siRNA Gene Silencing Approach for AATD Liver Disease

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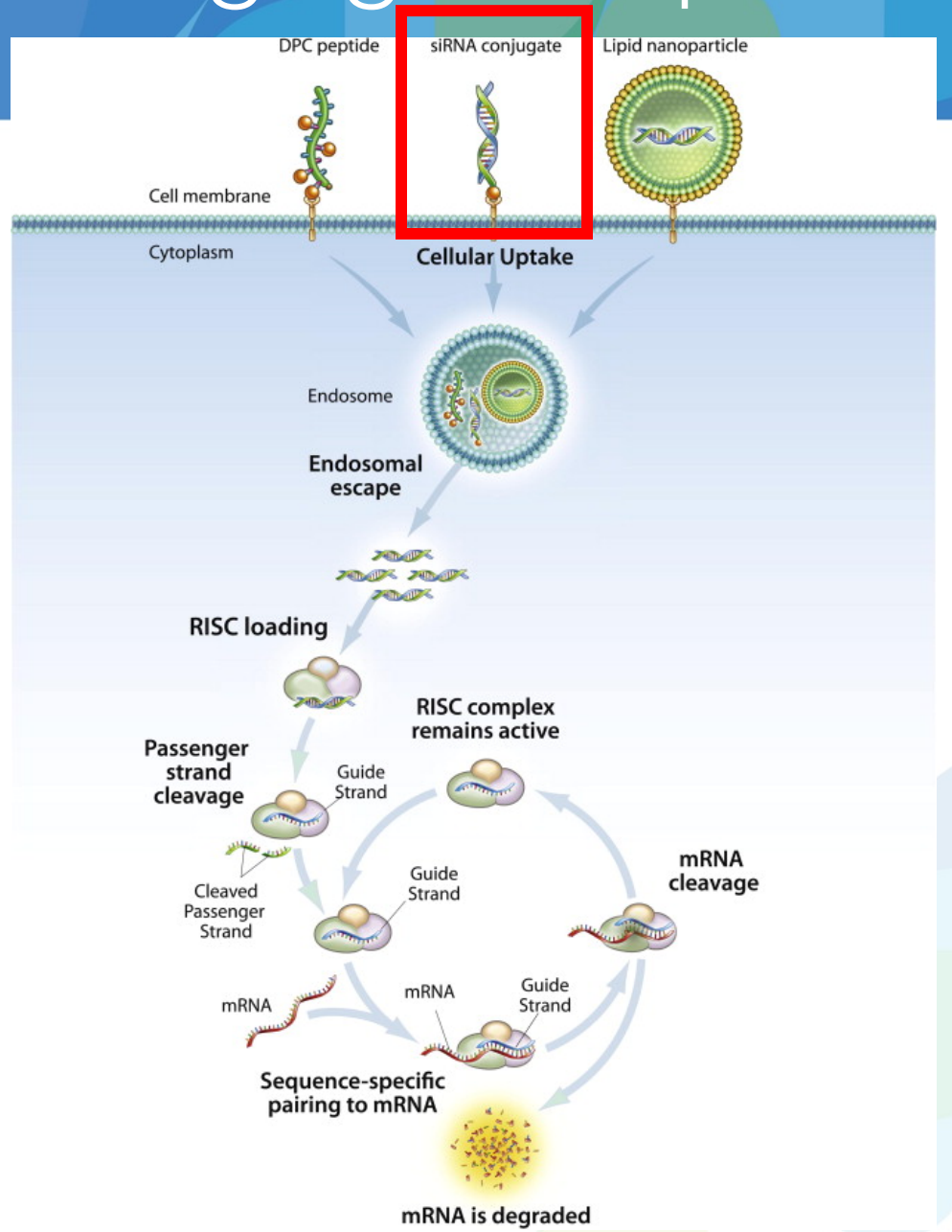
Agenda

- Background: siRNA and Therapeutic Approach
- Animal model efficacy data: preventative and improvement
- Clinical Studies with RNAi therapeutic ARO-AAT

siRNA Gene Silencing: An Emerging Therapeutic Modality

- RNAi is a method of silencing gene targets and is an emerging therapeutic modality
- Relies on delivery of siRNA into the cytoplasm
  - Liposomes or ligand directed hepatocyte uptake via asialoglycoprotein receptor
- Stable siRNA molecules survive endosome, engage with RISC to silence mRNA
- Catalytic nature of siRNA leads to long duration of potent gene silencing



siRNA Gene Silencing: A Maturing Therapeutic Approach

- May be ideal for:
  - Targets not addressable with small molecules or monoclonal antibodies
  - Where systemic exposure and off target effects may lead to unacceptable toxicity.

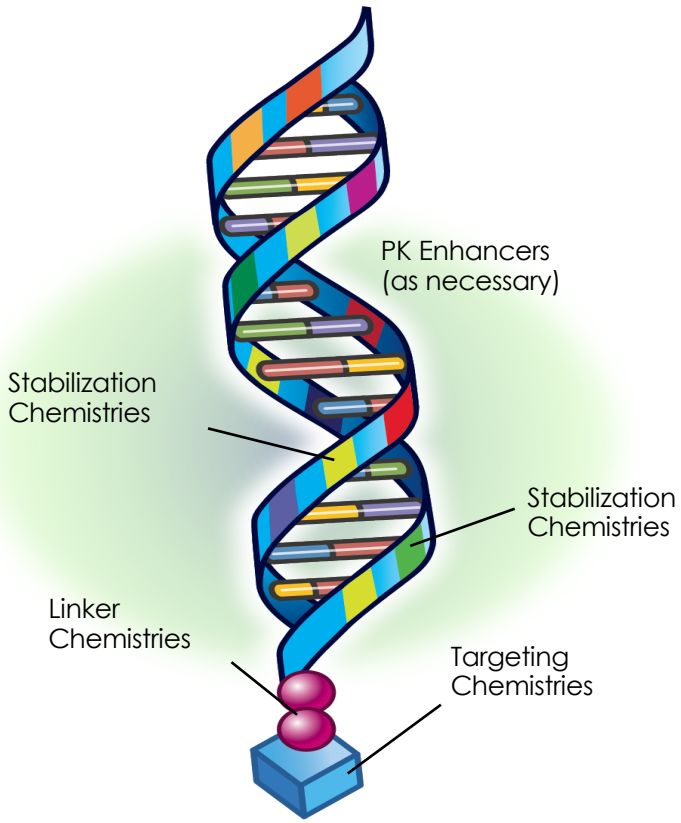
- One FDA approved product (patisiran for hereditary transthyretin mediated amyloidosis) utilizing liposomal intravenous delivery

- Multiple “GalNac” conjugates in late stage development

ARO-AAT

Targeted RNAi Molecule

TRiM™ platform



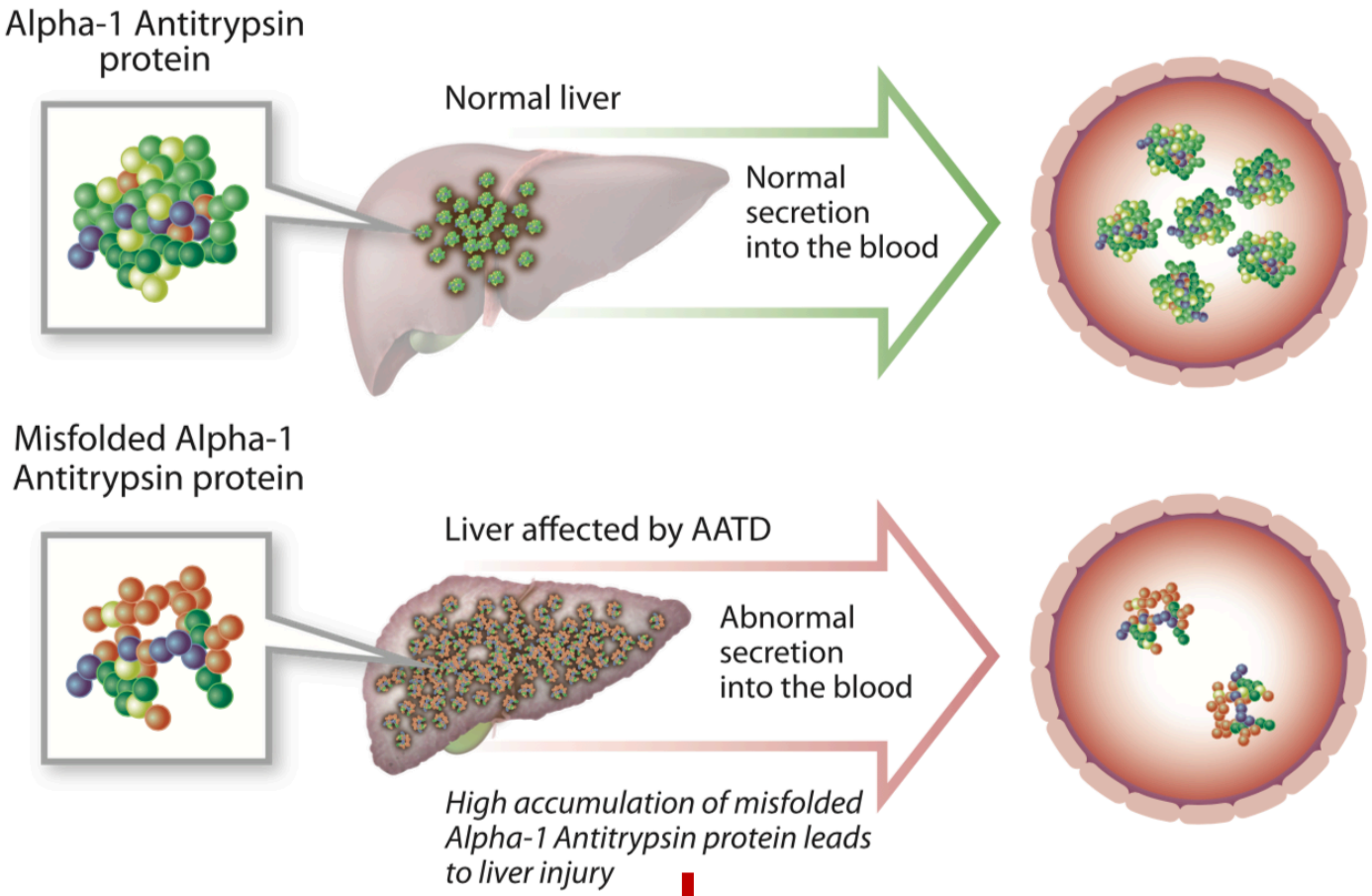
ARO-AAT: Investigational product in development to address liver disease in AATD

Hepatocyte targeted RNAi molecule

Specifically targets AAT mRNA

- Silencing is hepatocyte specific
- Designed to minimize off-target gene silencing

Liver Disease in Alpha-1 Antitrypsin Deficiency



Normal blood levels of normal protein protect lungs, no liver accumulation

Low blood levels of abnormal protein leaves lung susceptible to damage from inflammation caused by inhaled irritants or infection, accumulated protein injures liver

No current treatment

Lung Disease Treated with AAT protein replacement therapy today

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What is the Risk of Developing Liver Disease

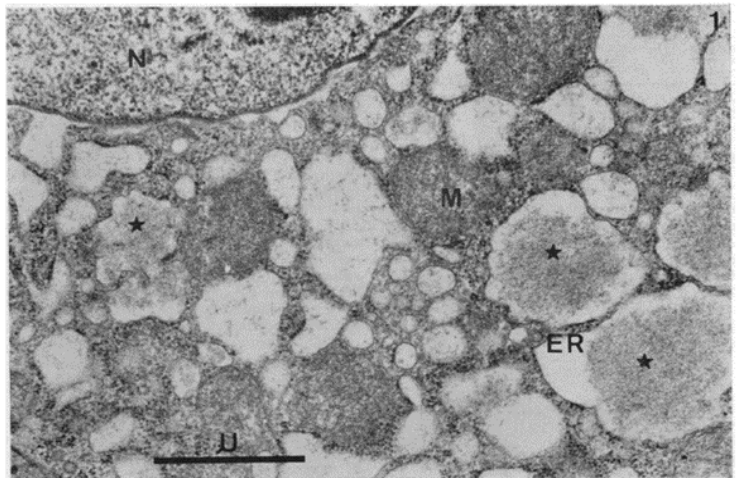
Recent baseline data from natural history study on liver involvement in AATD (Clark et al., 2018)

- Evaluated liver biopsy in 94 PiZZ AATD adult patients
- 35% demonstrated clinically significant (≥ F2) liver fibrosis based on biopsy
- Additionally, common medical conditions may further increase risk
  - Obesity
  - Hypertension
  - High cholesterol
  - Diabetes

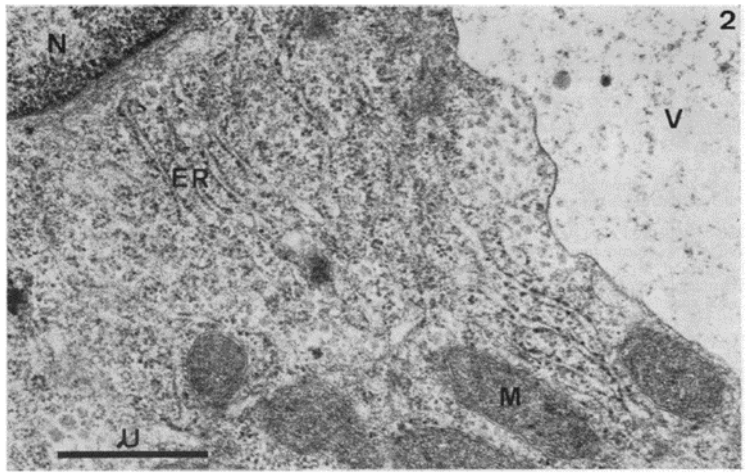
RNAi Therapeutic Rationale

- RNAi trigger designed to stop Z-AAT production by silencing AAT gene to:
  - Prevent accumulation of Z-AAT in liver
  - Allow clearance of accumulated Z-AAT protein
  - Prevent repeated cycles of cellular damage
  - Prevent/Reverse progression of liver fibrosis

PiZZ phenotype (diseased)

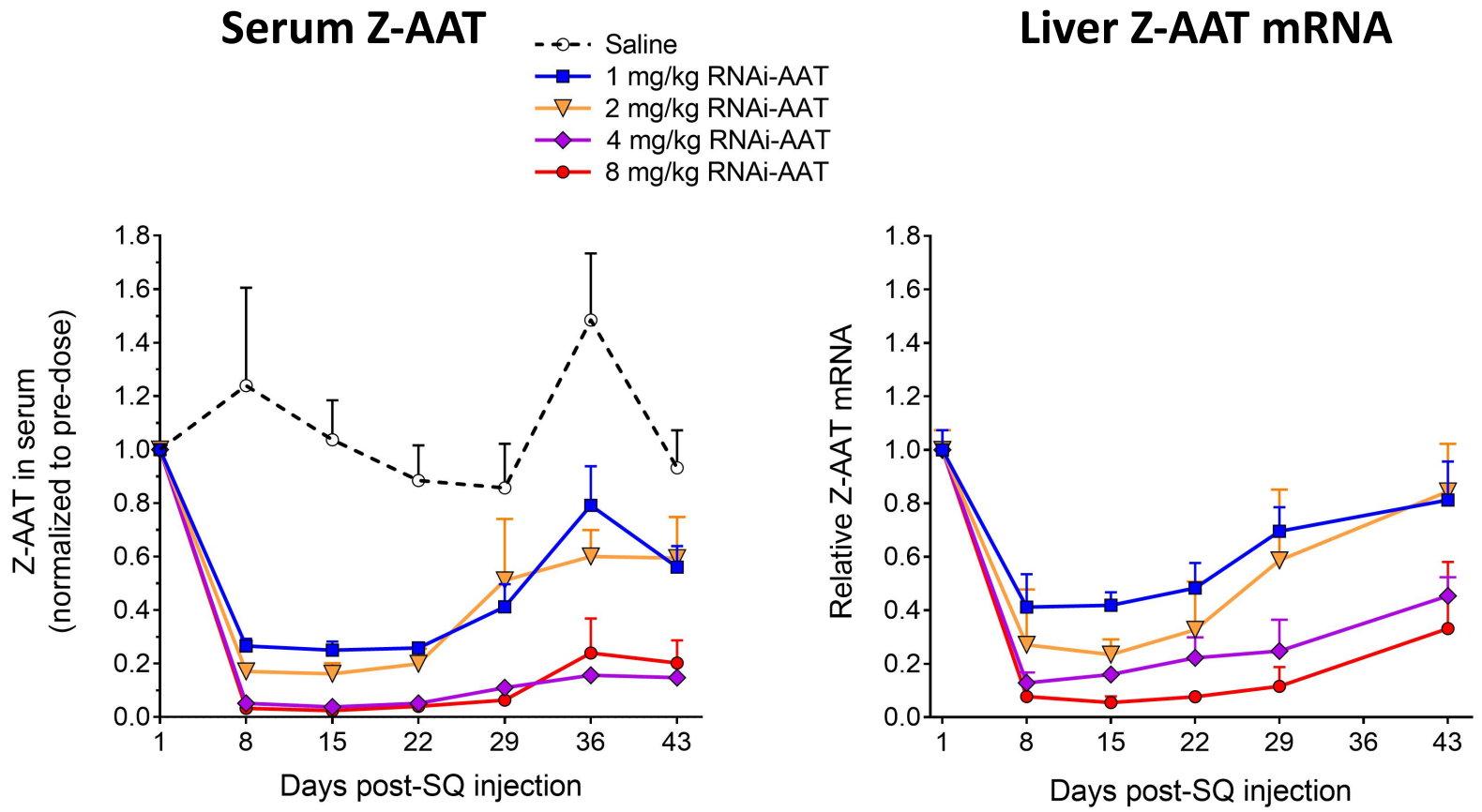


Pi null phenotype (normal)



RNAi Produces Deep AAT Knockdown

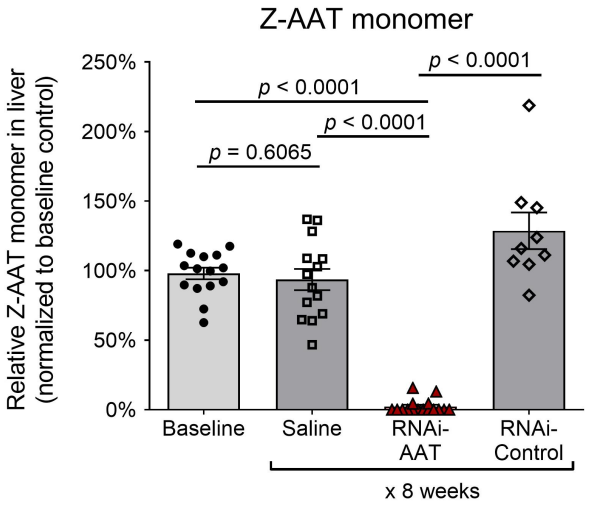
PiZ transgenic mouse model

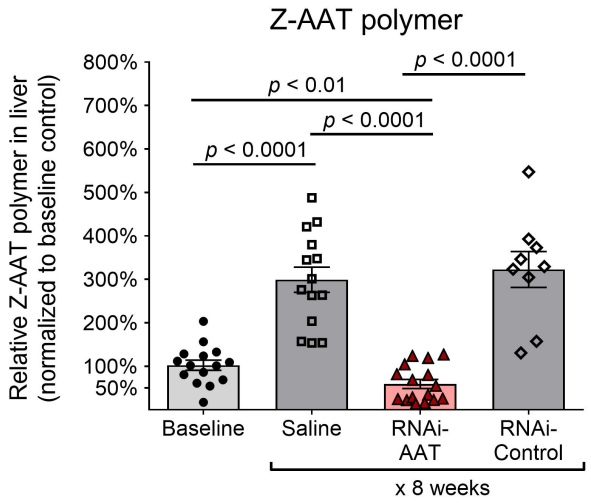


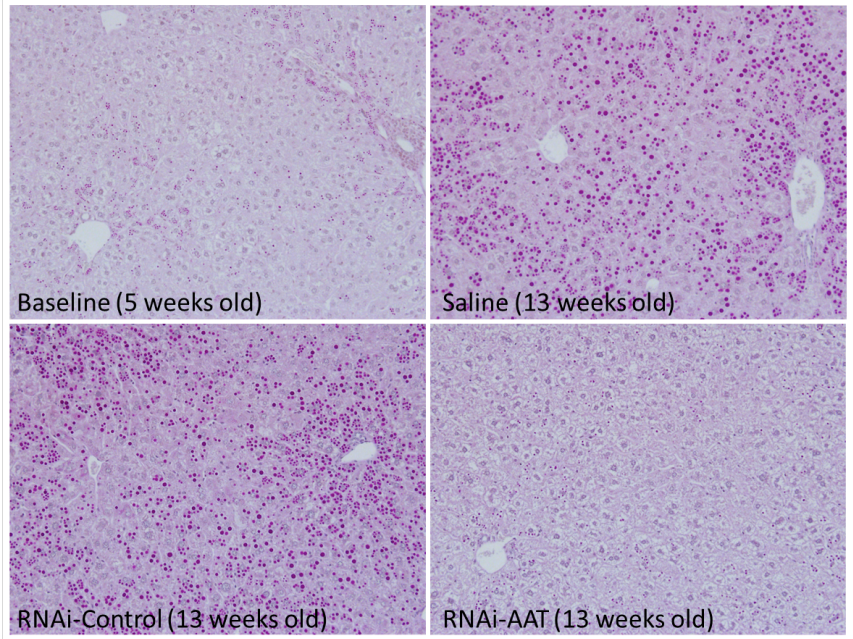
RNAi Dose (mg/kg)	Maximum Serum AAT Reduction	Maximum Liver mRNA Reduction
1	75%	59%
2	84%	77%
4	96%	87%
8	98%	95%

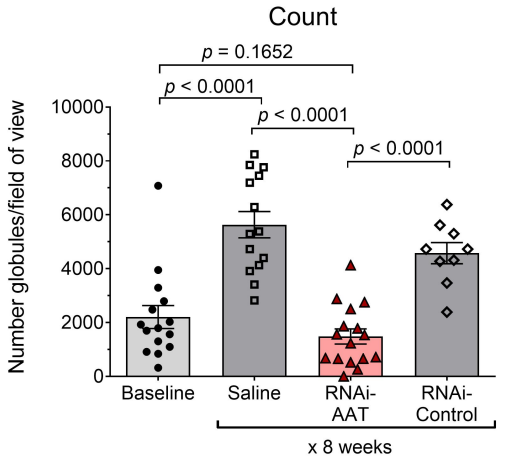
RNAi Prevents Progression of Liver Disease in Young PiZ Mice: liver Z-AAT

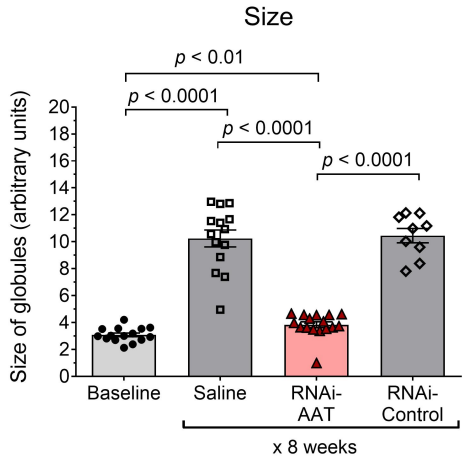
5 weeks old; *Q2W x 4*











98% less soluble (monomer) Z-AAT

41% less insoluble (polymer) Z-AAT

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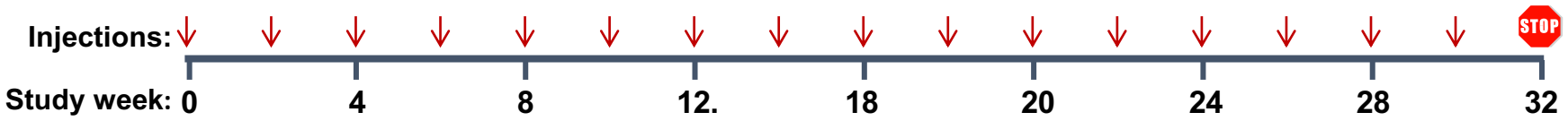
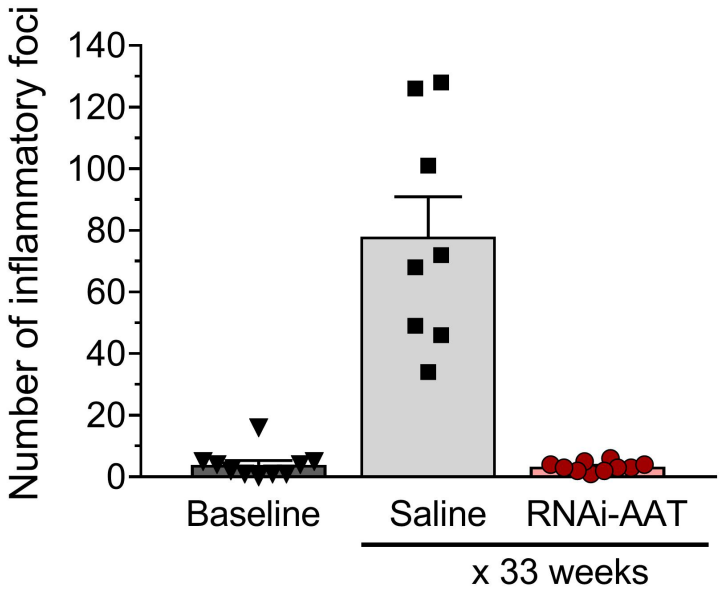
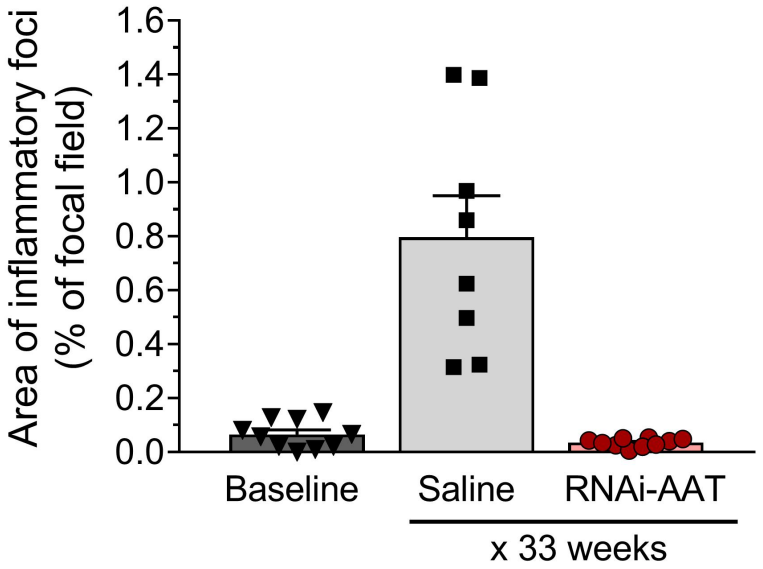
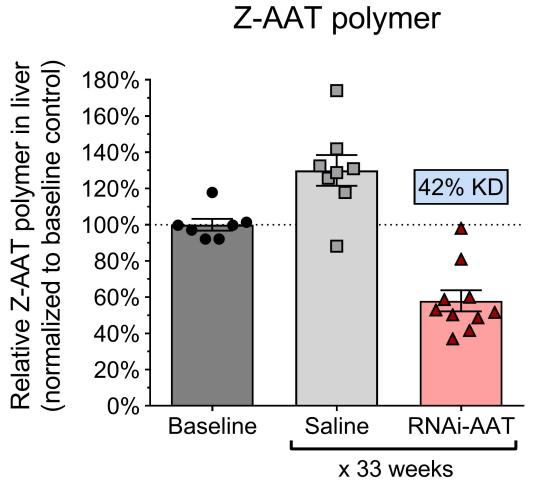
RNAi Improves Liver Disease Phenotype in Older PiZ Mice: liver histology

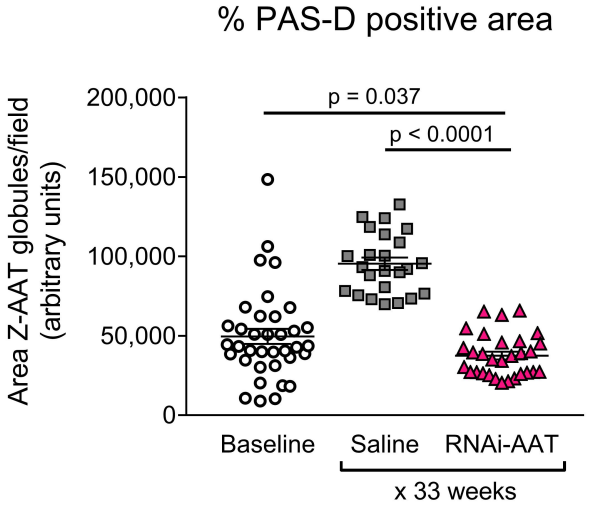
11-17 weeks old; *Q2W x 16*











RNAi treatment improves liver physiology and prevents further damage;
Fewer inflammatory foci and reduced total area of inflammation

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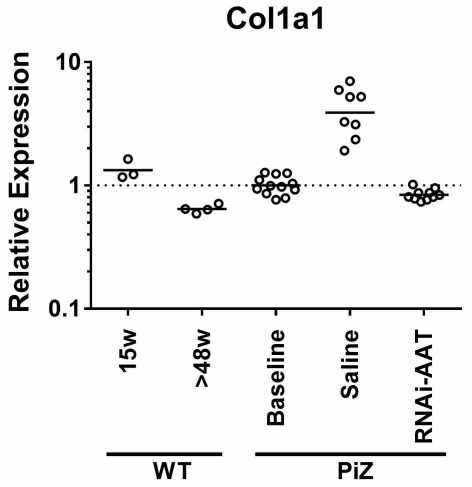
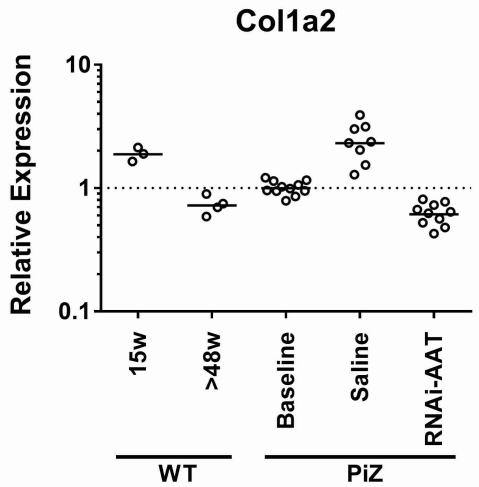
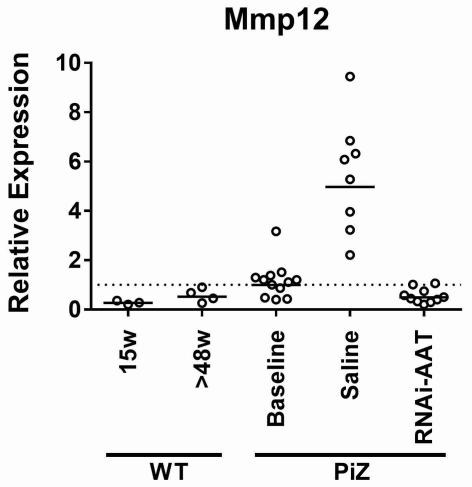
RNAi Reduces Fibrosis Gene Expression

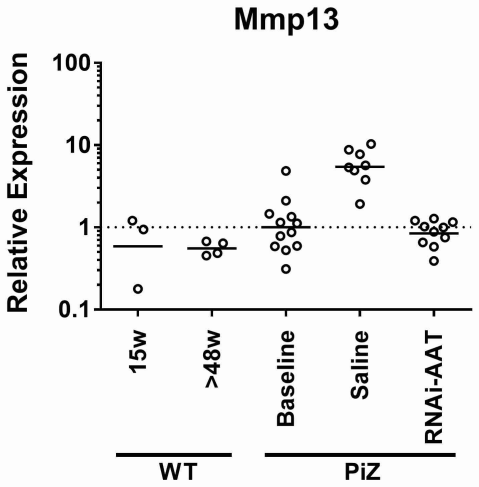
Reduced gene expression associated with fibrosis in the liver
PiZ transgenic mouse model

- Fibrosis gene expression increases with age in untreated (saline group) PiZ mice
- RNAi prevents the increase in fibrosis gene expression









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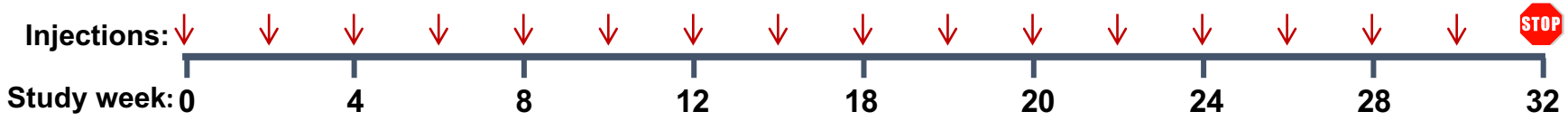
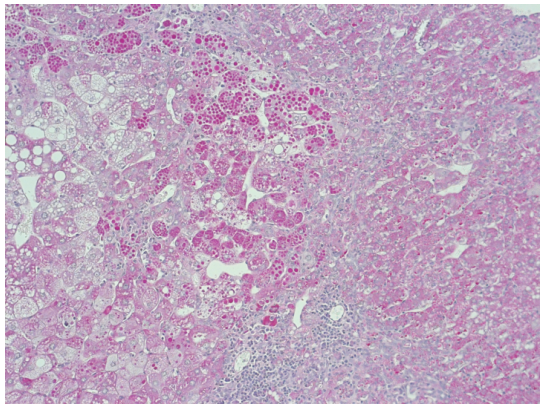
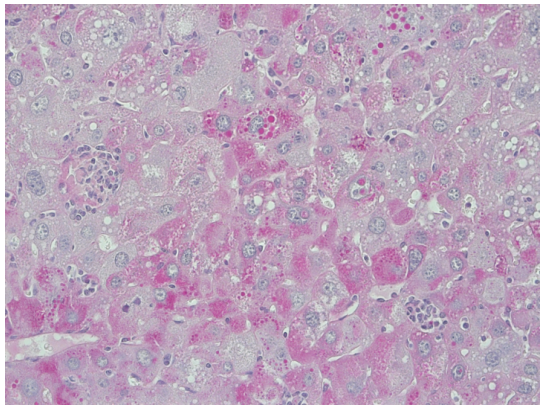
RNAi Prevents Liver Tumors in Old PiZ Mice

15-16 months old; *Q2W x 16*

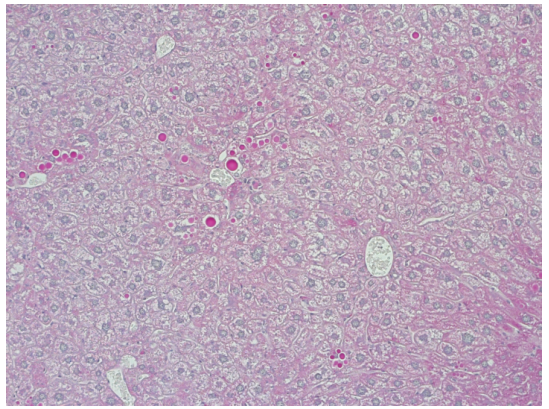




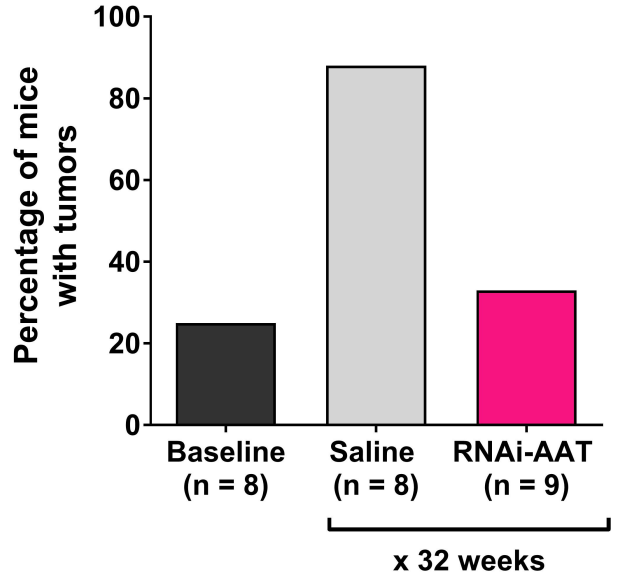
Baseline (15-16 months old)
globules, inflammation, neoplastic hepatocytes in some mice



Saline x 32 weeks
globules, inflammation, neoplastic hepatocytes, tumors



RNAi x 32 weeks
Rare globules, normal morphology



RNAi reduced tumor incidence over the treatment period

ARO-AAT Phase 1 Study in Healthy Volunteers

OPEN LABEL

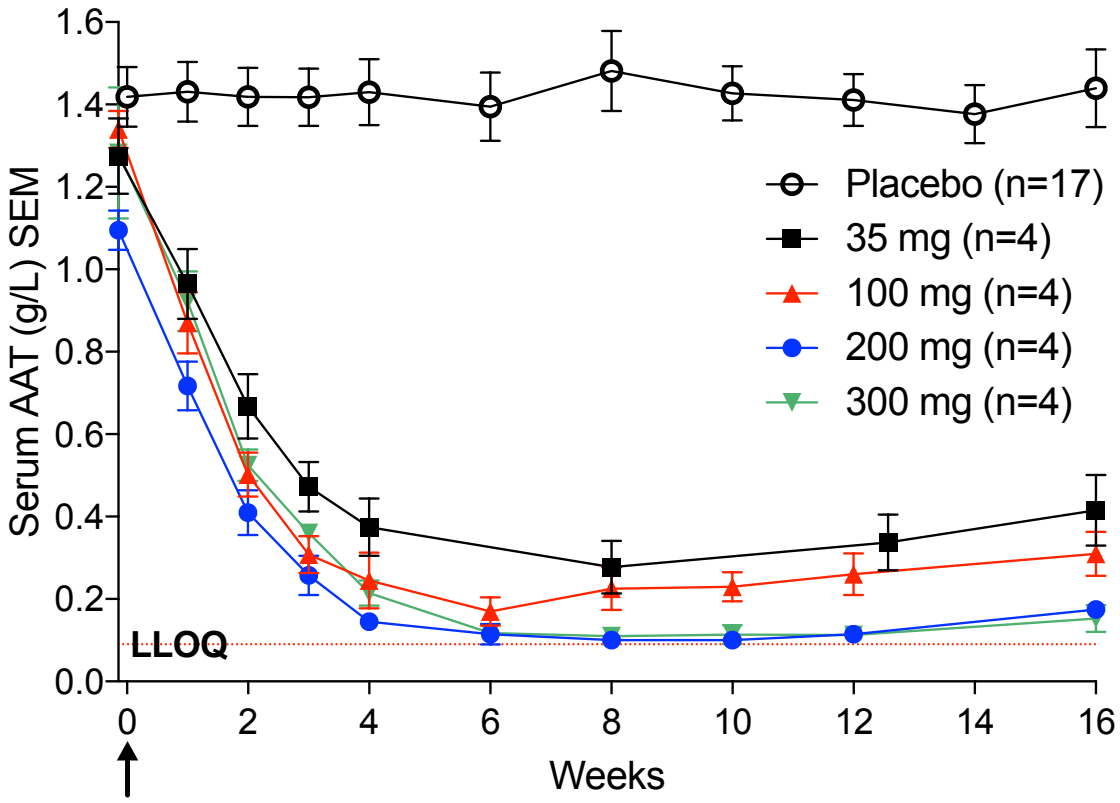
- 3 groups
  - ***Single dose*** of 100, 200 and 300 mg of ARO-AAT
  - 4 per cohort
- Assessments of safety, tolerability, depth and duration of AAT reductions after a single dose

DOUBLE BLIND

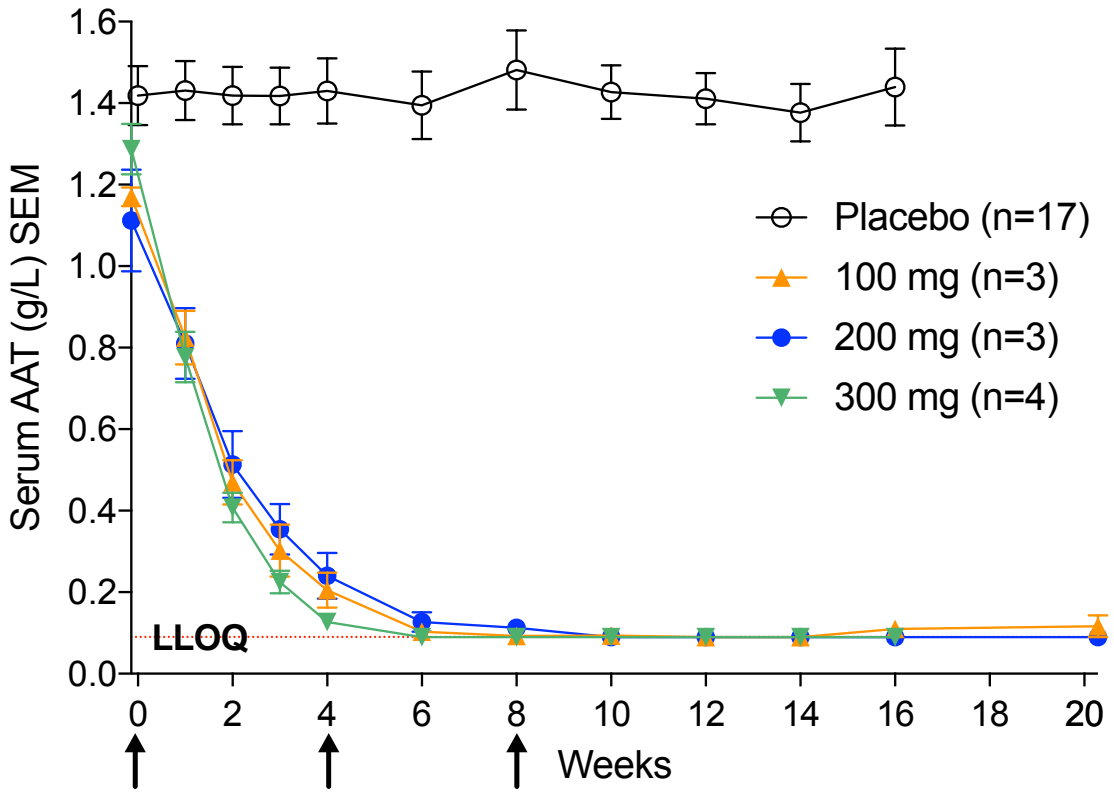
- 4 treatment arms
  - 35, 100, 200 and 300 mg
  - 100, 200, 300 mg receive ***3 monthly doses***
  - 4 active, 4 placebo
- Assessments of safety, tolerability, plasma levels of ARO-AAT, plasma AAT changes

ARO-AAT Phase 1, NHV Dose Response

Single dose Cohorts

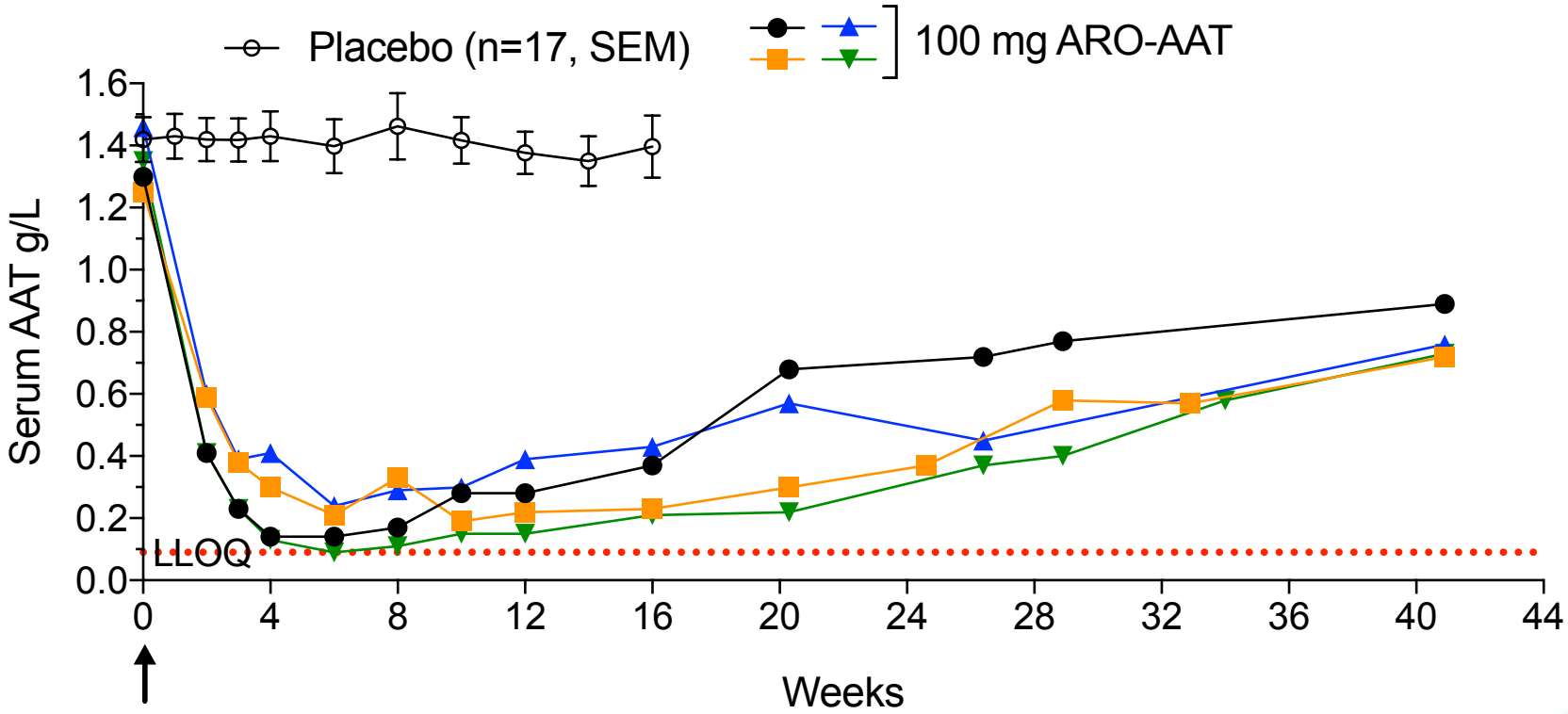


Multiple dose Cohorts



ARO-AAT Phase 1: Serum AAT Reduction Duration

Single dose ARO-AAT



ARO-AAT Phase 1: Summary Safety

ARO-AAT Phase 1, NHV SAD/MAD study Safety Summary

- 45 NHVs received at least 1 dose (28 active, 17 placebo)
- No deaths, severe AEs or serious AEs reported
- Mild Local Injection Site Reaction (LISR) in 4% of ARO-AAT injections
  - LISR defined based on MedDRA preferred term for injection site AEs with duration of at least 48 hours
- No AEs secondary to platelet count declines, changes in renal function parameters or changes in markers of liver injury/function
  - 3 treatment emergent grade 1 ALT elevations, all returned to baseline by end of study, with max elevation < 2X ULN

Safety Considerations with this Approach

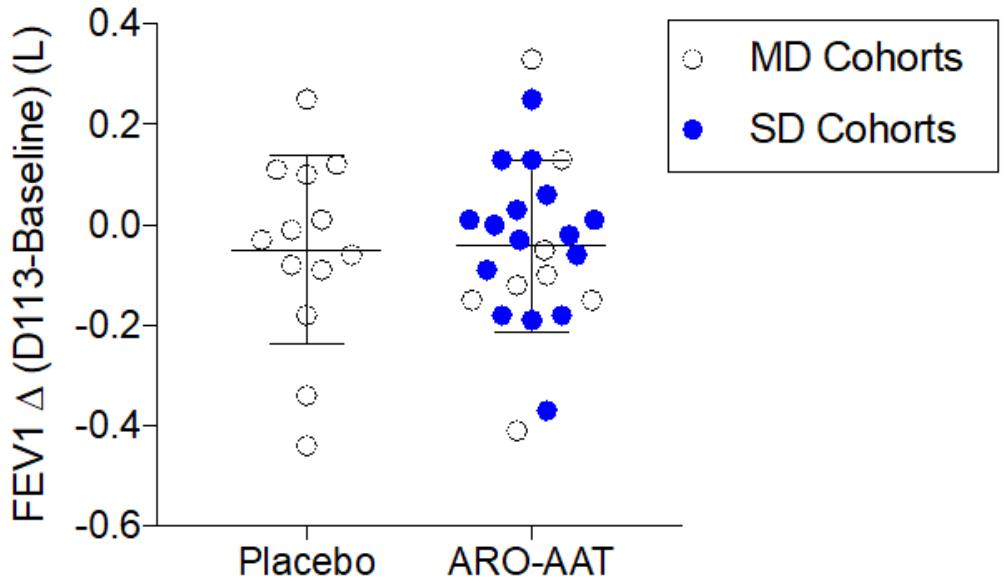
- While AATD is a storage disease in the liver, it is a deficiency disease relative to the lung
- Emphysema takes decades to develop in AATD patients
- Null/null patients are thought to develop emphysema earlier
- While not creating true null/null plasma levels due to extra-hepatic production, RNAi will significantly reduce serum AAT levels and pulmonary risk is the key disease-specific toxicity to be assessed in clinical programs. Thus, finite therapy would be preferred, if feasible

Pulmonary Safety: Considerations and Inclusion Criteria

AROAAT1001 lung related I/E criteria

- Required non-smoker, normal FEV1 (based on ATS-ERS guidelines) at baseline
- Normal serum AAT at baseline (above lower limit of normal range, 90 mg/dL)
- Conducted spirometry at multiple timepoint throughout study and during post-study follow up
- FEV1 decline of at least 200 mL from baseline was pre-specified minimal important difference
- FEV1 is an effort dependent test, intra-subject variability can be a difficult issue during a short study

FEV1 Summary Through Day 113/EOS



AASLD 2018

- No AEs of dyspnea or other symptoms consistent with lung parenchymal damage
- 3 AEs of FEV1 decline, 1 active (3.6%) v 2 placebo (11.8%). None with reported symptoms. 1 on active rebounded above baseline FEV1 in extended follow up with near max AAT KD
- Declines in FEV1 of at least 200 mL on D113: 2 (8.6%) active v 2 (15.4%) placebo
- Declines in FEV1 of at least 200 mL at any visit through D113: 6 (21%) active v 2 (11.7%) placebo
- No statistically significant difference (ANCOVA) between active versus placebo FEV1 changes (% predicted or mL) at any study visit.

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Current Clinical Studies

AROAAT2001 SEQUOIA

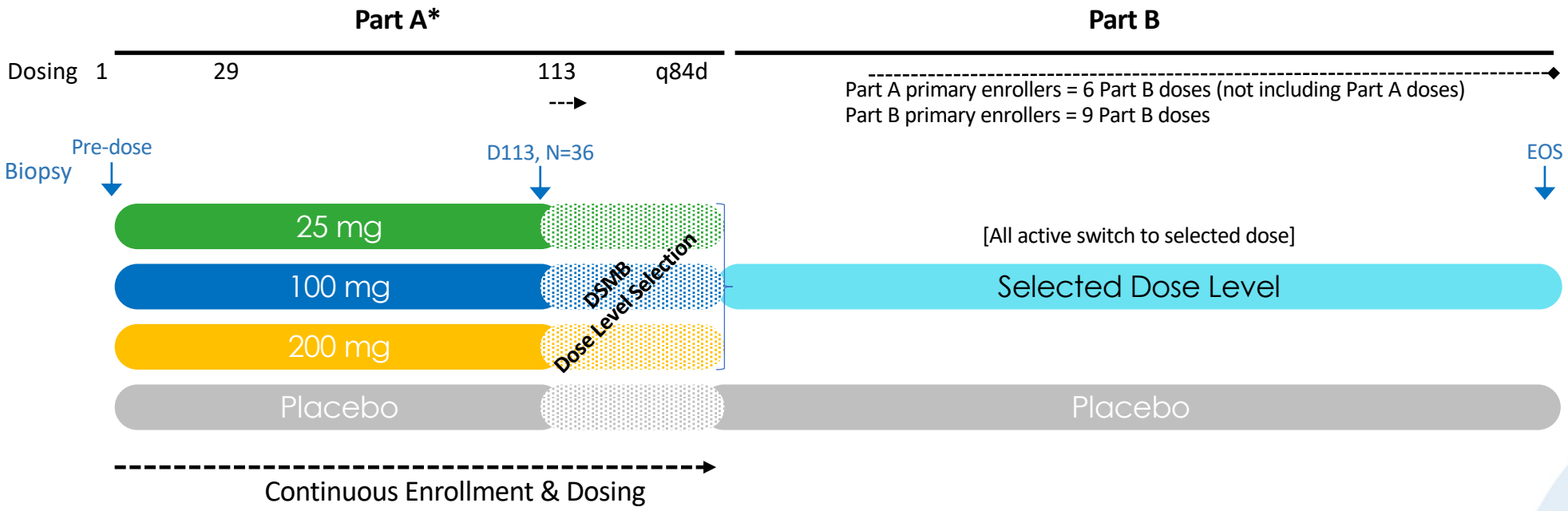
- Phase 2/3 adaptive design study
- # of ZZ Patients planned=120
- Location: Multiple sites in UK, EU, US and Canada
- Duration: 2-year minimum treatment
- Subcutaneous injection every 3 months after 2nd dose
- Biopsy required
- Placebo controlled
- At end of study all placebo will have the option to receive active in an extension study
- Part A Objective: to select a dose level for Part B
- Part B Objective: To evaluate efficacy based on biopsy
- Status: Currently Enrolling

AROAAT2002

- Phase 2 study
- # of ZZ patients planned=12
- Location: UK, Germany, Austria
- Duration: 6 to 24 month treatment
- Subcutaneous injection every 3 months after 2nd dose
- Biopsy required
- No Placebo
- Objective: To assess changes in liver disease activity scale based on biopsy
- Status: Expect to be recruiting by end of year (2019)

AROAAT2001 Study Design (SEQUOIA)

N=120 total, Randomization = 2:1 (active:placebo)



* All patients enrolled prior to Part B dose selection will be randomized to Part A cohorts and receive at least 3 doses at the Part A dose level before switching to Part B dose level. Only 1st 36 will require D113 biopsy.

Placebo patients will be rolled over to ARO-AAT at end of study

Key Questions to Answer in SEQUOIA Phase 2/3 Adaptive Trial

- Phase 2
  - Dose response for Z-AAT (monomer and polymer) knockdown in PiZZ AATD patients
  - Safety/tolerability of multi-dose treatment in PiZZ AATD patients
  - Best dose for maximizing AAT knockdown in context of safety/tolerability
  - Best dose selection by DSMB in consultation with FDA (sponsor remains blinded)
- Phase 3
  - Improvement in an AATD specific histological scale without worsening of fibrosis
  - Safety with special attention to pulmonary effects

Summary

- ARO-AAT consistently induces deep and prolonged reductions in serum AAT levels, likely due to hepatocyte gene silencing
- In NHVs, no clear association between AAT decline and adverse FEV1 changes or pulmonary AEs over a several month period
- While FEV1 declines as a measure of pulmonary toxicity were not expected in Phase 1, results from this study are reassuring, particularly if ARO-AAT can be used as a finite duration therapy (e.g. 2-3 years) to ameliorate Z-AAT liver accumulation
- More data is needed in an AATD patient population with longer treatment periods
- The AROAAT2001 study is the result of constructive collaboration with U.S. regulators to develop a novel clinical trial approach to AATD liver disease
- Both studies are open for enrollment and are the first studies to evaluate the impact of gene silencing on AATD liver histology and pulmonary function

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