The Emerging Safety and Activity of TRiM™ Platform Based siRNA Drugs

Oligonucleotide-Based Therapeutics Conference
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DIA

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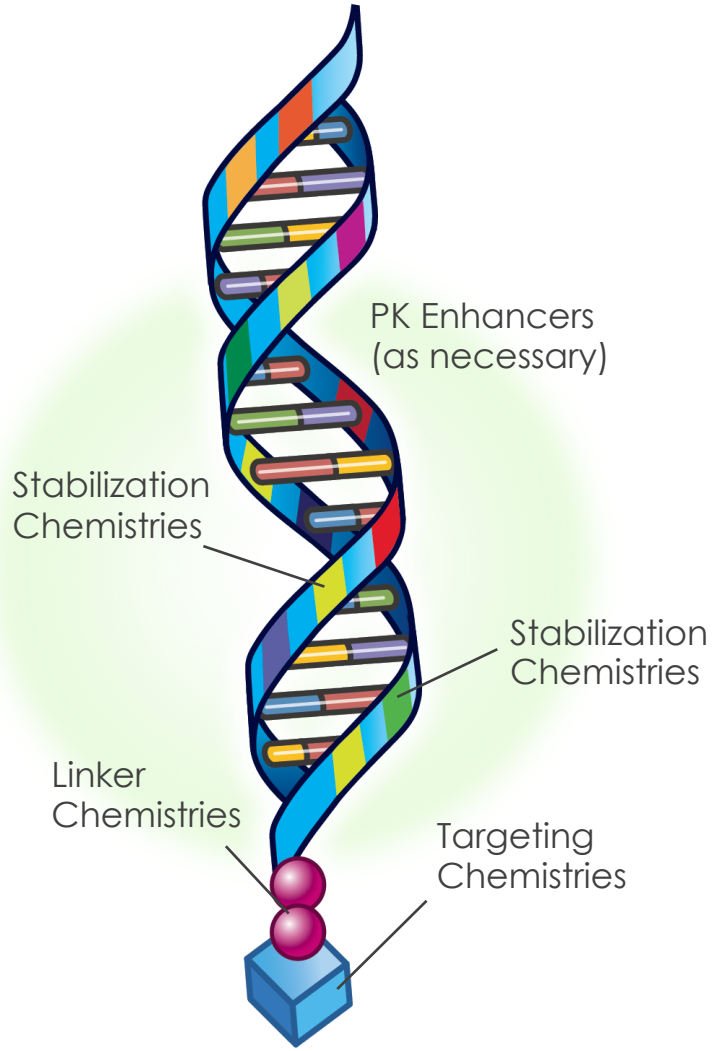
Disclosures

Arrowhead Pharmaceuticals: Employee and Shareholder

Agenda

- Technology/Platform Introduction
- Summary pharmacodynamic data by program
- Across program platform safety data

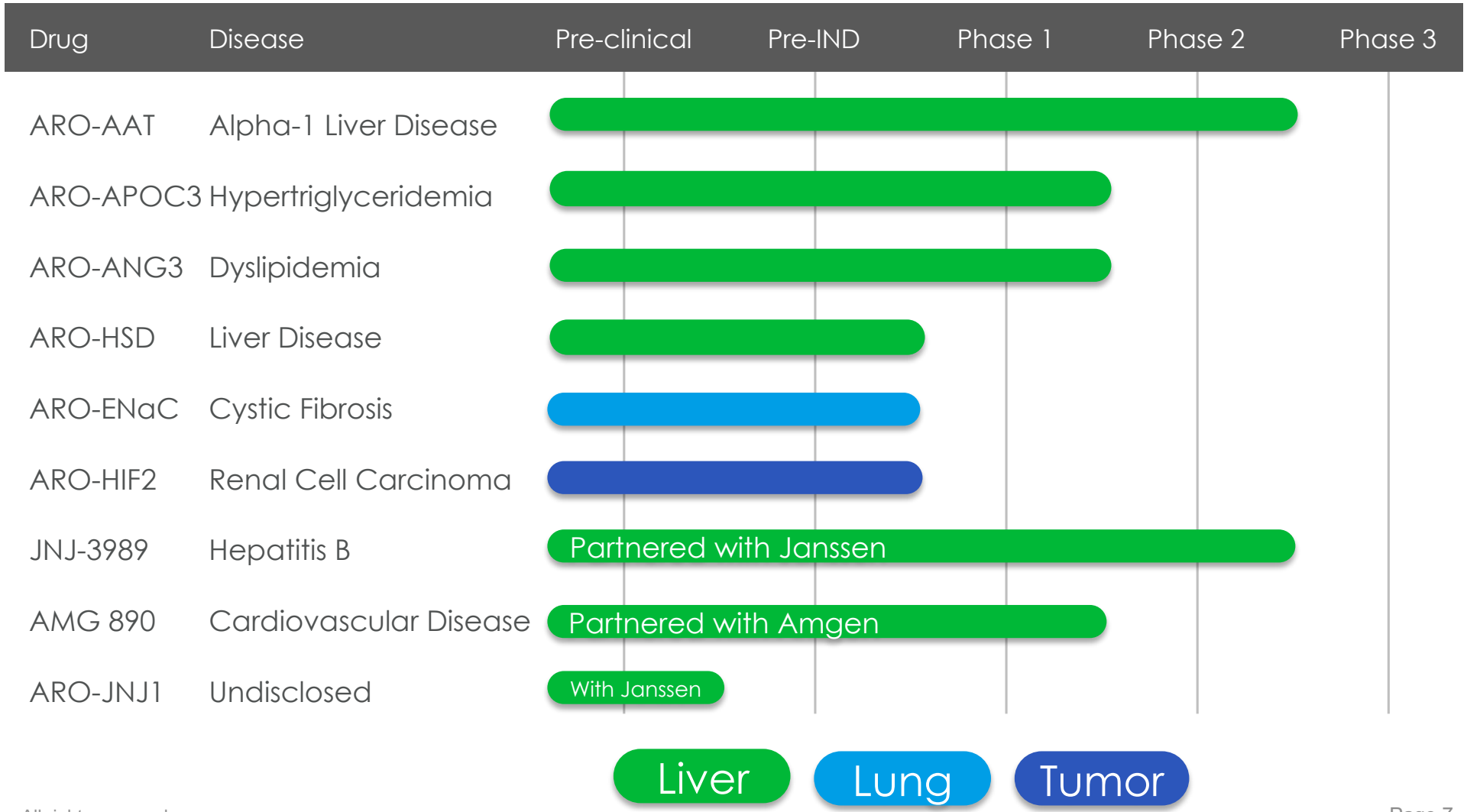
TRiM™ Platform



Components:

- Stabilization chemistries
- PK enhancers as necessary
- Linker chemistries
- Targeting ligands

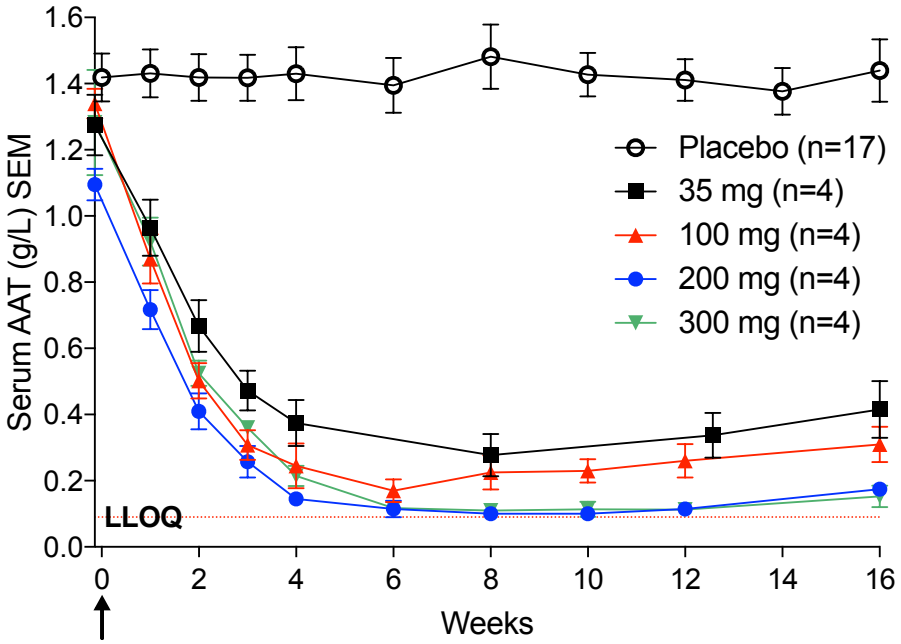
Pipeline



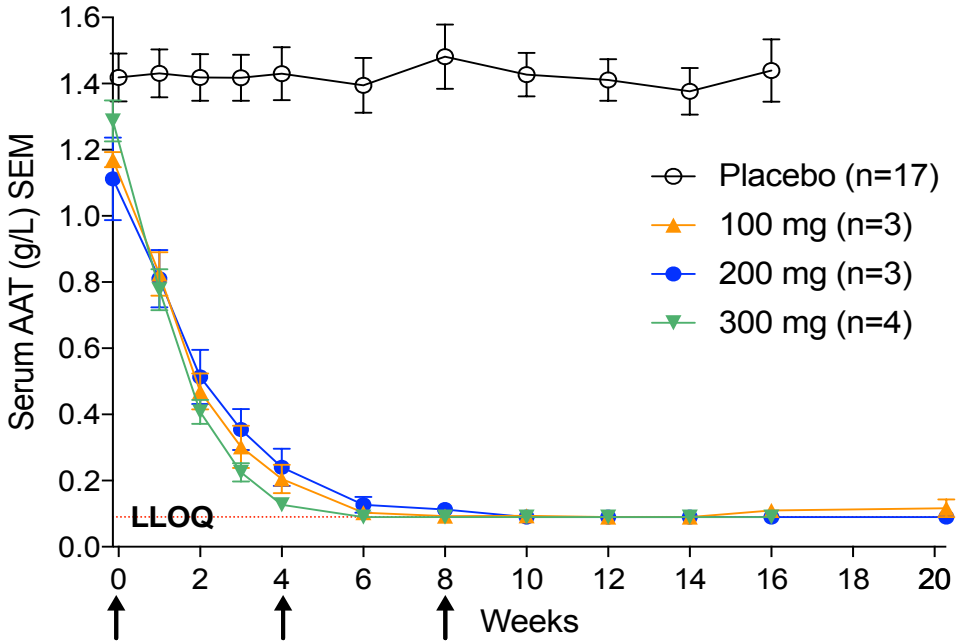
TRiM™ Clinical Pharmacodynamic Profile

ARO-AAT Phase 1, NHV SAD/MAD Study

Single dose ARO-AAT

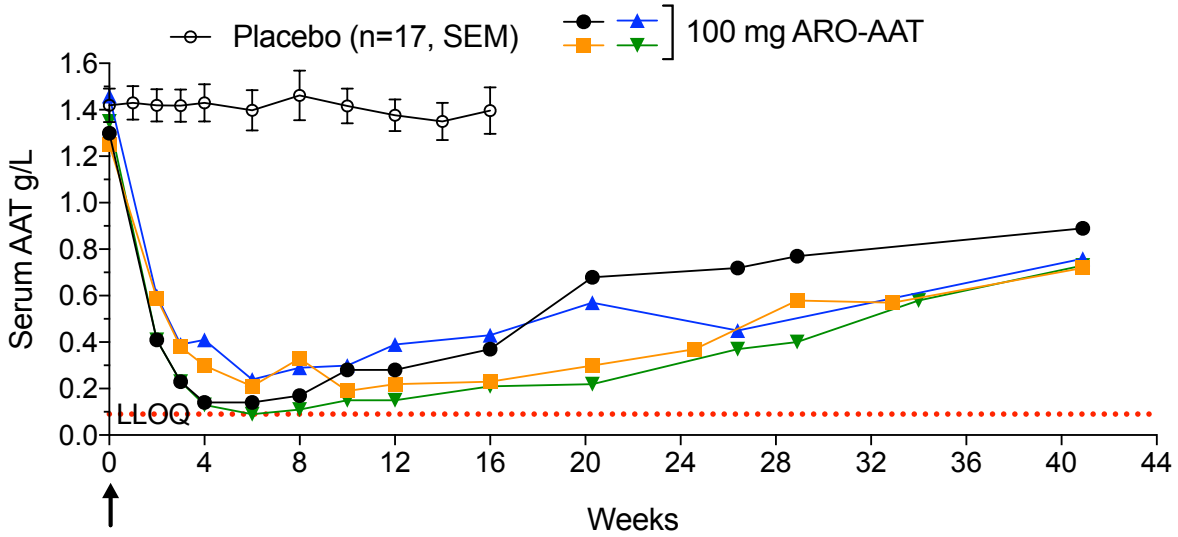


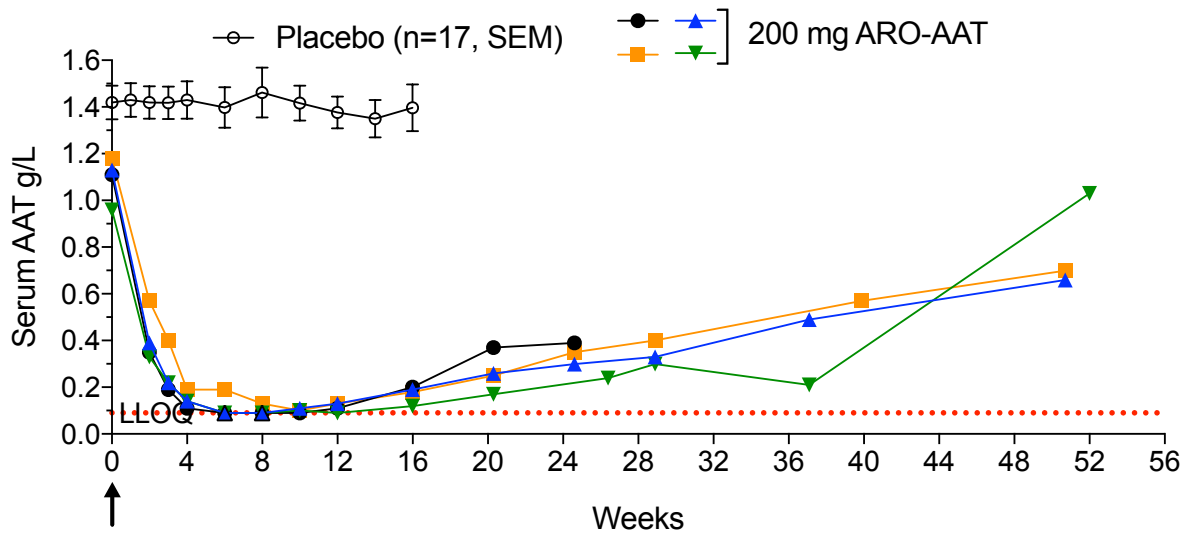
Multiple dose ARO-AAT



Supports quarterly or less frequent dosing

AROAAT1001 Serum AAT Duration

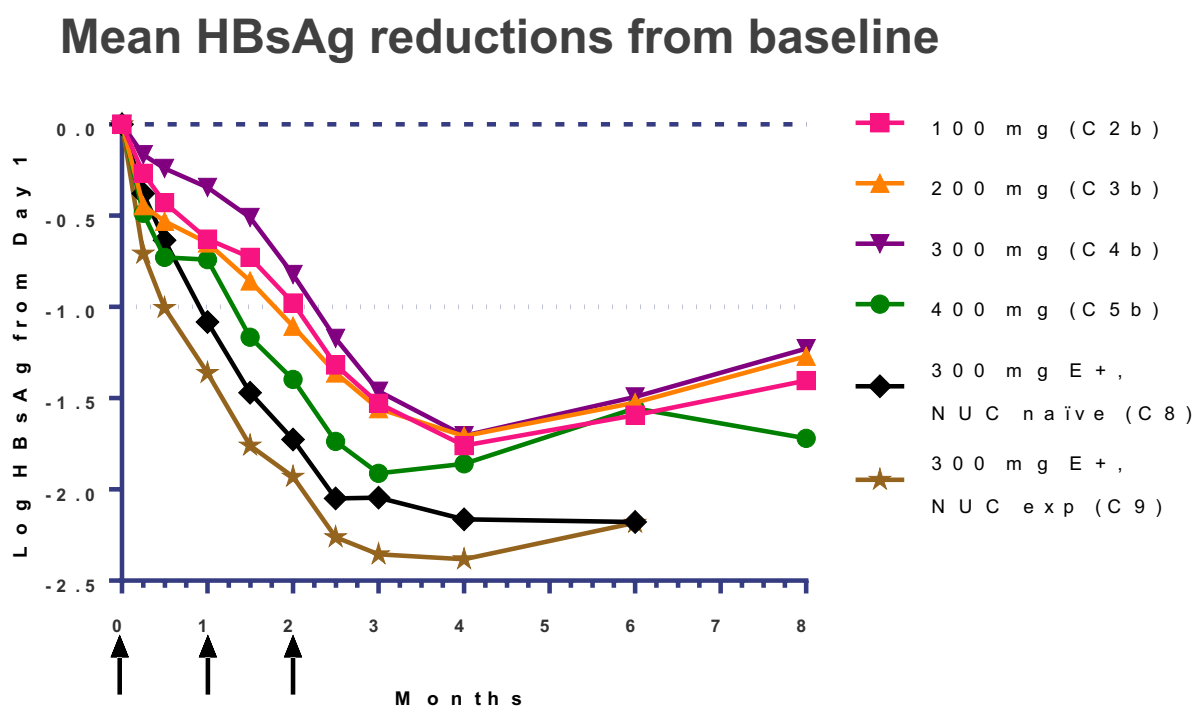




- Rebound initiates at approximately week 12
- All subjects return towards baseline although duration of effect remains durable

AROHBV1001: CHB Patient Data

AROHBV1001: double blind, single dose escalating study in healthy volunteers and open label, multi-dose escalating study in patients with CHB

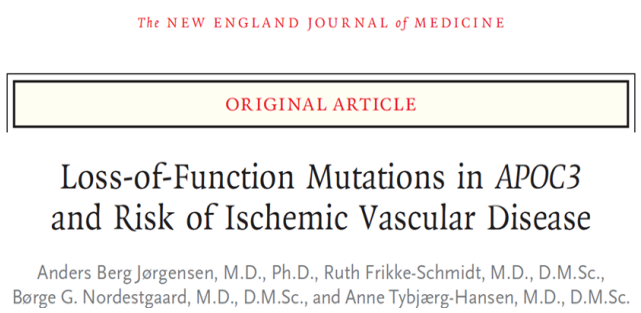


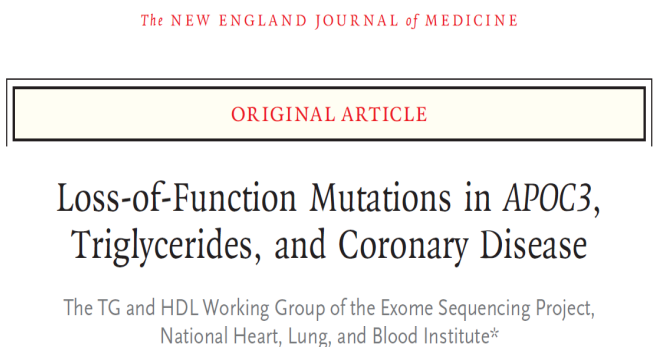
- NADIR in HBsAg is reached around 4 months post start of therapy
- Duration of pharmacologic effect persisted for > 4 months after last dose

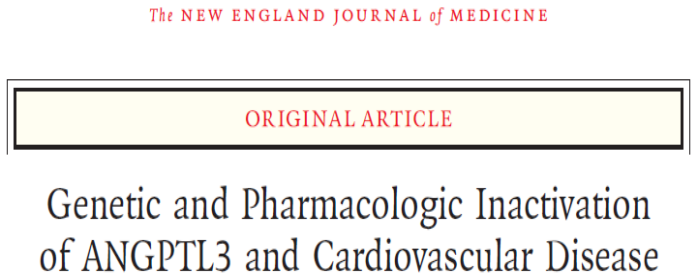
Triglyceride Targets Emerge: APOC3, ANGPTL3

Plasma triglyceride levels are an independent risk factor for cardiovascular disease (Rosenson, ACC, 2014)

- Genetic studies support causal relationship
- Independent of LDL-C or HDL-C

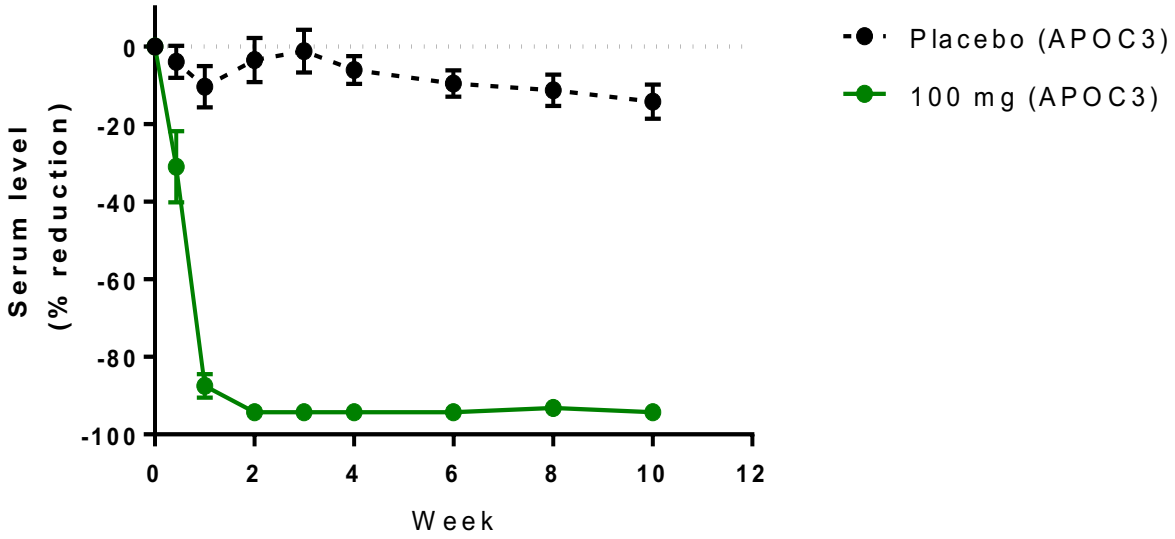




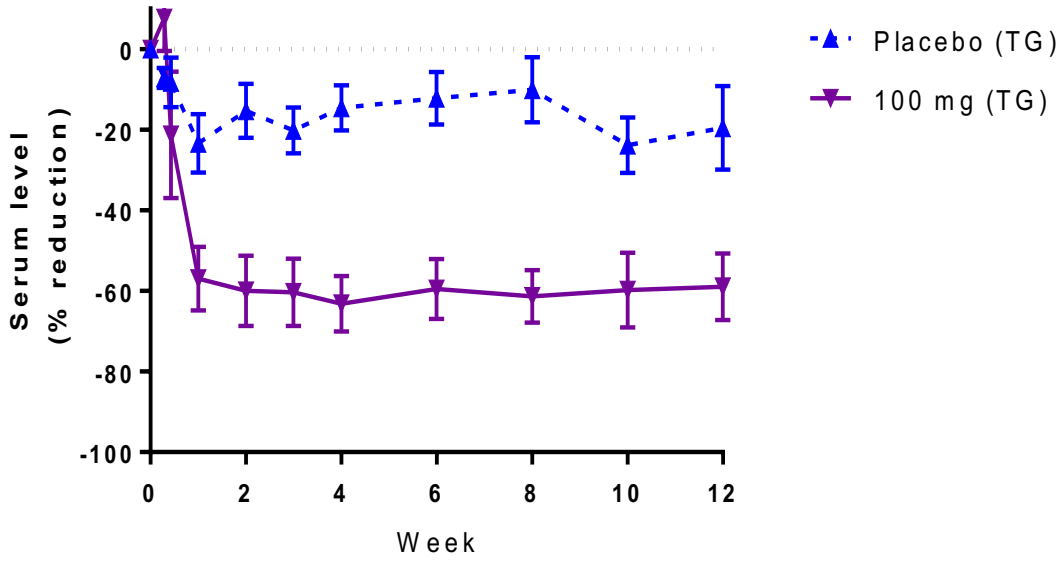


ARO-APOC3 in Healthy Volunteers - Single 100 mg dose through week 12

APOC3

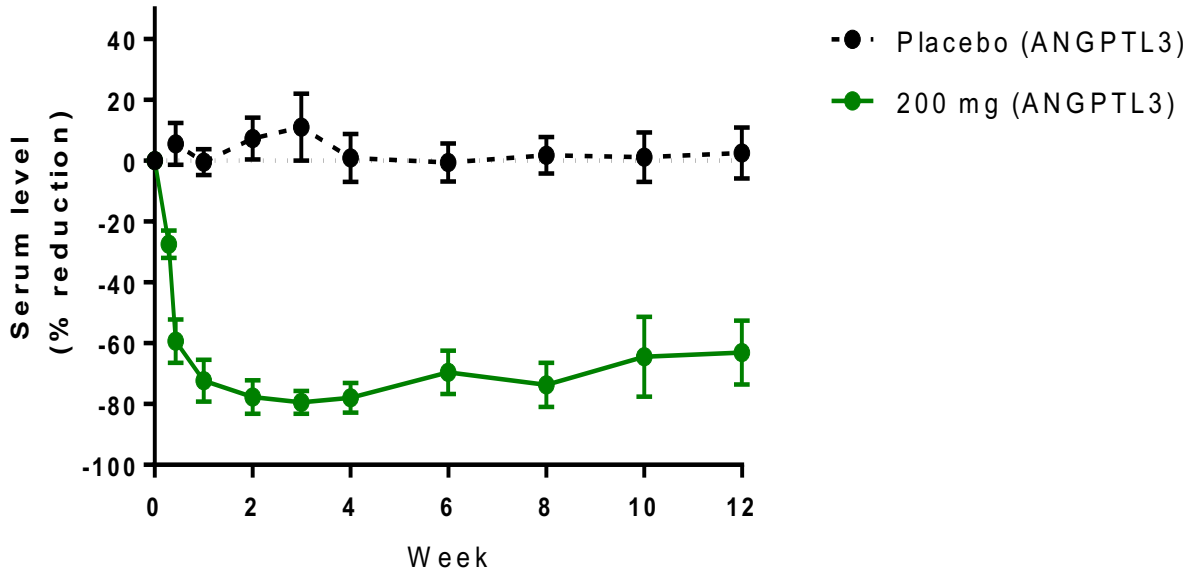


Triglycerides

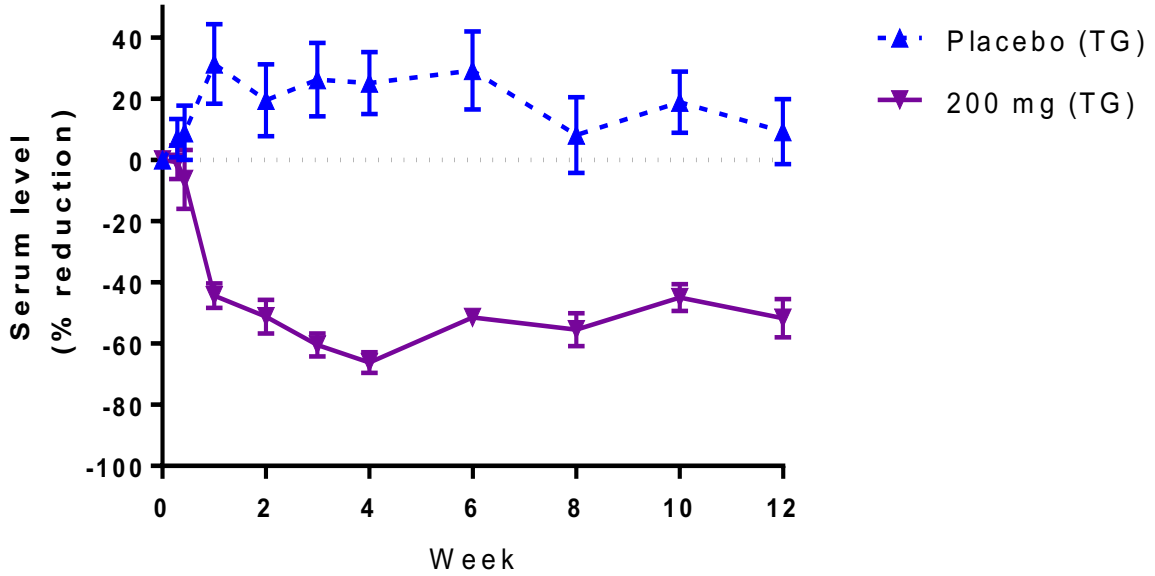


ARO-ANG3 in Healthy Volunteers – Single 200 mg dose through week 12

ANGPTL3



Triglycerides



TRiM™ Platform Pharmacodynamic Summary

- For hepatocyte gene targets, single dose induces deep and prolonged gene target silencing.
- Nadir typically reached within 4 weeks but varies (biology and trigger dependent).
- For single dose administration, dose level to reach maximum hepatocyte gene silencing varies (also biology and trigger dependent).
- Duration implies opportunity for Q3-6 month dosing intervals

TRiM™ Clinical Safety Profile

Safety: Are There siRNA Class Effects?

Thoughts on oligonucleotide therapeutic safety profile primarily derived from older generation ASOs. siRNA specific profile becoming more clear with late stage data.

<u>Historical Profile Based on ASO, siRNA Literature:</u>

- Renal accumulation/toxicity: Primarily reported in relation to ASOs[1]
- Thrombocytopenia: Only reported for phosphorothioate ASOs[2]
  - MOA not entirely clear[3]
  - To our knowledge, has not been associated with siRNA therapeutics
- Transaminase elevations occasionally seen[4]
- Injection site reactions, also generally mild[5]

1. Benson et al., NEJM 2018, Drisapersen briefing document, NDA 206031, van Poelgeest, Am J Kidney Dix, 2013
2. Witztum et al., NEJM, 2019, Drisapersen briefing document NDA 206031, etc., Chi et al., 2017
3. Volanesorsen advisory committee briefing document, Chi et al., 2017
4. Alnylam RNAi Roundtable 2018
5. Alnylam RNAi Roundtable 2018, van Meer, Br J Clin Pharmacol, 2016

Emerging TRiM™ Platform Safety Data

- Reflecting on fully unblinded placebo controlled studies (AROAAT1001, AROHBV1001 NHV Cohorts, AROANG31001 NHV Cohorts)
- Total enrollment: active (at least 1 dose) = 72, placebo = 43
- Total of 94 doses active drug administered

	Active (n=72) #/%	Placebo (n=43) #/%
Serious Adverse Events	0	1 (2%)
AEs from renal function changes	0	0
AEs of thrombocytopenia or low platelets	0	0
AEs from ALT changes	1(1.4%)	1 (2%)
Local Injection Site Reaction (LISR), all “mild”	4 (5.6% of patients, 4.3% injections)	0

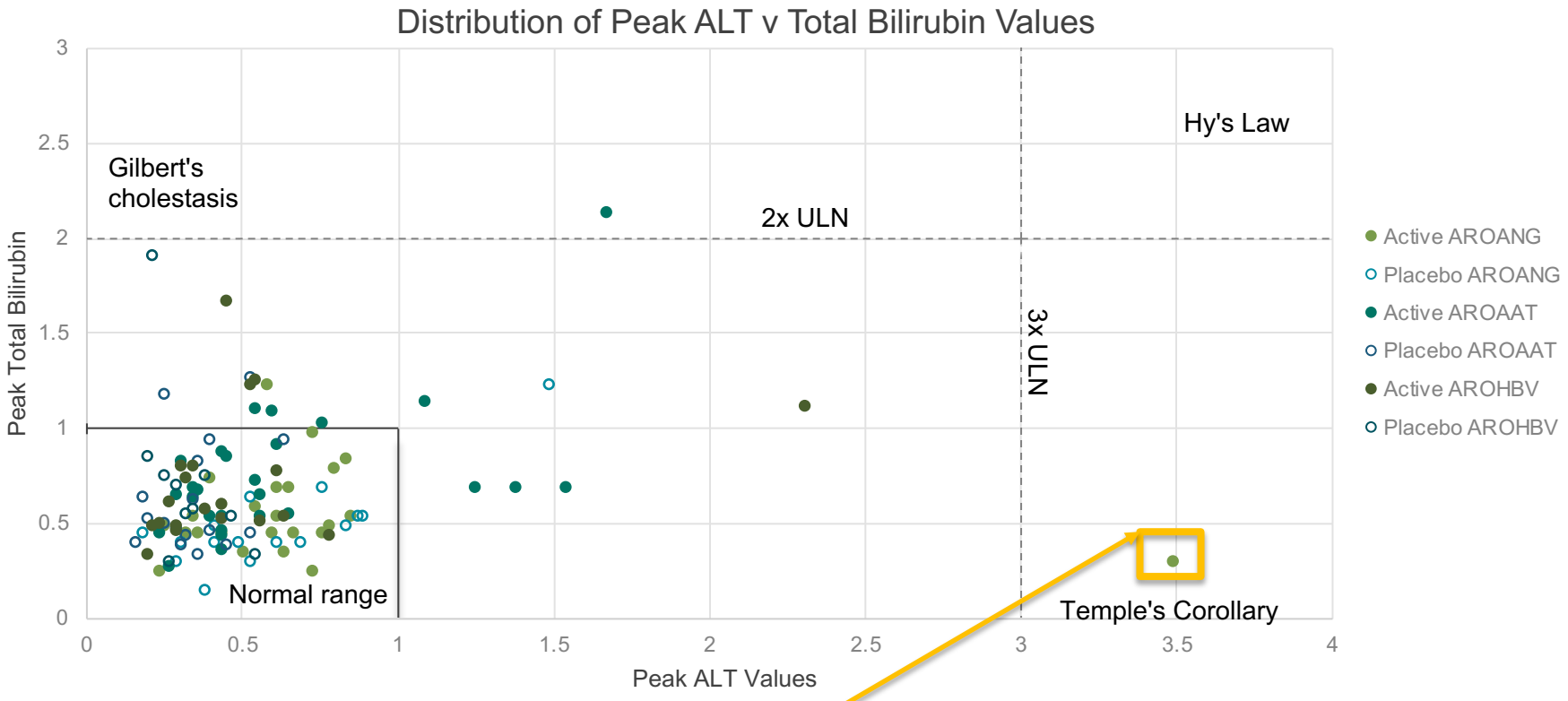
- LISRs: All mild, no drop outs due to LISRs

Emerging TRiM™ Safety: Platelets, Renal

Shift Table	Active (n=72)	Placebo (n=43)
Treatment emergent creatinine increase from Grade 0 to Grade 1	7 (9.7%)	4 (9%)
Treatment emergent creatinine increase to > Grade 1	0 (0%)	0 (0%)
Treatment emergent platelet count decline from Grade 0 to Grade 1	1 (1.4%)	3 (7%)
Treatment emergent platelet count decline to > Grade 1	0 (0%)	0 (0%)

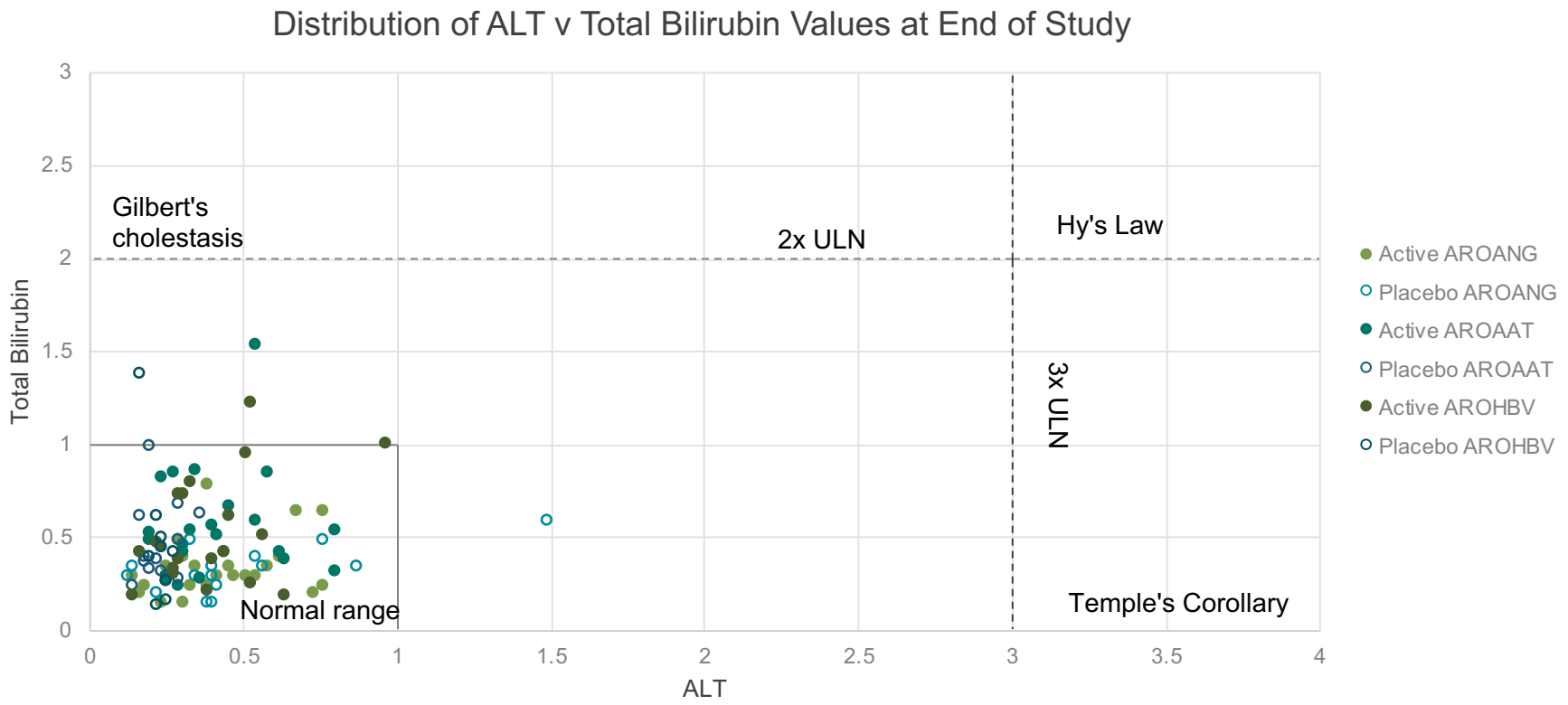
Emerging TRiM™ Safety: Evaluation of Drug Induced Severe Hepatotoxicity (eDISH)

Unblinded placebo controlled studies (AROAAT1001, AROANG1001 NHVs, AROHBV1001 NHVs)



ALT grade 1 at baseline (Day 1), shift to grade 2 (peak 192 U/L, Day 99) but confounded by temporally associated use of herbal supplement with published liver toxic profile. ALT normal at end of study.

Emerging TRiM™ Safety: eDISH



While pharmacologic effect lasts beyond Day 113 (typically End of Study), most excursions in ALT and total bilirubin have returned to baseline by End of Study

TRiM™ Summary Safety:

- Experience to date with platform suggests findings generally consistent with what has been reported for other liver targeted siRNA conjugates
  - No clear renal or platelet/immune/hematologic signals
  - LISRs occur but generally mild
  - Adverse ALT changes are infrequent, typically mild and of limited duration

Thank you!