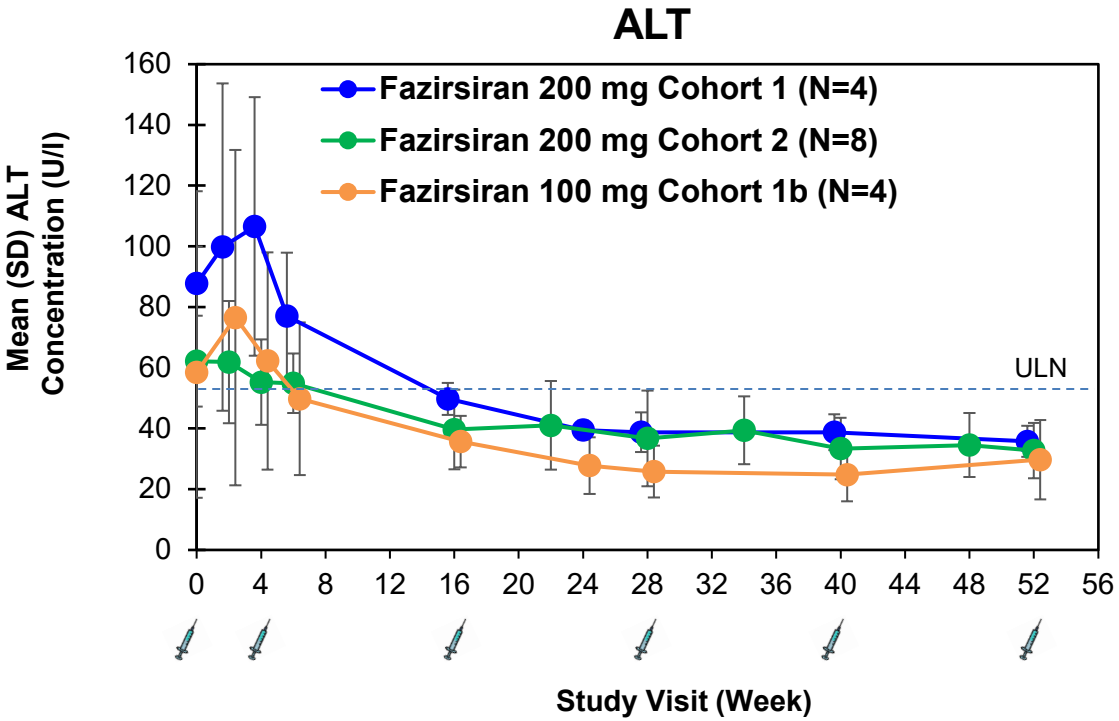
Relevant Con Meds: NA

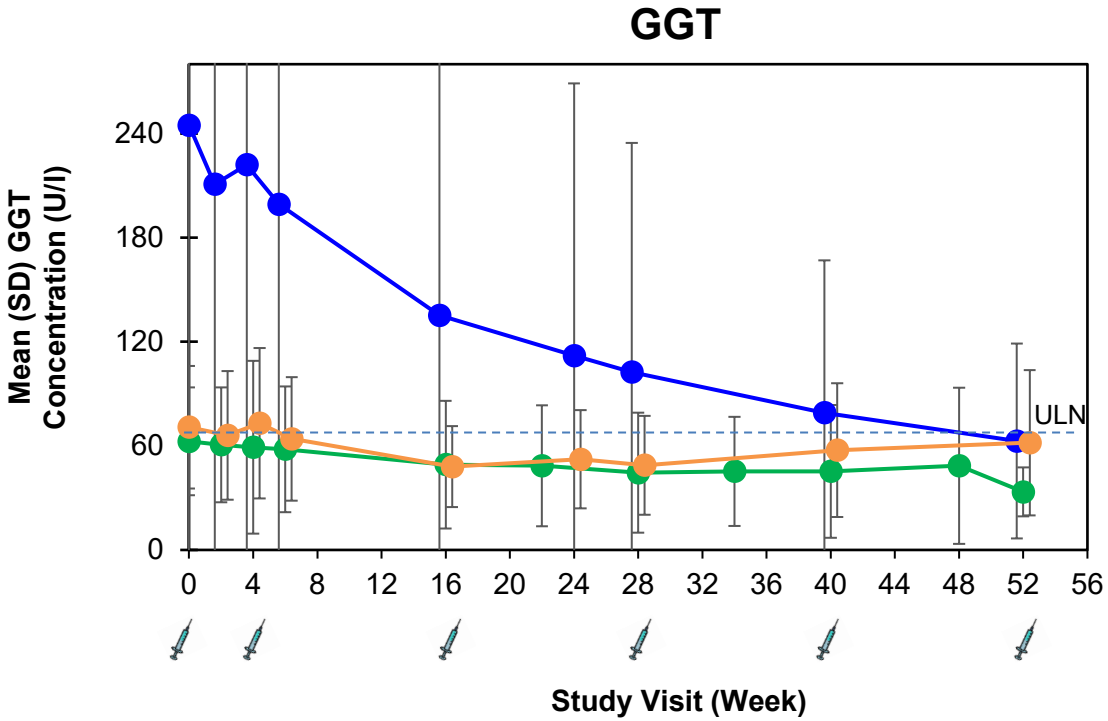
Relevant MedHx: Liver fibrosis, Hypercholesterolemia

F3 to F2 fibrosis

- Liver Z-AAT measured by LC-MS/MS
- PAS+D globule score measured histologically for extent of portal tract and periportal hepatocyte involvement and zonal location; total score of 0-9 with higher score indicating greater burden

Fazirsiran Improved Biomarkers of Liver Health





- Mean reduction in liver stiffness (VCTE)
  - Cohort 1: -18% at Week 24
  - Cohort 2: -15% at Week 48
  - Cohort 1b: -2% at Week 24

- Mean reduction in serum Pro-C3
  - Cohort 1: -36% at Week 28; -39% at Week 52
  - Cohort 2: -21% at Week 28; -17% at Week 52
  - Cohort 1b: +5% at last observation at Week 28

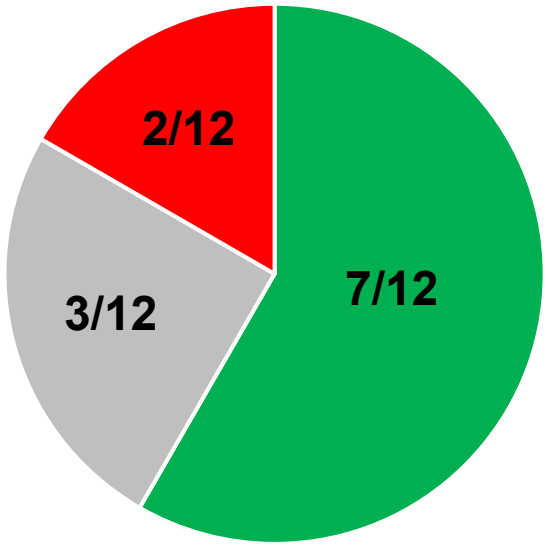
Fazirsiran Treatment Reduced Histological Signs of Inflammation

Baseline → Week 24 or 48		Portal Inflammation (Score 0-3)	Interface Hepatitis (Score 0-3)	Hepatocyte Cell Death (Score 0-2)
Cohorts 1 and 2 (200 mg)	Patient 1	2 → 1	1 → 1	1 → 0
	Patient 2	0 → 0	0 → 0	1 → 0
	Patient 3	2 → 1	2 → 2	2 → 0
	Patient 4	2 → 2	2 → 2	1 → 2
	Patient 5	2 → 2	2 → 2	2 → 2
	Patient 6	1 → 1	2 → 1	1 → 1
	Patient 7	1 → 0	1 → 0	1 → 1
	Patient 8	1 → 0	1 → 0	0 → 0
	Patient 9	2 → 1	2 → 1	2 → 0
	Patient 10	0 → 0	0 → 0	1 → 0
	Patient 11	1 → 0	1 → 0	2 → 0
	Patient 12	1 → 0	1 → 0	0 → 0
Cohort 1b (100 mg)	Patient 13	1 → 1	1 → 0	1 → 0
	Patient 14	0 → 1	0 → 1	0 → 1
	Patient 15	2 → 1	2 → 1	1 → 0
	Patient 16	1 → 1	2 → 1	0 → 0

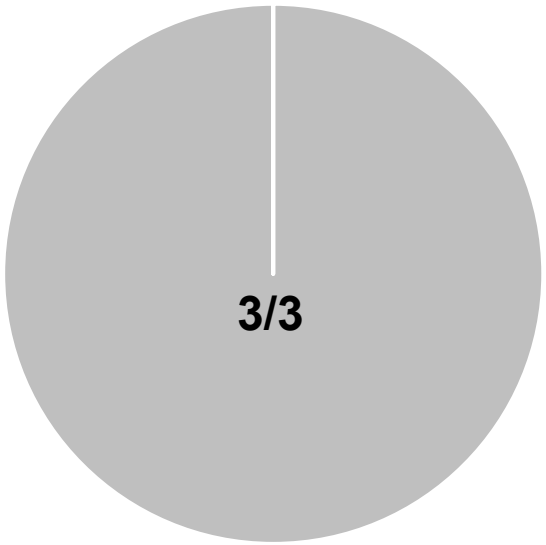
Green = ≥ 1-point improvement at Week 24 or 48; grey = no change; red = ≥ 1-point worsening at Week 24 or 48

Among subjects with a baseline score of ≥ 1, about two-thirds had an improvement in histological assessments of inflammation

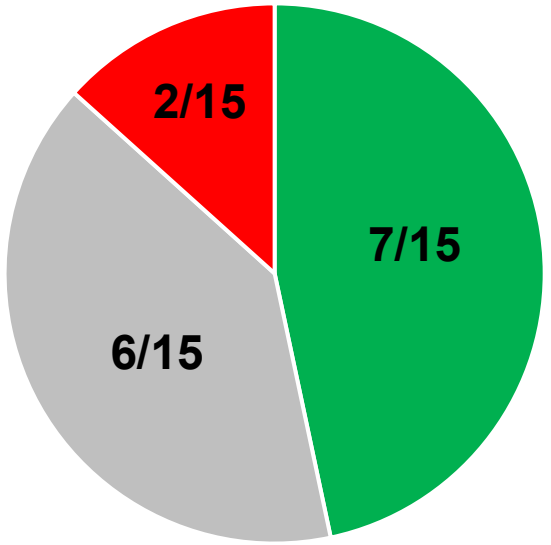
Fazirsiran Improved Liver Fibrosis in About Half of Subjects



Cohorts 1 and 2
(200 mg; N=12)



Cohort 1b
(100 mg; N=3)*



Total
(N=15)

- ≥ 1-point improvement at Week 24/48
- No change at Week 24/48
- ≥ 1-point worsening at Week 24/48

* One subject in Cohort 1b had baseline biopsy that was not evaluable for METAVIR fibrosis

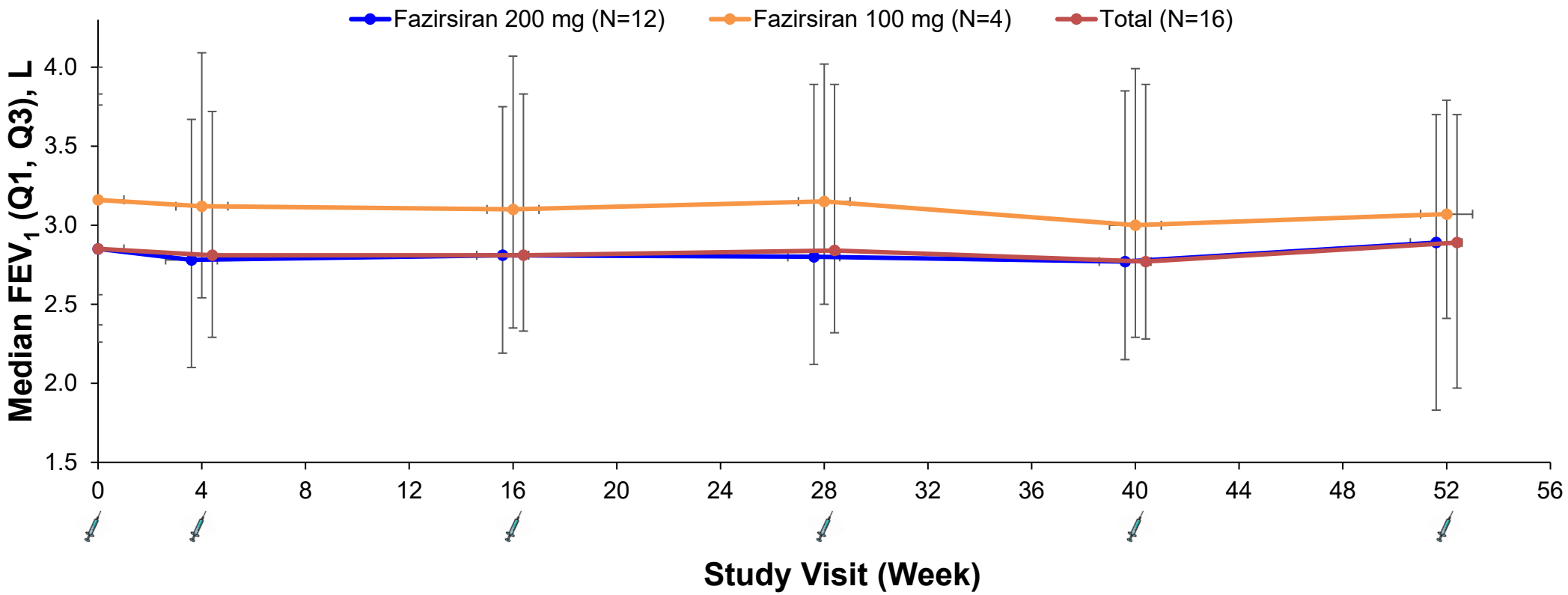
- Two patients in Cohort 2 had worsening of fibrosis from baseline to Week 48 (both from F2 to F3)
  - Both patients had profound reductions in total globule burden
  - Subject 1: Maximum score of 9 at baseline to 0 at Week 48
  - Subject 2: Score of 4 at baseline to 0 at Week 48
  - Both had reduced ALT and GGT levels after treatment

Summary of Safety and Adverse Events

Subject Incidence, n (%)	Fazirsiran 200 mg (N=12)	Fazirsiran 100 mg (N=4)	All (N=16)
Treatment-emergent AEs (TEAEs)	11 (92%)	4 (100%)	15 (94%)
TEAEs in 3 or more subjects			
Arthralgia	3 (25%)	1 (25%)	4 (25%)
Blood CK increased	3 (25%)	1 (25%)	4 (25%)
Back pain	2 (17%)	1 (25%)	3 (19%)
Chest pain	2 (17%)	1 (25%)	3 (19%)
Diarrhea	3 (25%)	0 (0%)	3 (19%)
Dizziness	1 (8%)	2 (50%)	3 (19%)
Dyspnea	2 (17%)	1 (25%)	3 (19%)
Headache	2 (17%)	1 (25%)	3 (19%)
Nasopharyngitis	2 (17%)	1 (25%)	3 (19%)
Treatment-related TEAEs	6 (50%)	3 (75%)	9 (56%)
Serious TEAEs	4 (33%)	0 (0%)	4 (25%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)	0 (0%)	0 (0%)
TEAEs causing deaths	0 (0%)	0 (0%)	0 (0%)

- No TEAE-related study drug discontinuation, dose interruptions, or premature study withdrawals
- 4 SAEs reported in the 200 mg cohorts
  - All moderate in severity and all resolved
  - Viral myocarditis associated with EBV infection
  - Diverticulitis
  - Dyspnea in subject with medical history of nonobstructive pulmonary emphysema and delayed pulmonary care
  - Vestibular neuronitis occurred following COVID-19 vaccination

Changes in FEV_1 After ARO-AAT Treatment



- No clear evidence to suggest a safety issue/concern of pulmonary function test (PFT) decline associated with fazirsiran treatment
- PFT changes confounded by multiple factors, including preexisting respiratory medical conditions, intercurrent events prior to PFT decline (eg, infection, COVID-19), and natural disease progression in patients with AATD lung disease

Summary and Conclusions

- Fazirsiran reduced serum and liver Z-AAT and histological globule burden in all patients leading to:
  - Reduction in histological signs of portal inflammation in two-thirds of patients
  - Substantial and sustained reductions in clinically relevant biomarkers of liver health
  - Improvement in liver fibrosis
- Fazirsiran was generally well tolerated

Acknowledgments

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