Emerging Therapies for AAT Liver Disease

ARO-AAT-2002 Clinical Data Review

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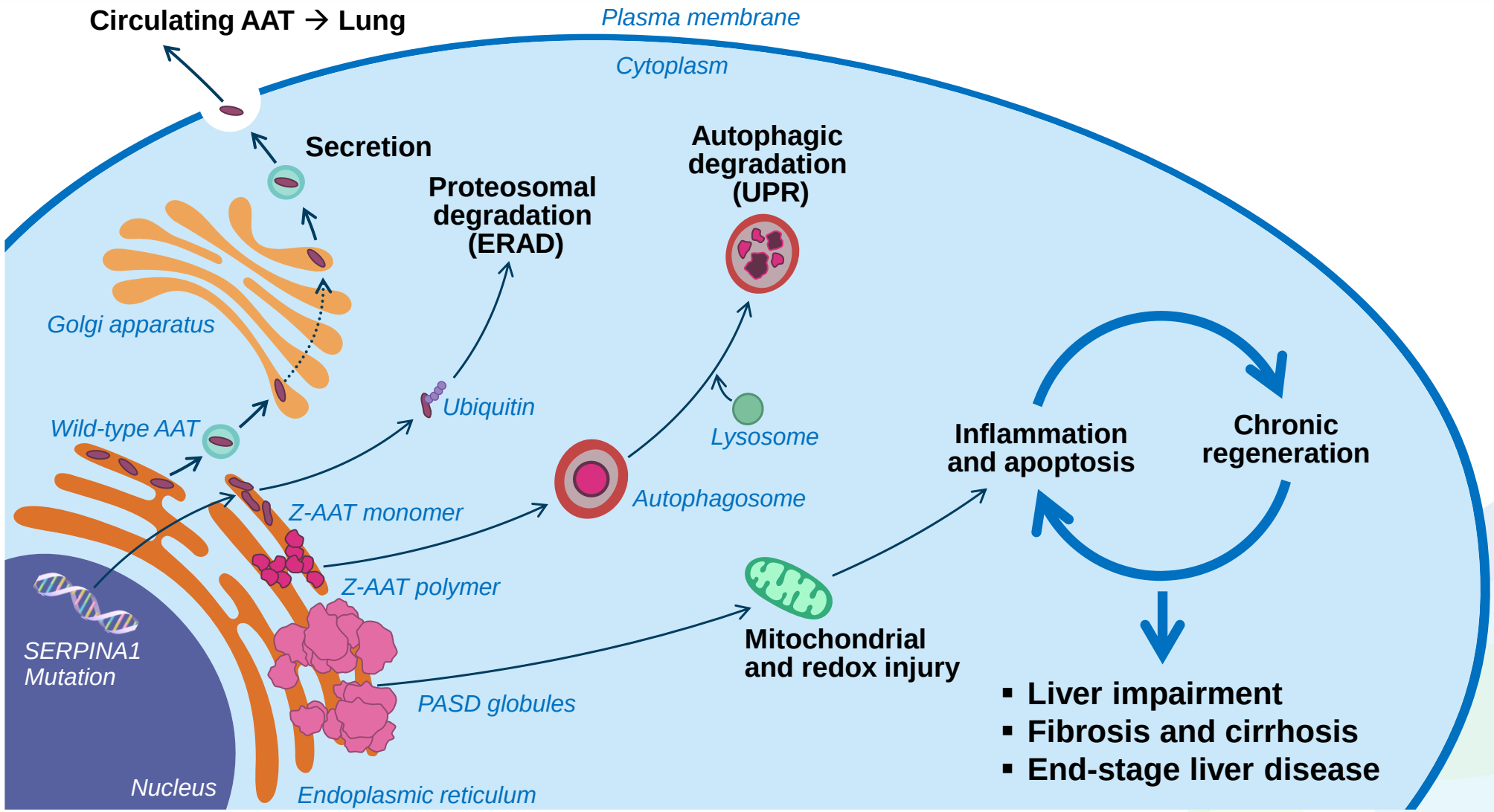
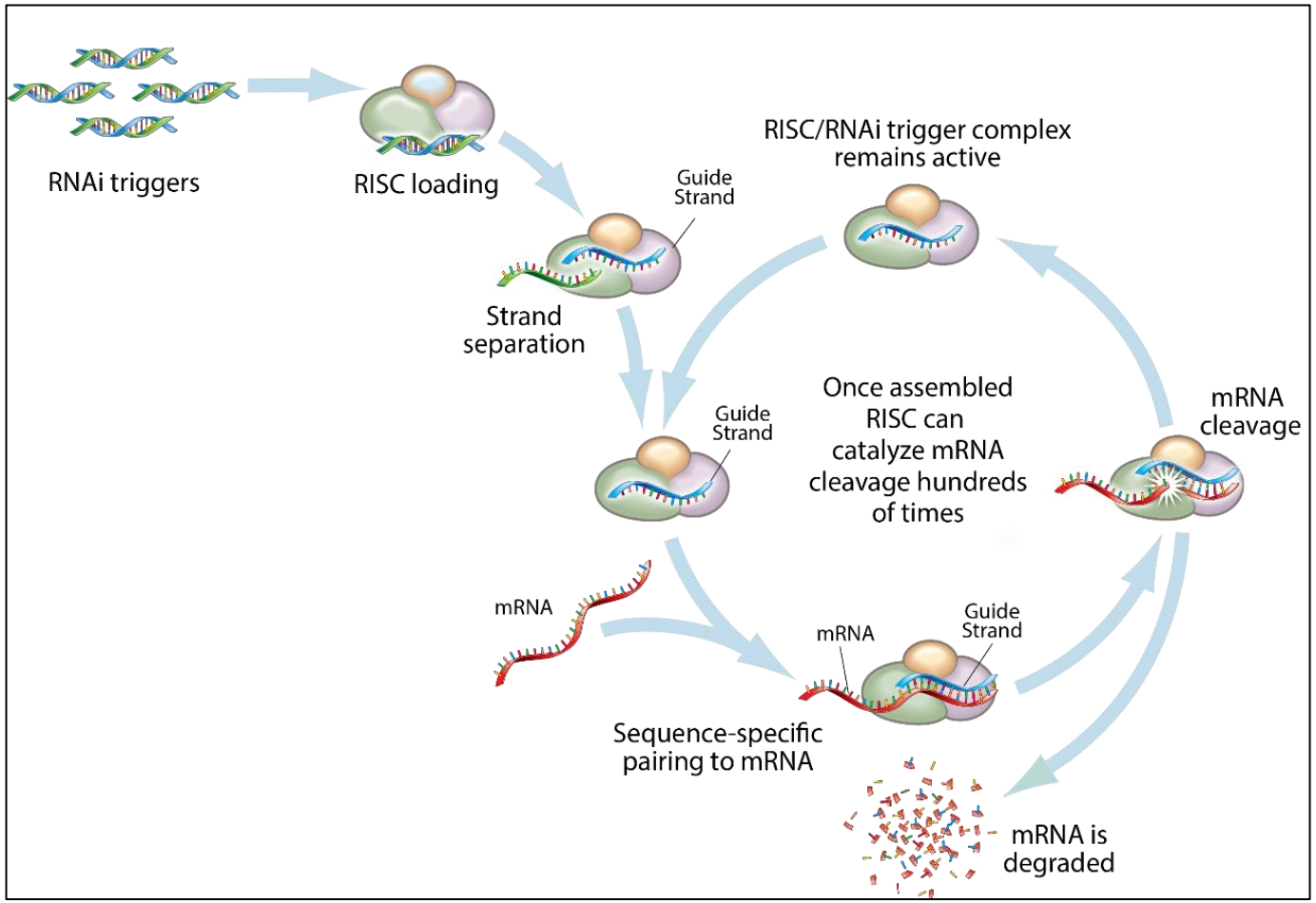
Accumulation of Hepatotoxic Z-AAT Protein Causes Liver Disease in Alpha-1 Antitrypsin Deficiency (AATD)



RNAi as Therapeutic Approach to Silence Protein Expression
Targeted RNA Interference Molecule (TRiM™)



- ARO-AAT: A Hepatocyte Targeted RNAi Molecule to Silence Hepatocyte AAT Synthesis

- Arrowhead's TRiM™ Platform:
  - **Targeted:** designed to deliver drug to cells in the liver
  - **Precise:** small interfering RNA molecules (RNAi triggers) designed to silence specific gene of interest and prevent protein synthesis
  - **Efficient:** uses natural cellular mechanism

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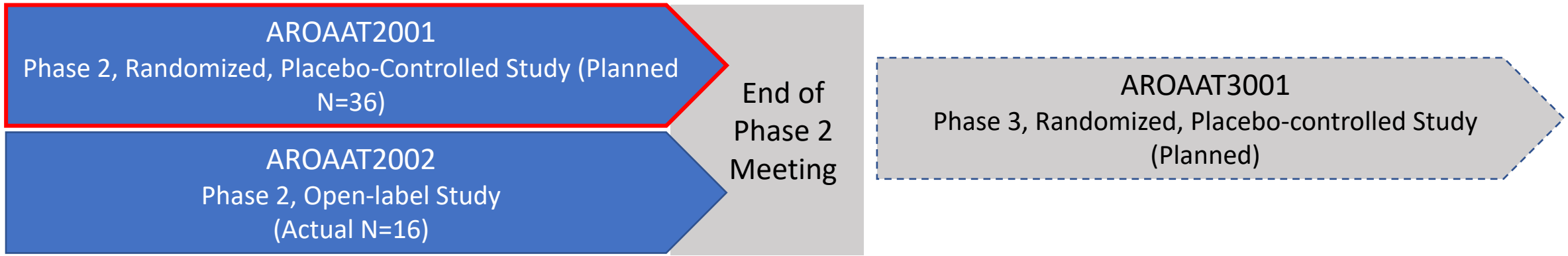
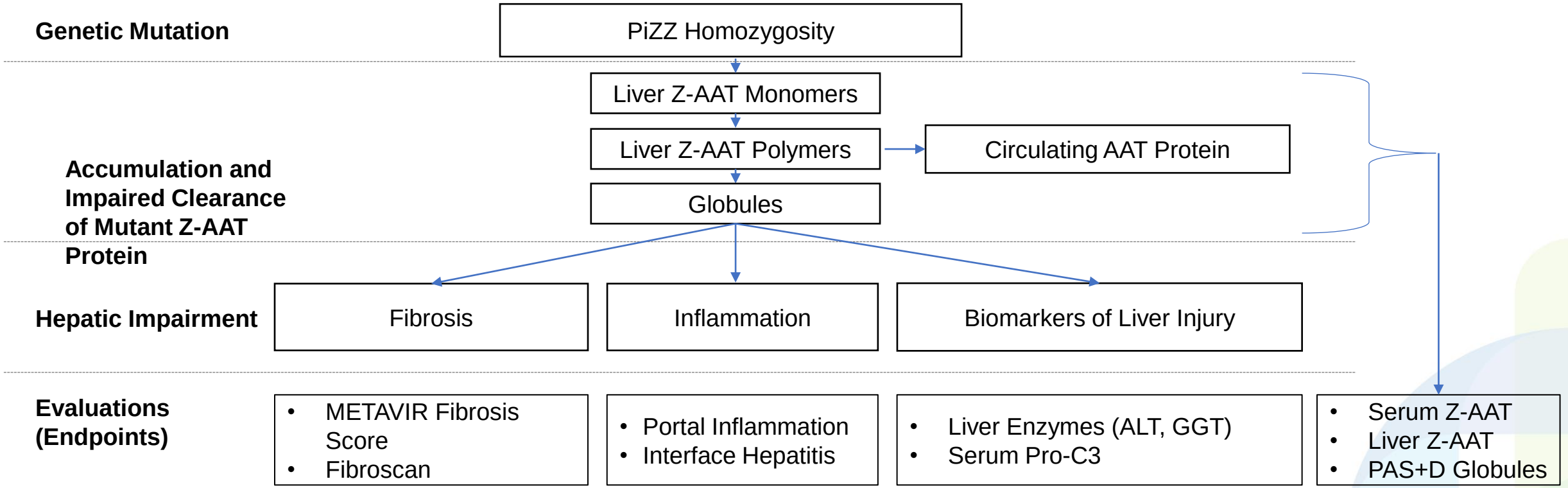
ARO-AAT Clinical Development Program Overview



- On October 8, 2020, Arrowhead Pharmaceuticals and Takeda entered into an agreement to co-develop ARO-AAT
- Arrowhead will continue to conduct the Phase 2 studies through completion
  - The primary analysis of AROAAT2001 at Week 16 is intended to enable End of Phase 2 meeting with FDA
  - Dose selection based on AROAAT2001 results will be used in subsequent Phase 3 study
- Takeda will design and conduct the Phase 3 study in collaboration with Arrowhead

Clinically Relevant Endpoints in ARO-AAT Studies



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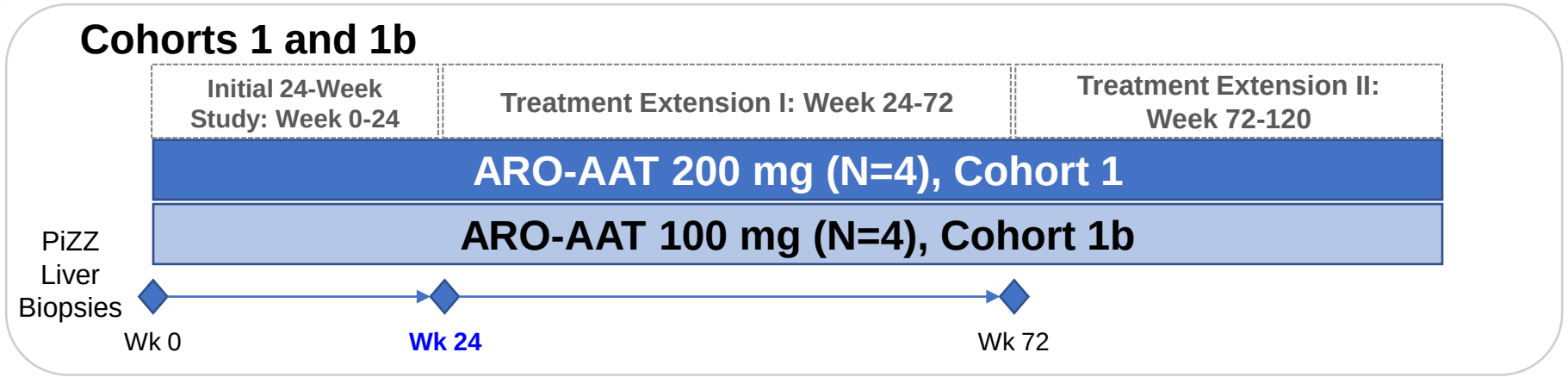
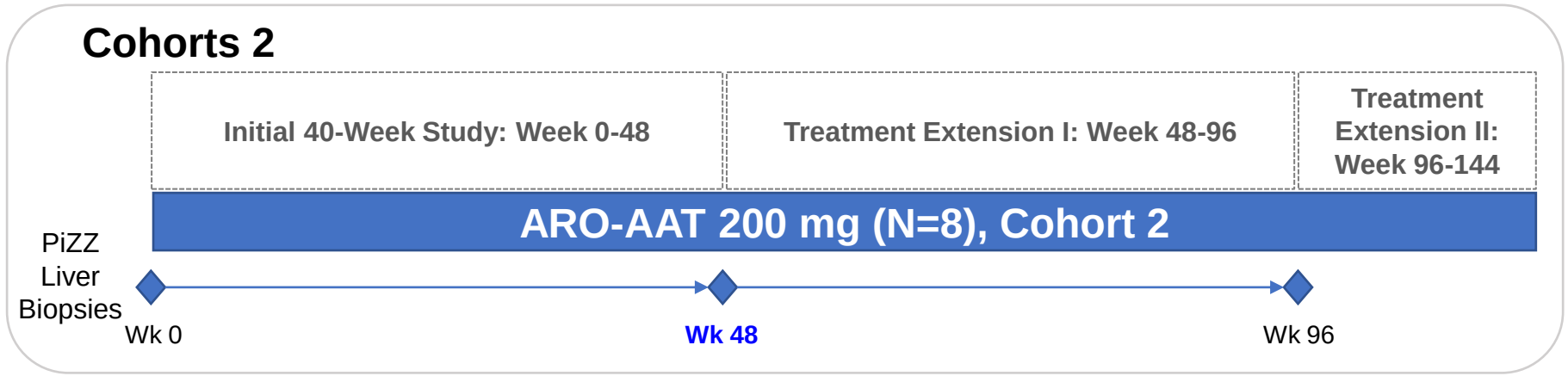
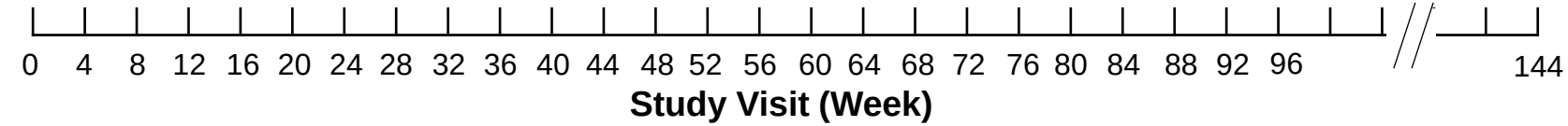
AROAAT-2002 Study Design







Endpoints

- Serum Z-AAT and liver Z-AAT (total, monomer, polymer)
- Adjudicated Histology
  - PAS+D Globules
  - METAVIR fibrosis score
- Serum ALT, GGT, 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%)
Adjudicated METAVIR 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%)

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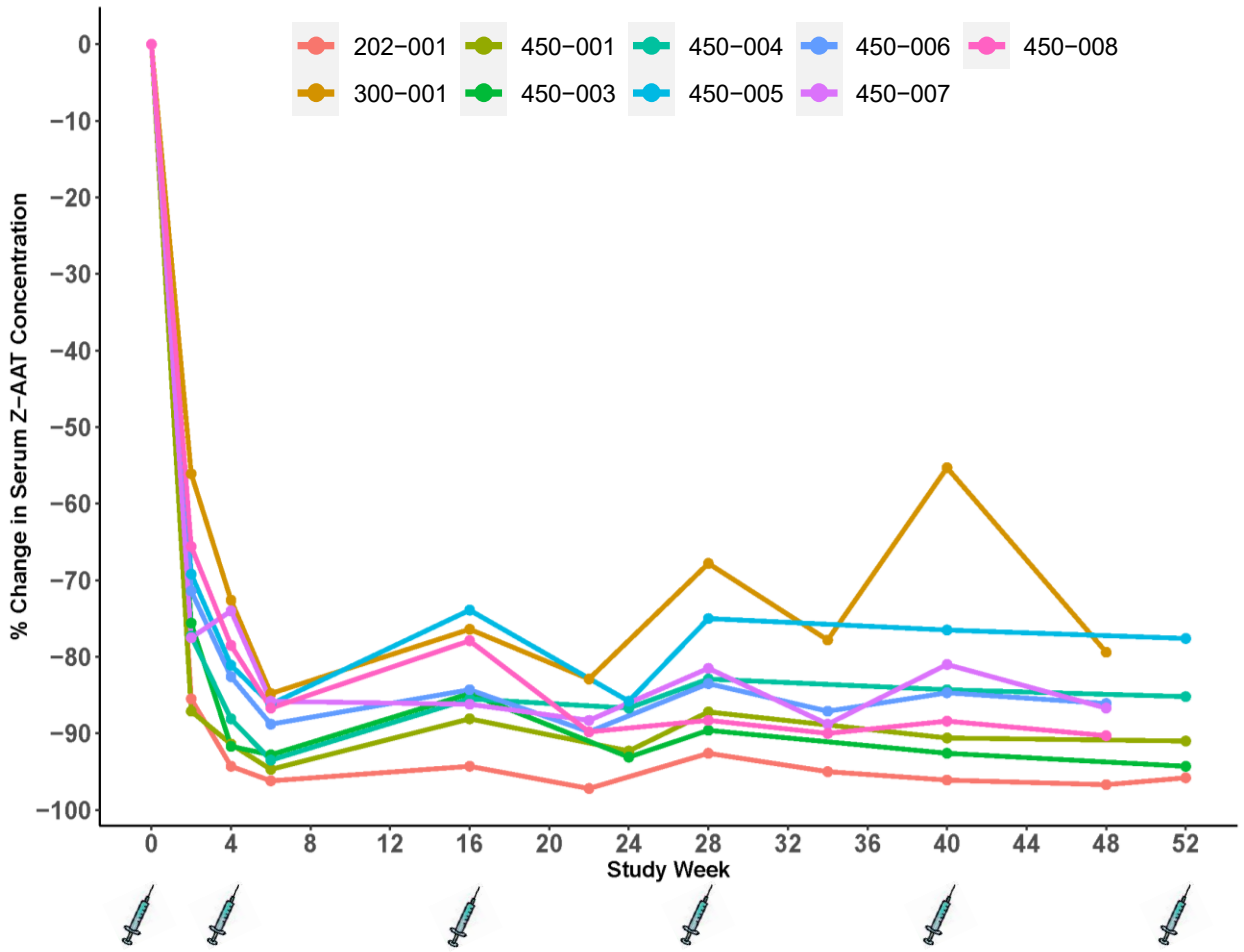
ARO-AAT Treatment Was Associated with Reduced Serum and Intra-hepatic Z-AAT Concentration



		% Change in Intra-hepatic Z-AAT Concentration
		Total
Cohort 1 (**Week 24**)	450-001	-78.6
	450-003	-95.1
	450-004	-72.2
	450-005	-73.4
Cohort 2 (**Week 48**)	202-001	-89.7
	300-001	-80.1
	450-006	-89.4
	450-007	-77.0
	450-008	-97.0
All Median (N=9)		**-80.1**

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ARO-AAT Treatment was Associated with Reduced Histological Globule Burden and Improvement in Liver Fibrosis

At 48 weeks (cohort 2)
Four of the five patients achieved a 1 stage improvement in Metavir fibrosis score with no change in the other patient.

At 24 weeks (cohort1)
Two of the 4 patients achieved improvement in Metavir Fibrosis stage, both had F4 (cirrhosis) at baseline

All 9 subjects had a decrease in histological liver globule burden

Conclusions and Next Steps

ARO-AAT, a RNAi designed to silence Z-AAT expression, was associated with:

- Rapid and Profound Reduction in serum and intrahepatic levels of Z-AAT.
- All 9 patients demonstrated a reduction in histologic globule assessment scores.
- Improvement in Fibrosis score in 6/9 patients including 2 patients with baseline cirrhosis.
- Safety profile and tolerability favorable.

- **Interactions with FDA are ongoing to identify path forward toward a registration plan.**

- **Collaboration with Takeda and transition plan on target**