ARO-AAT, an Investigational RNAi Therapeutic, Demonstrates Improvement in Liver Fibrosis with Reduction in Intra-hepatic Z-AAT Burden

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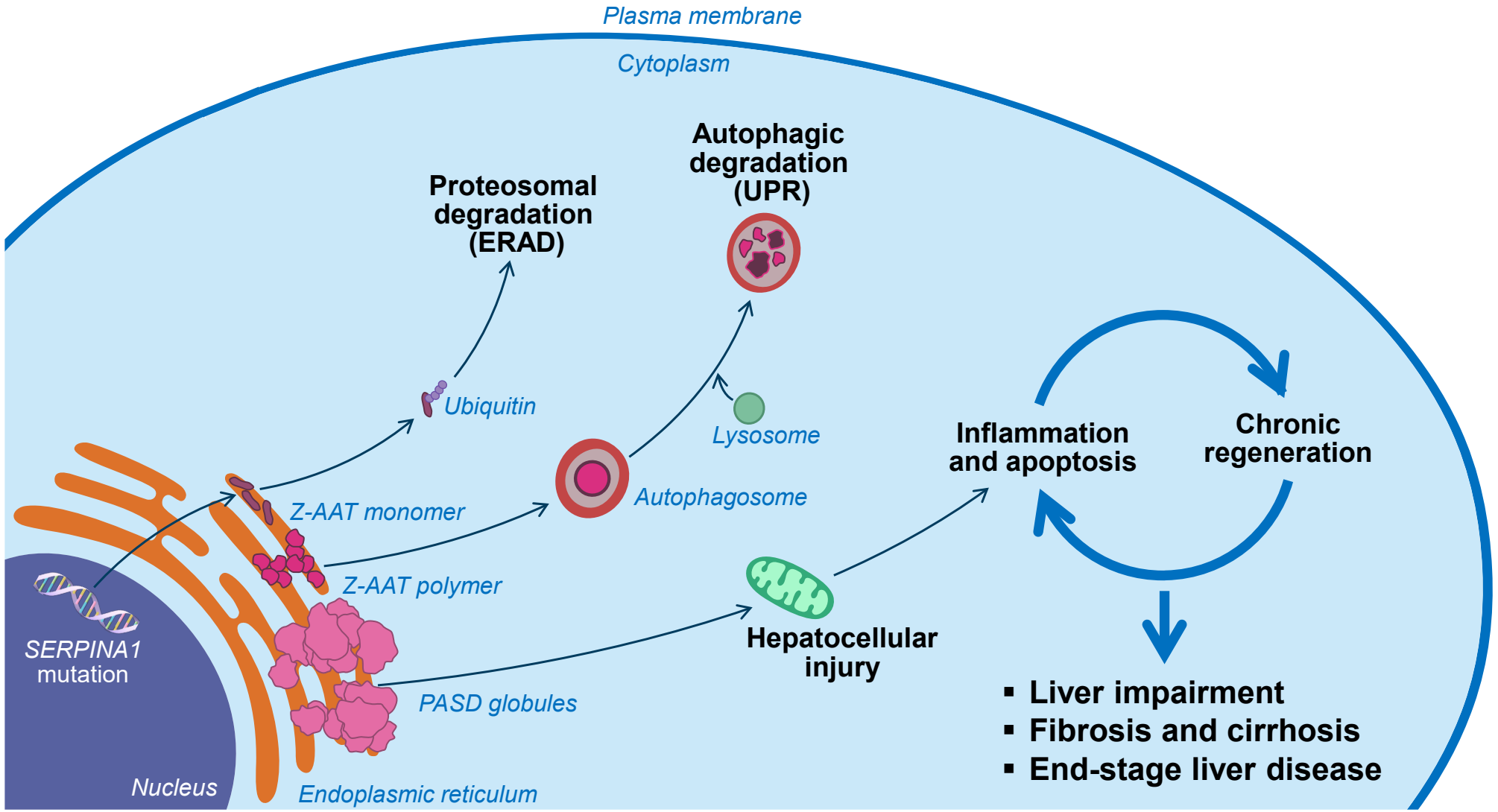
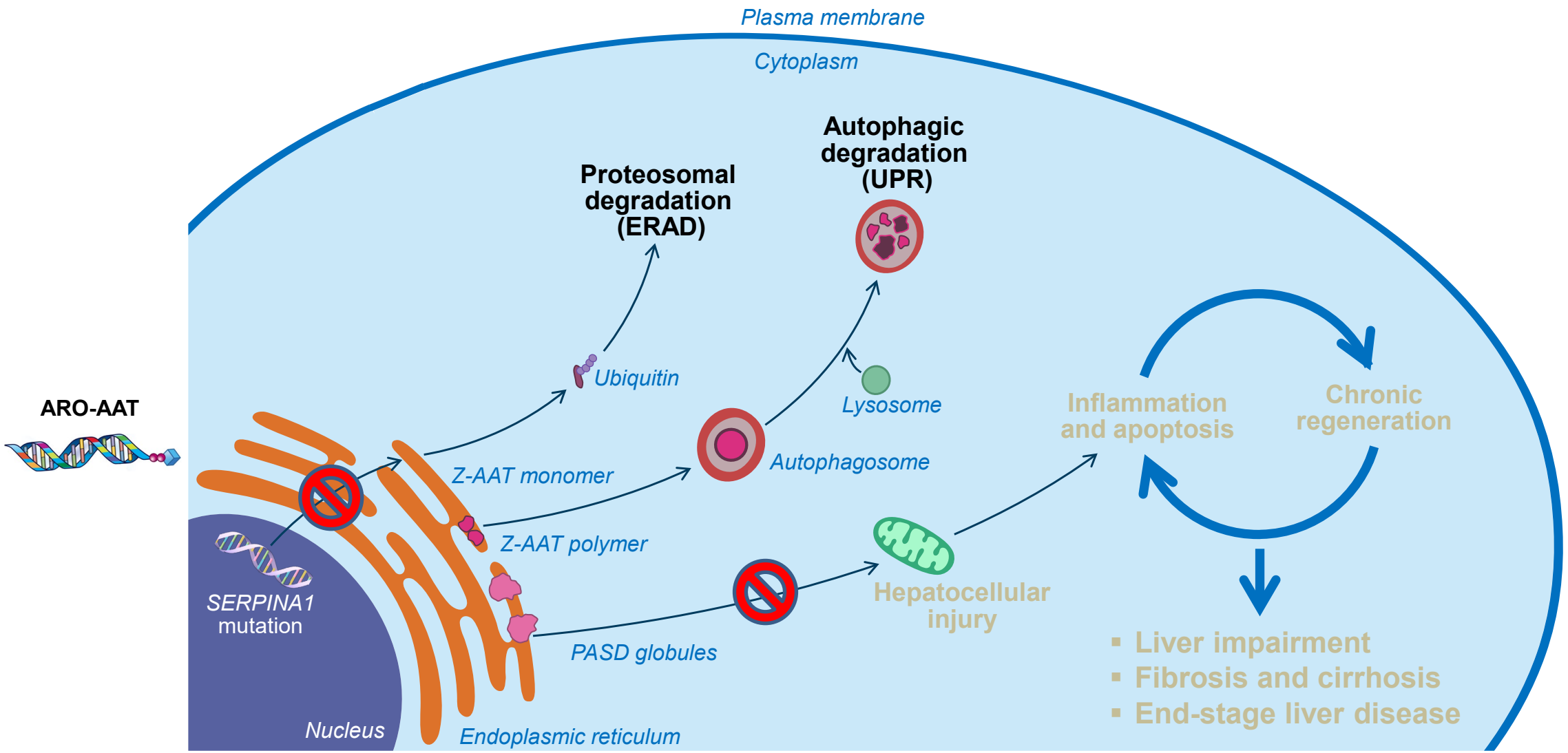
- P Strnad received grant support and lecture fees from Grifols and CSL Behring, grant support and advisory board fees from Arrowhead Pharmaceuticals, service fees from Vertex Pharmaceuticals, advisory board fees from Dicerna Pharmaceuticals and Takeda Pharmaceuticals, and lecture fees from Alnylam Pharmaceuticals
- M Mandorfer served as a speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, and W. L. Gore & Associates and received travel support from AbbVie, Bristol-Myers Squibb, and Gilead.
- G Choudhury, W Griffiths, and C Trautwein have nothing to disclose.
- R Loomba serves as a consultant for Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharm, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Pfizer, and Sonic Incytes. He is also co-founder of Liponexus, Inc.
- D Christianson and B Given are former employees of Arrowhead Pharmaceuticals, Inc.
- N Rajicic, T Chang, JC Hamilton, and J San Martin are employees of Arrowhead Pharmaceuticals, Inc.
- J Teckman received grant support from Arrowhead Pharmaceuticals, Dicerna, Vertex, NIH, Alpha-1 Foundation, KorroBio, and Gilead, and consulting fees from Arrowhead Pharmaceuticals, Dicerna, Vertex, Alpha-1 Foundation, KorroBio, Takeda, BioMarin, and RxCellerate.

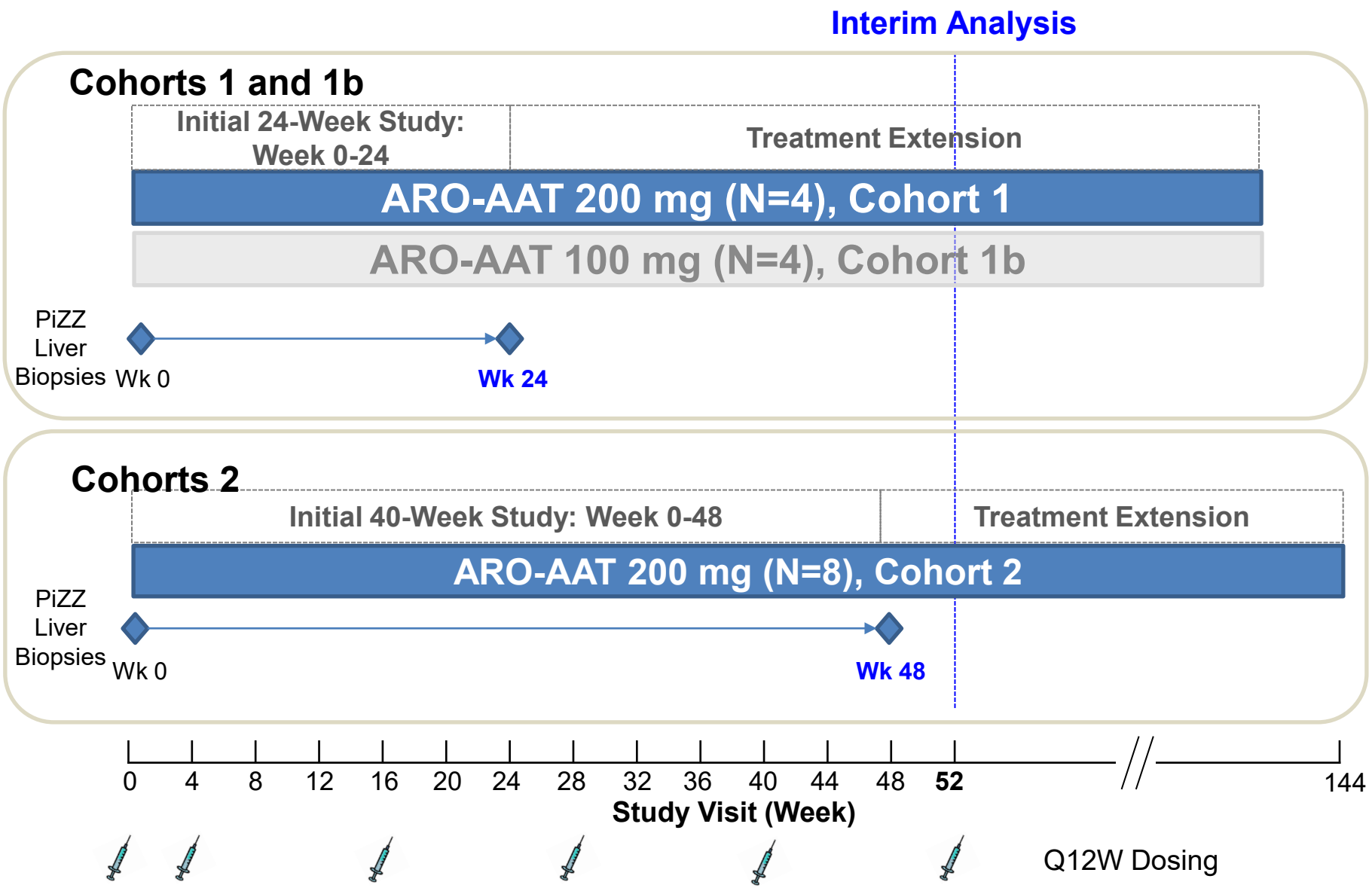
Accumulation of Hepatotoxic Z-AAT Protein Causes Liver Disease in Alpha-1 Antitrypsin Deficiency (AATD)



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



AROAAT-2002 Study Design



Endpoints and Interim Analysis

Endpoints

- Serum Z-AAT and liver Z-AAT (total, monomer, polymer)
- Adjudicated histology by 3 pathologists
  - PAS+D Globules
  - Fibrosis stage (METAVIR)
- Serum ALT, GGT, liver stiffness (FibroScan), Pro-C3
- Treatment-emergent AEs (TEAEs), SAEs

Interim Analysis

PD & Efficacy

- All 9 subjects on 200 mg:
  - Cohort 1 (n=4): 24-week biopsy and 48-week lab
  - Cohort 2 (n=5): 48-week biopsy and 52-week lab

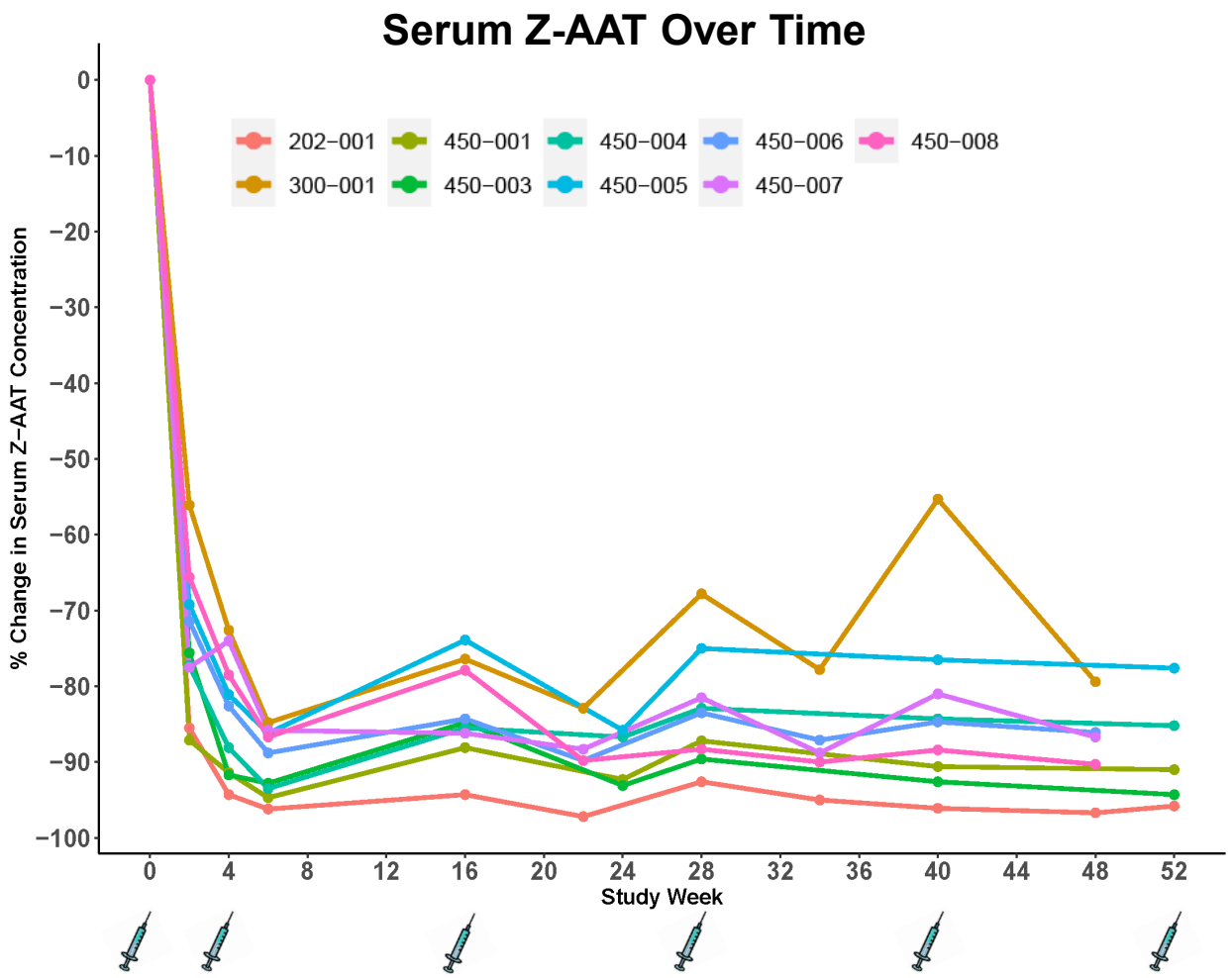
Safety

- All 16 subjects (median follow up of 60 weeks for 200 mg dose and 16 weeks for 100 mg dose)

Baseline Characteristics

Median (min, max) or n (%)	Cohort 1 (n=4)	Cohort 2 (n=5)	Total (n=9)
Age, years	51 (20, 56)	62 (50, 66)	56 (20, 66)
Male (%)	4 (100%)	4 (80%)	8 (89%)
Weight, kg	86 (71, 104)	84 (63, 105)	84.5 (63, 105)
BMI (kg/m^2)	25.5 (23.5, 30.7)	25.5 (19.1, 33.9)	25.5 (19.1, 33.9)
Genotype (PiZZ)	4 (100%)	5 (100%)	9 (100%)
Fibrosis Stage F1 F2 F3 F4	 0 (0%) 1 (25%) 1 (25%) 2 (50%)	 1 (20%) 1 (20%) 3 (60%) 0 (0%)	 1 (11%) 2 (22%) 4 (44%) 2 (22%)
FEV1 Percent Predicted	94 (54, 108)	78 (69,89)	82 (54, 108)
On AAT Augmentation Therapy	1 (25%)	2 (40%)	3 (33.3%)

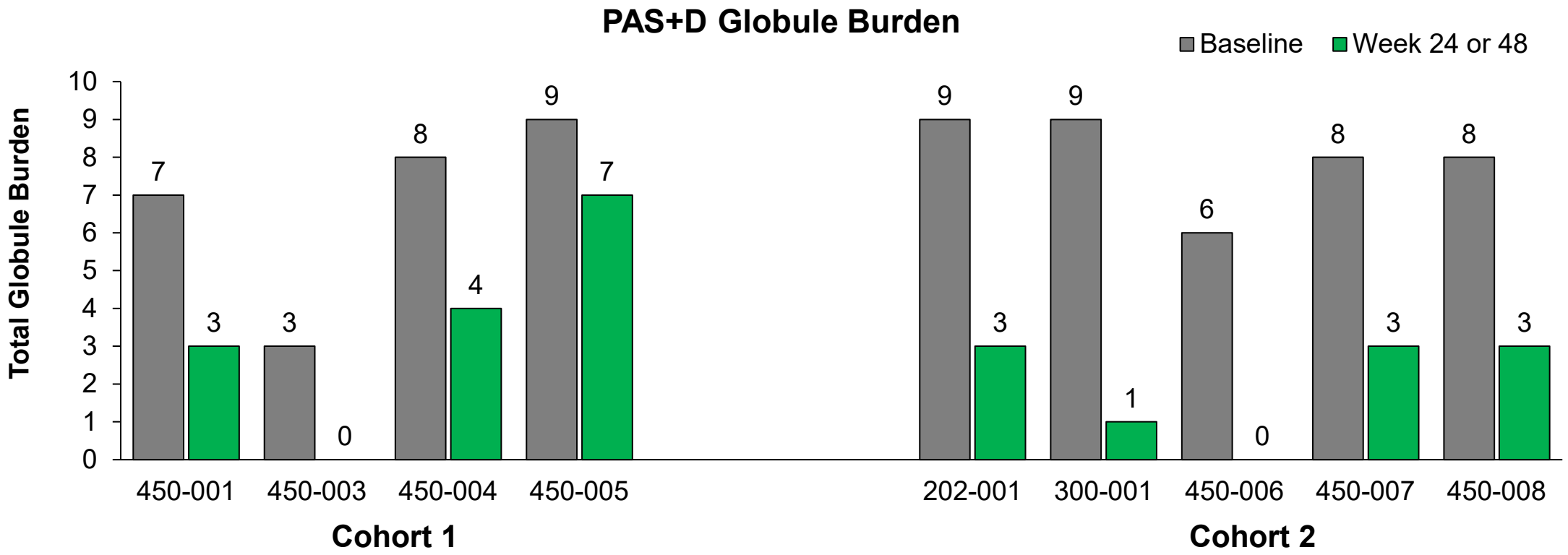
ARO-AAT Treatment Reduced Serum and Intra-hepatic Z-AAT Concentration



		% Change in Intra-hepatic Z-AAT Concentration		
		Total	Monomer	Polymer
Cohort 1 (Week 24)	450-001	-78.6	-89.8	-67.6
	450-003	-95.1	-94.9	-96.6
	450-004	-72.2	-86.8	183.7*
	450-005	-73.4	-81.2	-71.1
Cohort 2 (Week 48)	202-001	-89.7	-96.7	-86.2
	300-001	-80.1	-78.5	-80.8
	450-006	-89.4	-87.8	-92.1
	450-007	-77.0	-91.1	-42.2
	450-008	-97.0	-97.0	-97.1
All Median (N=9)		**-80.1**	**-89.8**	**-80.8**

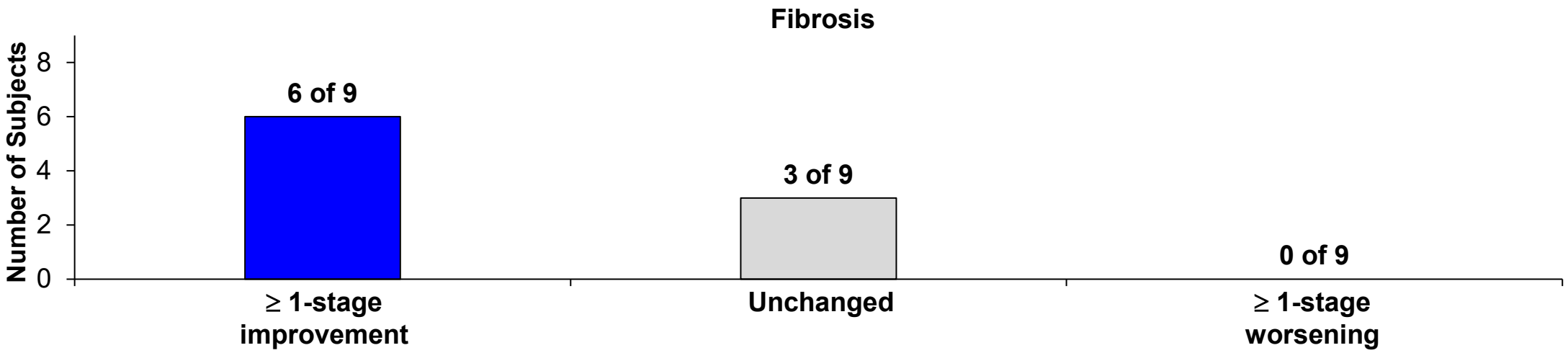
* 1 subject in Cohort 1 had very low Z-AAT polymer levels at baseline that increased at Week 24

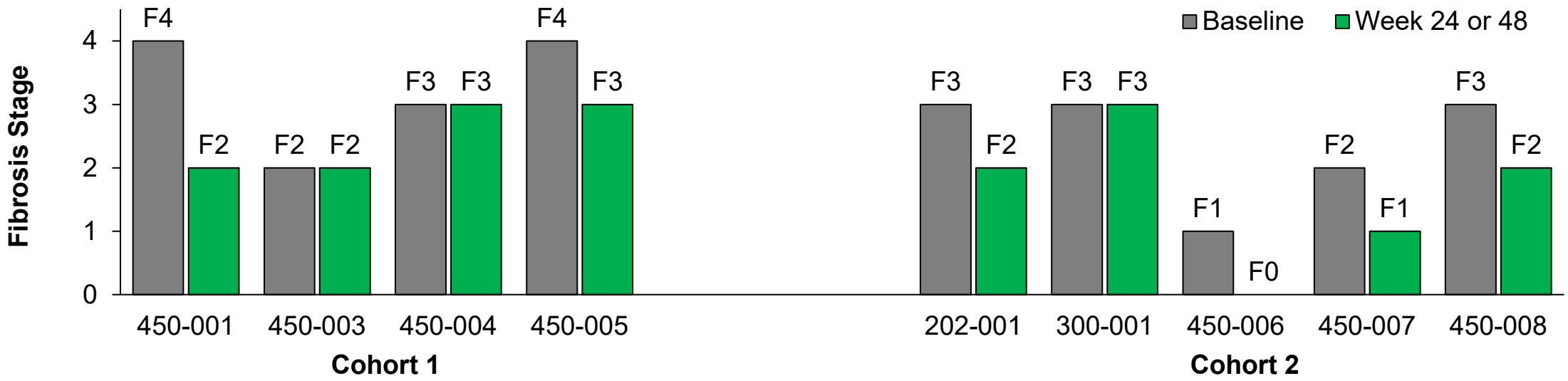
ARO-AAT Treatment Reduced Histological Globule Burden



- Histology assessed and adjudicated by 3 pathologists blinded to subject ID and time point
- Liver globule assessed semi-quantitatively (PAS+D staining): 1) Portal tract involvement, 2) periportal hepatocyte involvement, and 3) zonal location each given a score (0-3)
  - Portal tract and periportal hepatocyte involvement scoring: 0= no globules; 1= less than 1/3; 2= 1/3 to 2/3; 3= greater than 2/3
  - Zonal location: 0= no globules; 1= Zone 1; 2= Zone 1 & 2; 3= all Zones or only 2 & 3
  - Total aggregate score summarized (0-9)

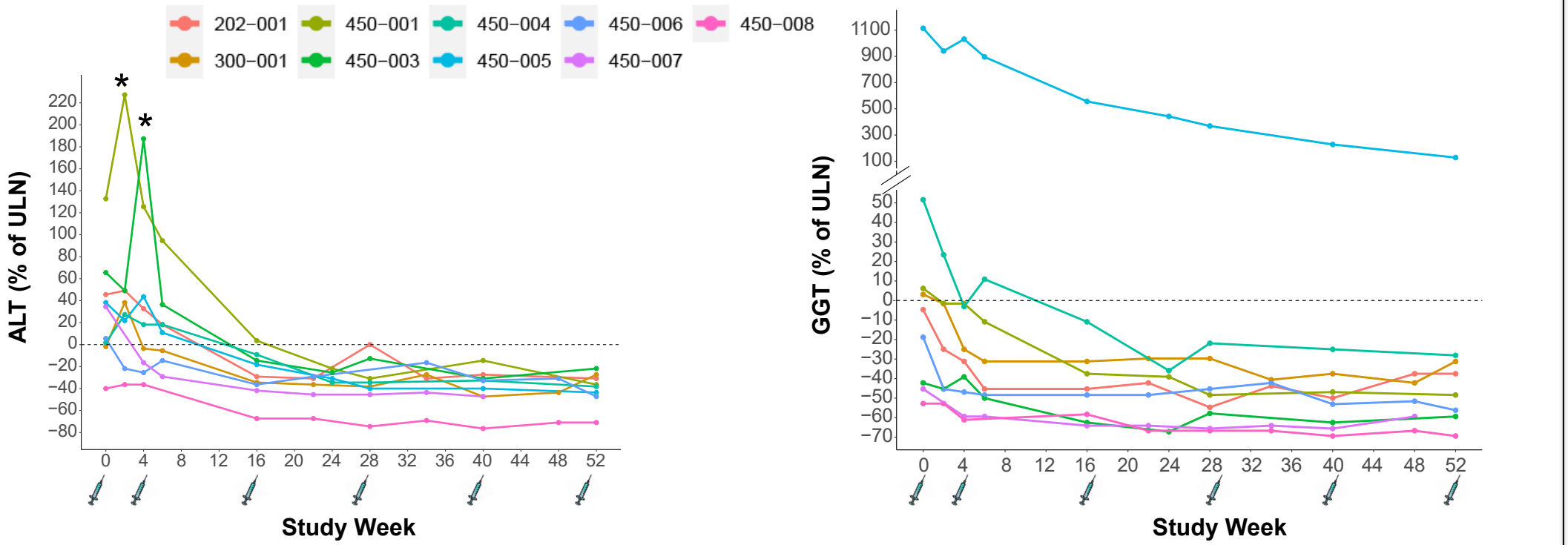
ARO-AAT Treatment Improved Liver Fibrosis





- Histology assessed and adjudicated by 3 pathologists blinded to subject ID and time point

ARO-AAT Treatment Improved Biomarkers of Liver Health



* Associated with viral infections; ULN = upper limit of normal

% Change in Liver Stiffness and Serum Pro-C3 Concentration										
	Cohort 1 (**Week 24**)				Cohort 2 (**Week 48**)					**All**
Subject Number	450-001	450-003	450-004	450-005	202-001	300-001	450-006	450-007	450-008	**Median (N=9)**
Liver stiffness	-25.8	-22.4	-0.8	-20.9	-17.7	-17.0	NM	-67.8	-35.6	**-21.6**
Pro-C3	-51.4	5.5	-30.9	-35.6	-36.6	-17.6	-25.5	-28.3	-30.8	**-30.8**

NM = not measured

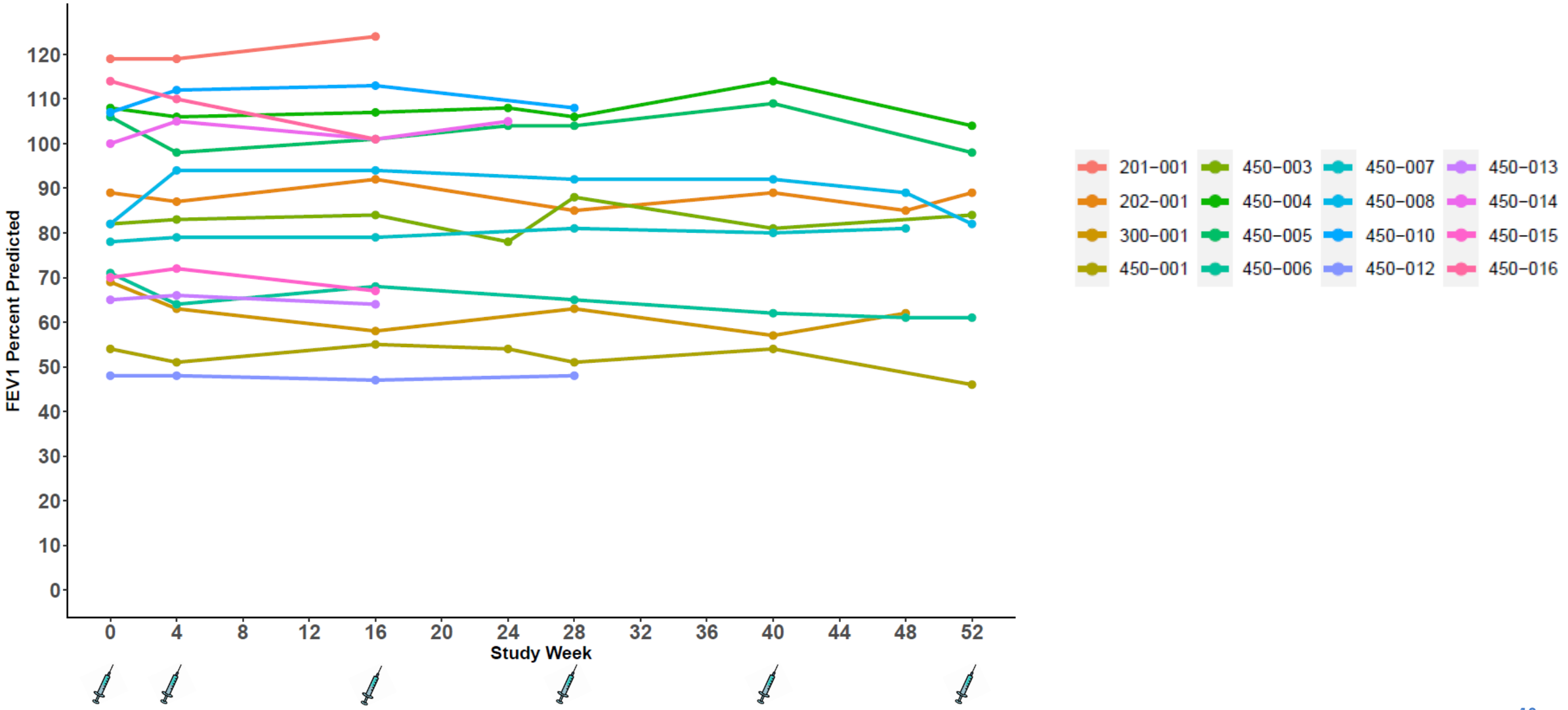
Summary of Safety and Adverse Events

Subject Incidence, n (%)	ARO-AAT 100 mg (N=4)	ARO-AAT 200 mg (N=12)	All (N=16)
Treatment-emergent AEs (TEAEs)	4 (100%)	11 (92%)	15 (94%)
TEAEs in 2 or more subjects			
Blood CK increased	1 (25%)	2 (17%)	3 (19%)
Diarrhoea	0 (0%)	3 (35%)	3 (19%)
Dizziness	2 (50%)	1 (8%)	3 (19%)
Headache	1 (25%)	2 (17%)	3 (19%)
Arthralgia	0 (0%)	2 (17%)	2 (13%)
Back pain	1 (25%)	1 (8%)	2 (13%)
Corona virus infection	0 (0%)	2 (17%)	2 (13%)
Fatigue	1 (25%)	1 (8%)	2 (13%)
Injection site reaction	1 (25%)	1 (8%)	2 (13%)
Paraesthesia	0 (0%)	2 (17%)	2 (13%)
Sciatica	2 (50%)	0 (0%)	2 (13%)
Treatment-related TEAEs	3 (75%)	6 (50%)	9 (56%)
Serious TEAEs	0 (0%)	3 (25%)	3 (19%)
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
- 3 SAEs reported in the 200 mg cohort
  - All moderate in severity and all resolved
  - SAE of viral myocarditis associated with EBV infection
  - SAE of diverticulitis in subject with risk factors – a 63-yr-old with PiZZ genotype and history of appendectomy
  - SAE of dyspnea in subject with medical history of non-obstructive pulmonary emphysema and delayed pulmonary care

Data Extract Date: 15March2021

No Clinically Meaningful Changes in FEV1 After ARO-AAT Treatment



Summary and Conclusions

In PiZZ AATD patients, treatment with ARO-AAT, an investigational RNAi therapeutic, for 24 or 48 weeks showed:

- 6 of 9 subjects with a ≥1-stage improvement in liver fibrosis, including 2 subjects who had stage F4 (cirrhosis) at baseline
- Substantial and sustained reductions in serum and intra-hepatic Z-AAT
- Decrease in histological liver globule burden
- Sustained reductions in clinically relevant biomarkers of liver health
- Acceptable safety profile
  - Generally, well tolerated after up to 1 year of treatment
  - No clinically meaningful changes in ppFEV1 or pattern of declining ppFEV1

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