

Fazirsiran SEQUOIA Topline Results

January 9, 2023



Welcome and Introductions

Vince Anzalone, CFA

Vice President, Finance & Investor Relations
Arrowhead Pharmaceuticals

Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Panelists

Virginia Clark, MD, MS

University of Florida, Division of Gastroenterology,
Hepatology, and Nutrition

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Javier San Martin, MD

Chief Medical Officer
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Agenda

Welcome and Introductions – Vince Anzalone

Fazirsiran SEQUOIA Topline Results – Javier San Martin

AATD Natural History and Significance of Fazirsiran Results – Virginia Clark

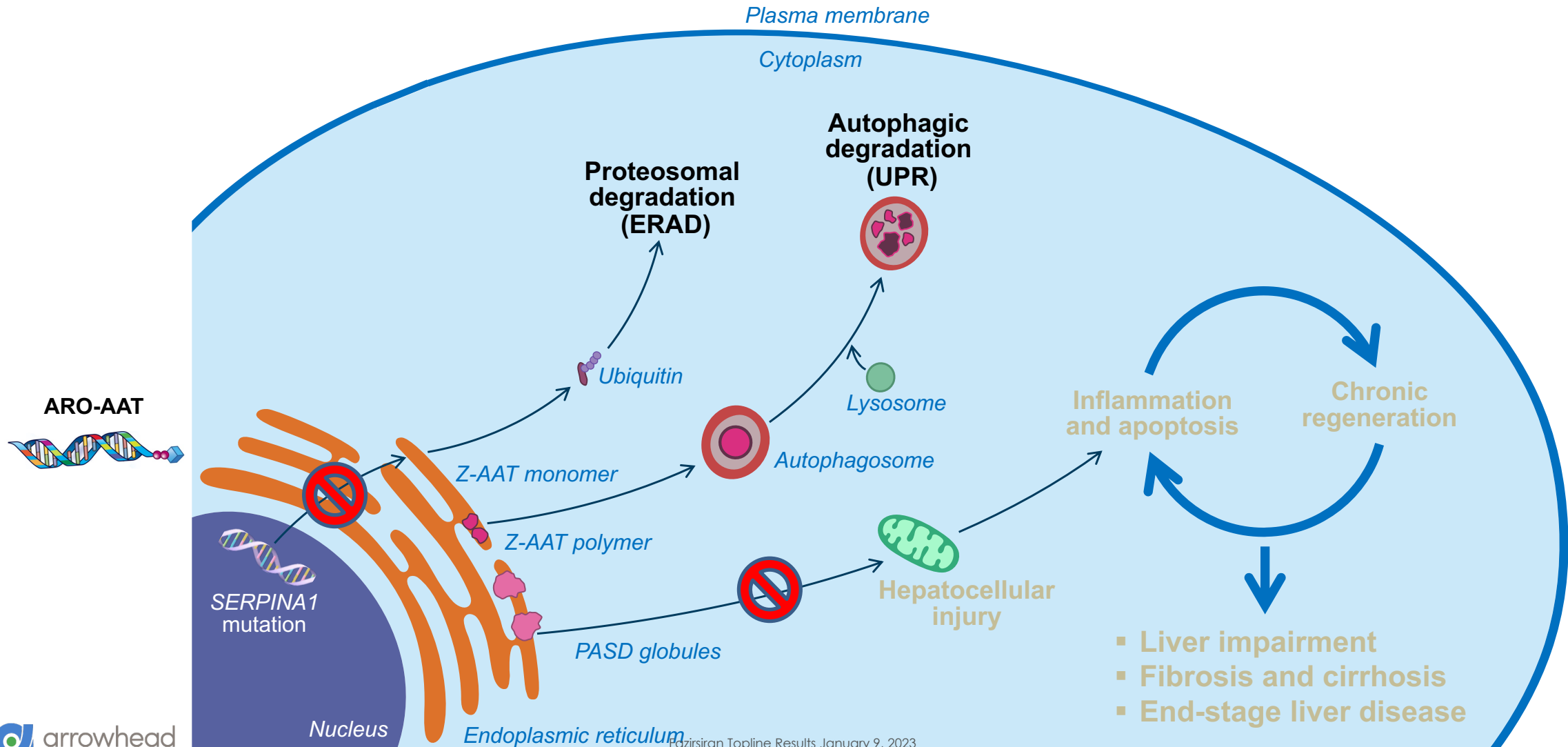
Fazirsiran Phase 3 Study – Javier San Martin

Concluding Remarks

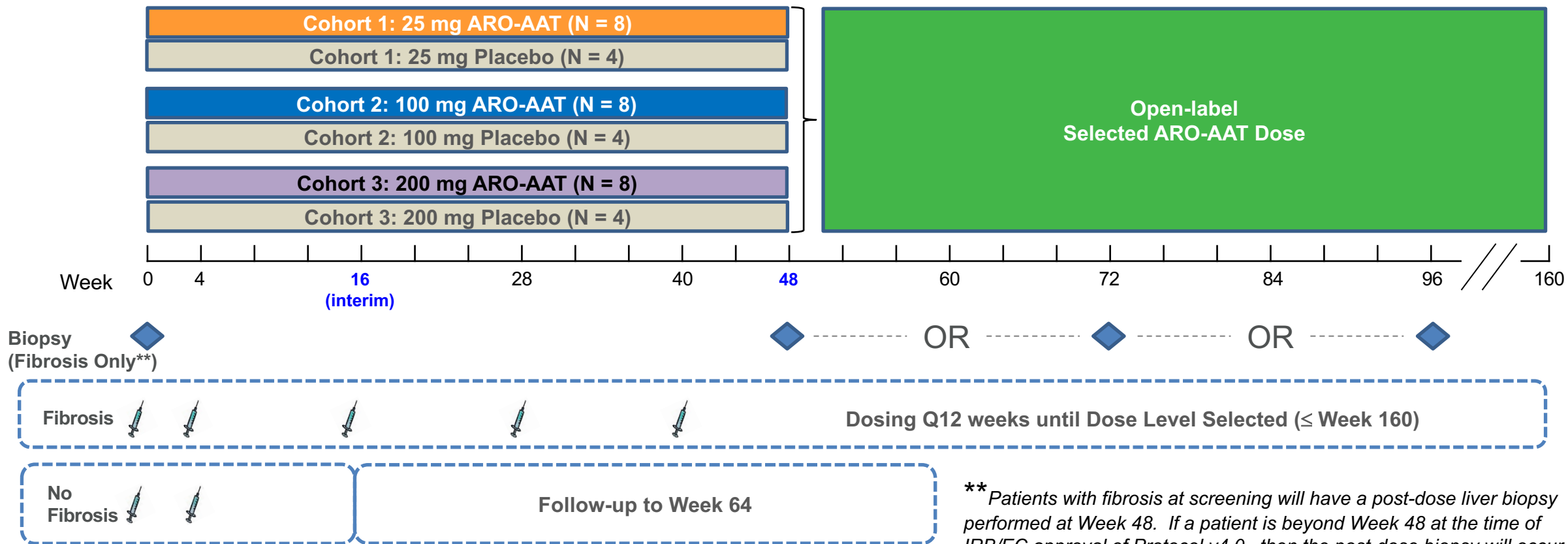
Fazirsiran Phase 2 SEQUOIA Study Results

Javier San Martin, MD
Chief Medical Officer,
Arrowhead Pharmaceuticals

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



SEQUOIA Study Design



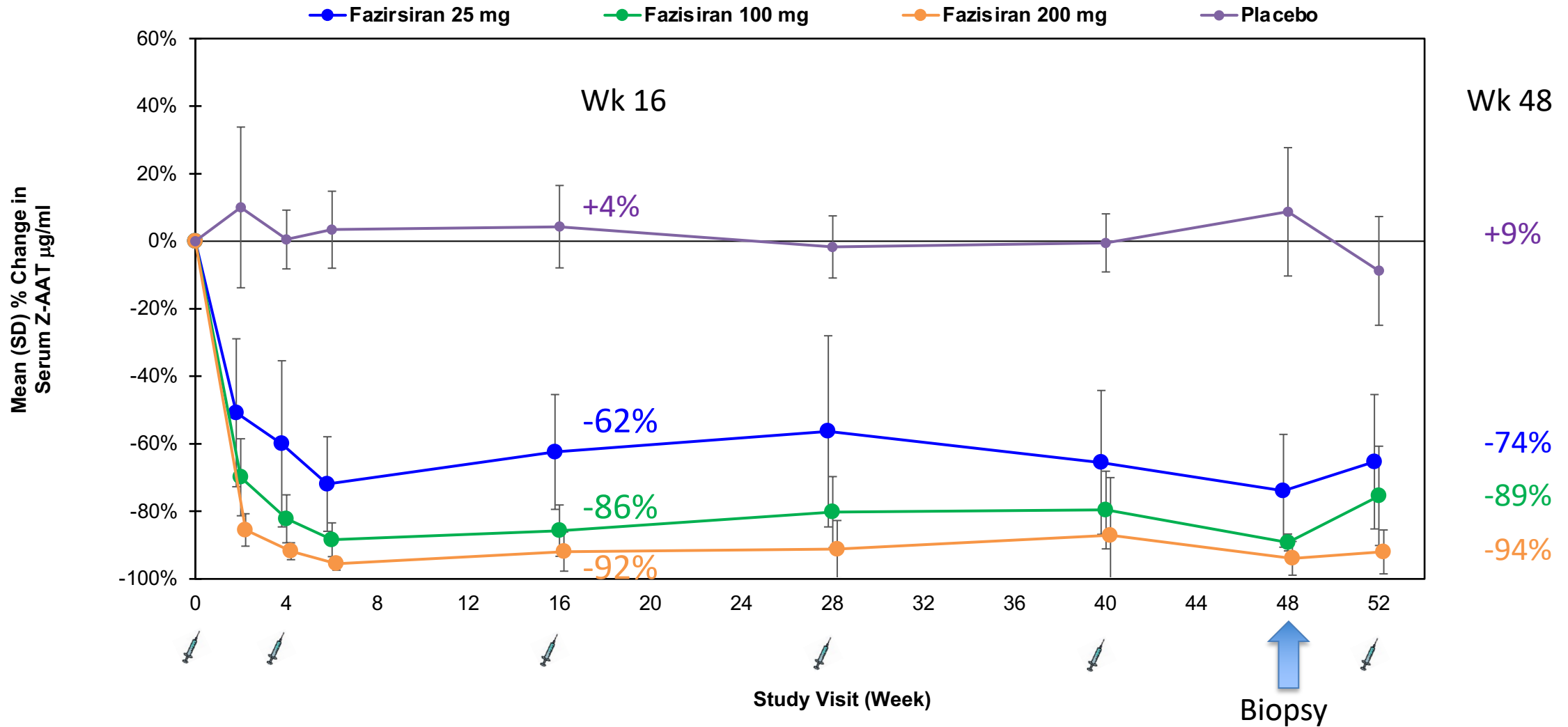
****** Patients with fibrosis at screening will have a post-dose liver biopsy performed at Week 48. If a patient is beyond Week 48 at the time of IRB/EC approval of Protocol v4.0, then the post-dose biopsy will occur at Week 72 or Week 96.

SEQUOIA Demographic and Baseline Characteristics

40 Patients Enrolled	Pooled Placebo (N=14)	25 mg (N=9)	100 mg (N=8)	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 (8.0)	27.7 (6.8)
Genotype (PiZZ-positive)	14 (100%)	9 (100%)	8 (100%)	9 (100%)
Fibrosis Stage				
No Fibrosis / Fibrosis (Local read Central read (adjudicated):	5 (36%) / 9 (64%)	5 (56%) / 4 (44%)	3 (38%) / 5 (62%)	2 (22%) / 7 (78%)
F0	1 (11%)	1 (25%)	0 (0%)	1 (14%)
F1	3 (33%)	0 (0%)	3 (60%)	3 (43%)
F2	5 (56%)	3 (75%)	1 (20%)	2 (29%)
F3	0 (0%)	0 (0%)	1 (20%)	1 (14%)
F4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not evaluable	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mean FEV1 Percent Predicted (SD)*	91 (11)	96 (12)	98 (6)	95 (18)
On AAT Augmentation Therapy	4 (29%)	3 (33%)	0 (0%)	3 (33%)

* post-bronchodilation percent predicted FEV1

Fazirsiran Reduced Serum Z-AAT Concentration in a Dose Dependent Manner (n=40 to wk 16, n=25 with fibrosis)



The Effect of Fazirsiran vs Placebo on PAS+D Globule Burden, Inflammation and Fibrosis Histology Results

	AAT-2001	AAT-2001
% change from baseline to Week 48+	Pooled Active (N=16)	Pooled Placebo (N=9)
Liver Z-AAT	-94%	26%
Globule Burden PAS+D Score	-68%	-3%

	AAT-2001	AAT-2001
Portal inflammation	Pooled Active (N=16)	Pooled Placebo (N=9)
≥ 1-point improvement	5/12 (42%)	0/8 (0%)
No change	10/16 (63%)	5/9 (56%)
≥ 1-point worsening	1/15 (7%)	4/9 (44%)

	AAT-2001	AAT-2001
METAVIR fibrosis	Pooled Active (N=16)	Pooled Placebo (N=9)
≥ 1-point improvement*	7/14 (50%)	3/8 (38%)
No change	5/16 (31%)	4/9 (44%)
≥ 1-point worsening**	4/16 (25%)	2/9 (22%)

*score of 0 by adjudication are ineligible for improvement

**Score of 4 (fibrosis) or 3 (Portal Inflammation) by adjudication are ineligible for worsening

Sequoia Active Treatment and -2002 Histology Results Show Consistency Across all 3 Key Histologic Parameters

	AAT-2001	AAT-2002
% change from baseline to Week 48+	Pooled Active (N=16)	Pooled Active (N=14)
Liver Z-AAT	-94%	-83%
Globule Burden PAS+D Score	-68%	-71%

	AAT-2001	AAT-2002
Portal inflammation	Pooled Active (N=16)	Pooled Active (N=16)
≥ 1-point improvement	5/12 (42%)	9/13 (69%)
No change	10/16 (63%)	6/16 (38%)
≥ 1-point worsening	1/15 (7%)	1/16 (6%)

	AAT-2001	AAT-2002
METAVIR fibrosis	Pooled Active (N=16)	Pooled Active (N=16)
≥ 1-point improvement*	7/14 (50%)	7/14 (50%)
No change	5/16 (31%)	6/15 (40%)
≥ 1-point worsening**	4/16 (25%)	2/13 (15%)

*score of 0 by adjudication are ineligible for improvement

**Score of 4 (fibrosis) or 3 (Portal Inflammation) by adjudication are ineligible for worsening

Summary of Safety and Adverse Events

Subject Incidence, n (%)	Fazirsiran 25 mg (N=9)	Fazirsiran 100 mg (N=8)	Fazirsiran 200 mg (N=9)	PBO (N=14)
Treatment-emergent AEs (TEAEs)	9 (100%)	8 (100%)	9 (100%)	13 (92.9%)
TEAEs in 4 or more subjects				
COVID19	0 (0%)	2 (25%)	6 (67%)	2 (14%)
Headache	4 (44%)	1 (13%)	2 (22%)	3 (21%)
Procedural pain	1 (11%)	0 (0%)	4 (44%)	3 (21%)
Arthralgia	2 (22%)	2 (25%)	0 (0%)	3 (21%)
Diarrhoea	1 (11%)	1 (13%)	0 (0%)	2 (14%)
Nausea	1 (11%)	0 (0%)	1 (11%)	3 (21%)
Back pain	1 (11%)	1 (13%)	2 (22%)	0 (0%)
Fatigue	1 (11%)	1 (13%)	0 (0%)	2 (14%)
Treatment-related TEAEs	2 (22%)	4 (50%)	3 (33%)	8 (57%)
Serious TEAEs	0 (0%)	0 (0%)	2 (22%)	3 (21%)
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
- 2 subjects with 2 TESAEs reported in the 200 mg cohort
 - Both were infective exacerbations of bronchiectasis (both with history of multiple pulmonary infections)
- 3 subjects with 6 TESAEs in PBO
 - One subject reported Influenza, Staph wound infection, and Acute pancreatitis
 - One subject reported PFT decreased and Hypertensive crisis
 - One subject reported Presyncope

Sequoia Topline Results Summary

- Fazirsiran reduced serum, liver Z-AAT and histological globule burden in all treated subjects, consistent with previous results
- This was in contrast to PBO, which showed no change or a slight increase in all three measures of Z-AAT burden
- At week 48 this resulted in
 - Improvement in portal inflammation in 42% for active vs 0% for PBO
 - Improvement in liver fibrosis in 50% for active vs. 38% for PBO
 - PBO rate for improvement in fibrosis was higher than expected from natural history data (16% over 3 years)
- Fazirsiran was well tolerated, pulmonary function test (PFT) was stable and similar to placebo.

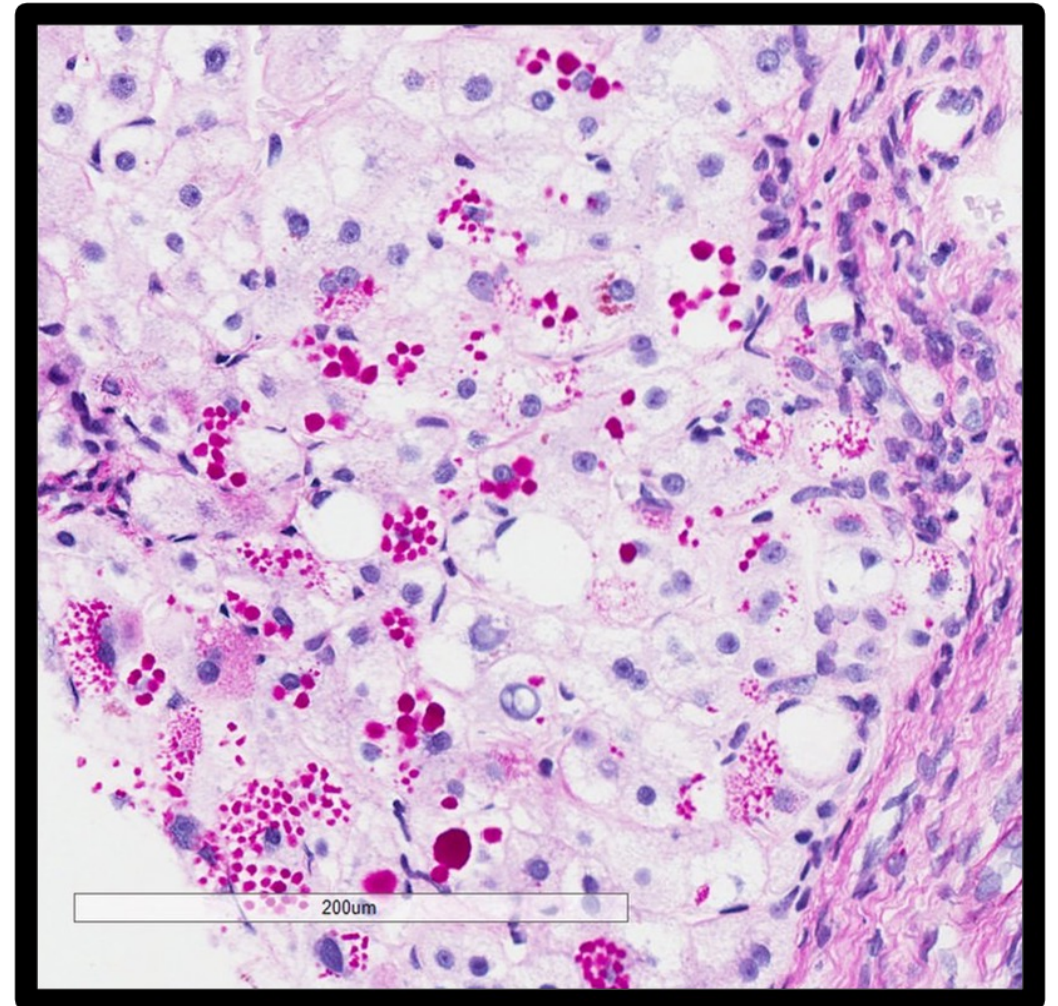
AATD Natural History and Significance of Fazirsiran Results

Virginia Clark, MD, MS

University of Florida, Division of Gastroenterology, Hepatology, and Nutrition

AATD is a Rare Disorder

- Population with an unmet need for liver disease treatment
- Many undiagnosed but affected individuals
- Most studies have small sample sizes



Liver Disease is Prevalent but Heterogeneous

- Asymptomatic to cirrhosis
- Modest elevation in liver enzymes
- Portal inflammation
- Z-AAT accumulation
- Spectrum of liver fibrosis



Require a liver biopsy

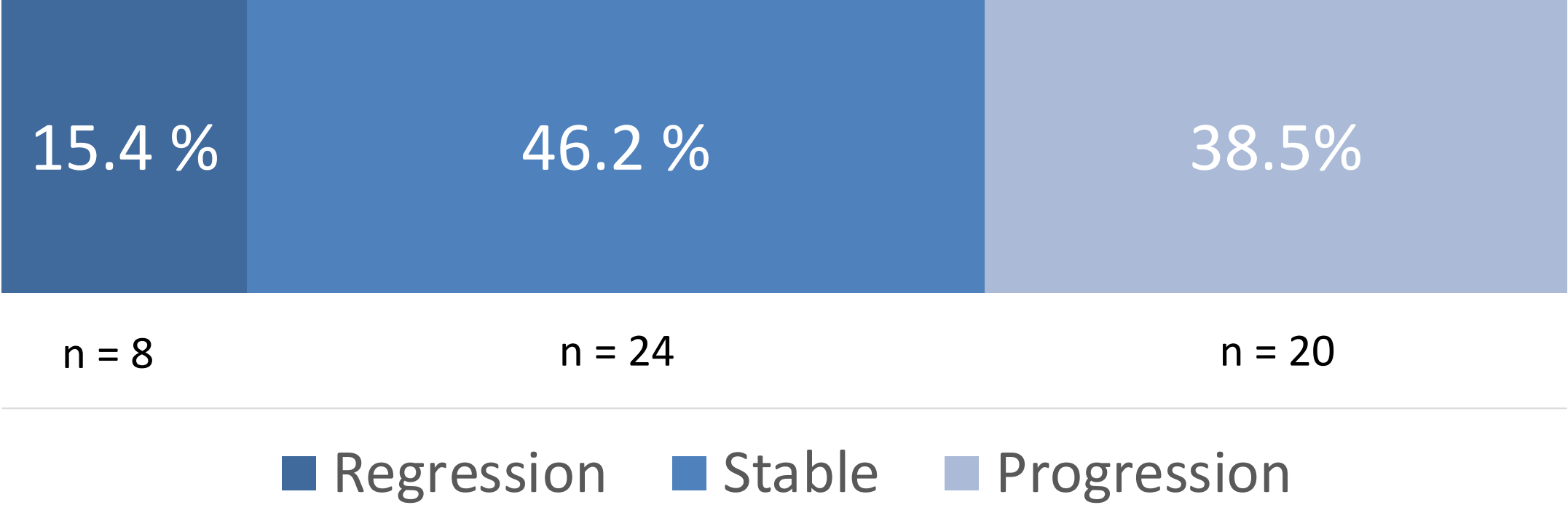
Underlying Liver Fibrosis in ZZ adults is Prevalent

	Year	Fibrosis Stage ≥ 2	Fibrosis Stage ≥ 3
Teckman (n=93)	2019	12%	8%
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%	

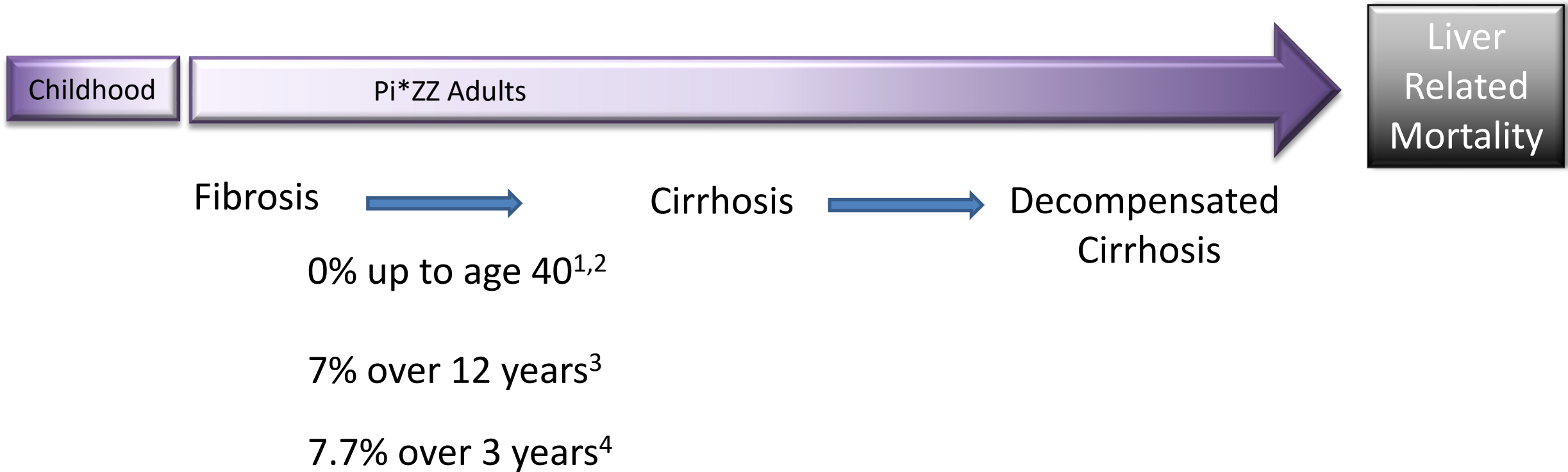
*determined by transient elastography

1. Teckman et al *Hepatology* 2019 1964A
2. Hamesch et al *Gastroenterology* 2019;157(3):705-719
3. Clark et al *J Hepatology* 2018;69(6):1357-1364
4. Morer et al *Am J Transplant* 2017;17:1389-1395
5. Dawwas MF et al *Am J Respir Crit Care Med* 2013;187:502-508

Natural History: Changes in Fibrosis by Biopsy at 3 Years



Progression to Cirrhosis



¹Bernspang et al Scand J Gastroenterol 2009

²Mostafavi B et al Medicine 2017

Fazirsiran Topline Results January 9, 2023

³Tanash H et al. J Gastroenterol 2019 54:541-548

⁴Clark et al 2021 AASLD

Significance of Fazirsiran Results

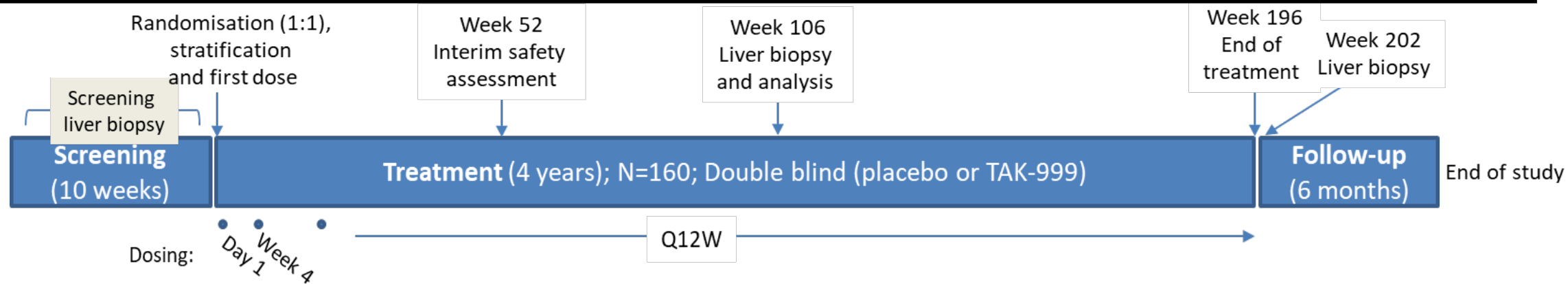
- Consistent findings in reduction of the toxic Z-AAT protein in liver
Accumulation of Z-AAT is the key to liver injury
- Improvement in portal inflammation
Portal inflammation increases risk of fibrosis progression
- Improvement in liver histology and fibrosis may be possible
Future trial designs will require biopsy, larger numbers of patients, and target ZZ individuals with fibrosis

Fazirsiran Phase 3 Study

Javier San Martin, MD
Chief Medical Officer,
Arrowhead Pharmaceuticals

Takeda's Fazirsiran Registrational Phase 3 Overview

Study design	<ul style="list-style-type: none"> Randomized, double-blind, placebo-controlled, parallel-arm, multicenter
Disease indication	<ul style="list-style-type: none"> PiZZ Alpha-1 Antitrypsin Deficiency (AATD) Associated Liver Disease
# Subjects	<ul style="list-style-type: none"> 160 subjects with F2, F3 and F4 Metavir Fibrosis at baseline
Primary EP	<ul style="list-style-type: none"> Decrease from baseline of at least 1 stage of histologic fibrosis (METAVIR staging) in the centrally read liver biopsy (F2/F3) done at Week 106
Dosing	<ul style="list-style-type: none"> Day 1, Wk 4, Wk 16 & then every 12 wks until EOT at Wk 196 (4 yrs) with liver biopsy at wks 106 and 202
Interim analysis (IA)	<ul style="list-style-type: none"> First IA is Safety Assessment at Wk 52 for safety to allow possible pulmonary inclusion/safety monitoring adjustment. Second IA is Primary analysis after F2/F3 reach Wk 106 for safety and efficacy



Concluding Remarks