



 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 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.

Our mission is to treat intractable medical conditions by silencing the genes that cause them using RNAi

Flexible TRiM™ platform

- Designed to silence genes across diverse tissue types

Broad pipeline

- 7 clinical programs built on TRiM™
 - 2 partnered; 5 wholly-owned
- 3 more CTAs expected to be submitted in 2020

Financial Highlights

ARWR - NASDAQ Global Select

Stock Price (3/6/20)	\$33.40
Common Shares Outstanding (12/31/19)	~101.1m
Market Capitalization	~\$3.4bn
Cash and Investments (10k 12/31/19)	~\$528m

Pipeline

Competitive Position	Drug	Disease	Pre-clinical	Pre-IND	Phase 1	Phase 2	Phase 3
First RNAi	ARO-AAT	Alpha-1 Liver Disease	[Green bar]				
First RNAi	ARO-APOC3	Hypertriglyceridemia	[Green bar]				
First RNAi	ARO-ANG3	Dyslipidemia	[Green bar]				
First RNAi	ARO-HSD	Liver Disease	[Green bar]				
First RNAi	ARO-ENaC	Cystic Fibrosis	[Blue bar]				
First RNAi	ARO-HIF2	Renal Cell Carcinoma	[Dark Blue bar]				
Leading RNAi	JNJ-3989	Hepatitis B	[Green bar] Licensed to Janssen				
First RNAi	AMG 890	Cardiovascular Disease	[Green bar] Licensed to Amgen				
Undisclosed Target	ARO-JNJ1	Undisclosed	[Green bar] With Janssen				

Liver

Lung

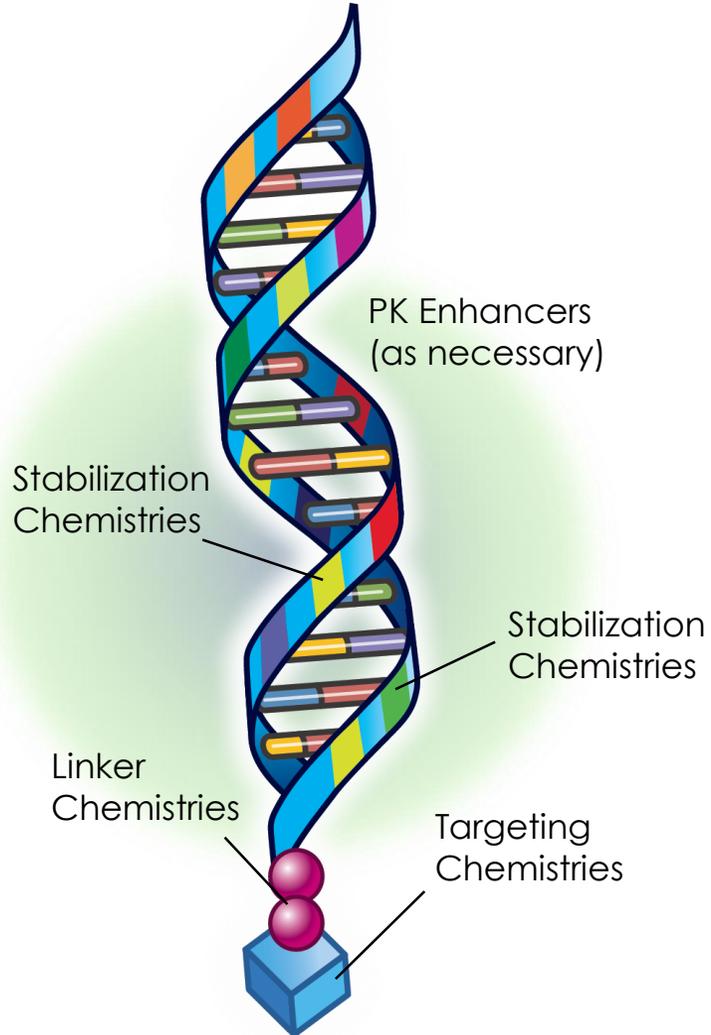
Tumor

Targeted RNAi Molecules TRiM™ Platform



Targeted RNAi Molecules - TRiM™ Platform

Simplicity, Specificity, and Activity



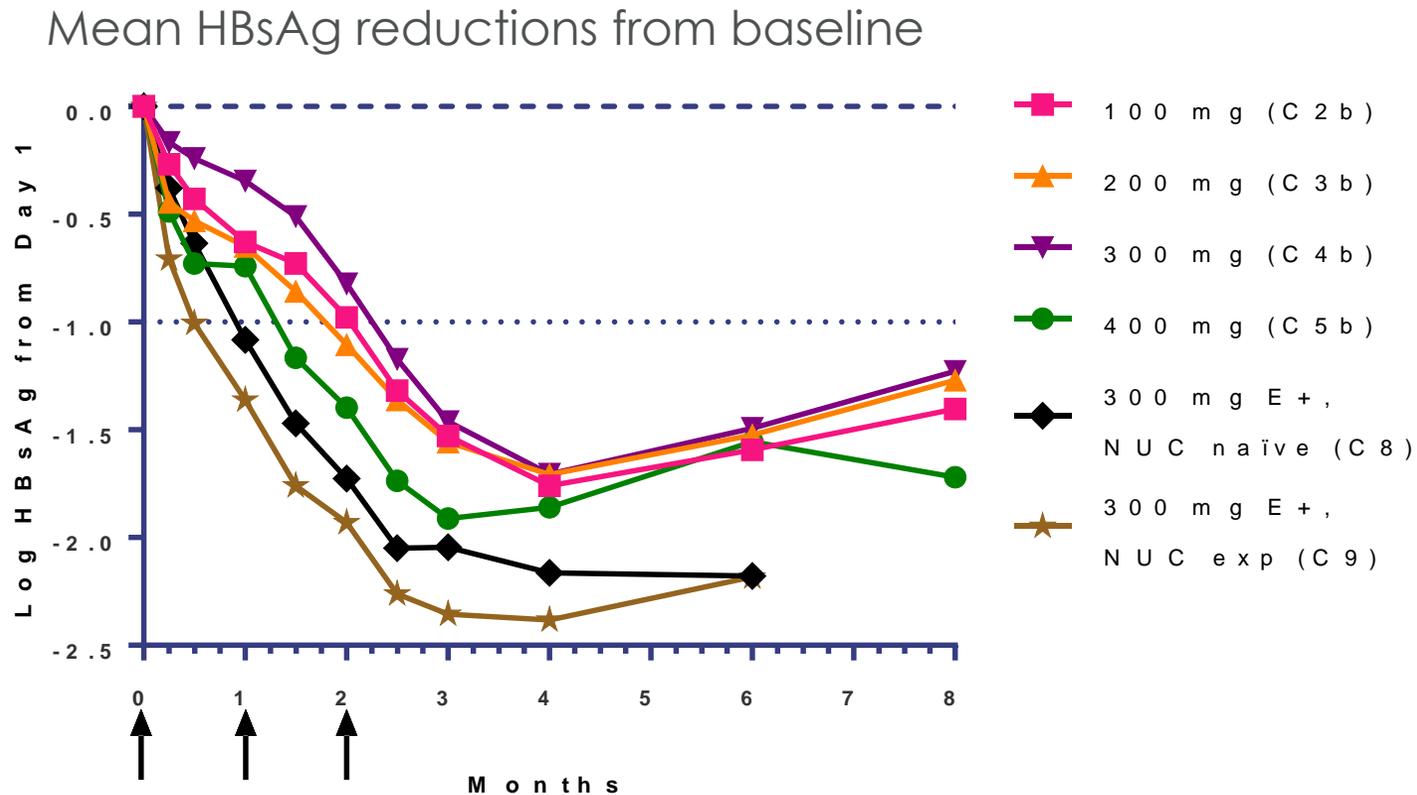
- Targeting ligands
- Linker chemistries
- Proprietary RNAi trigger selection technologies
 - Designed to maximize activity and innate stability
- Stabilization chemistries
- pk enhancers as necessary

Deep KD in diverse tissues using
subQ, iv, and inhaled
administration routes

Chronic Hepatitis B Virus Infection

JNJ-3989 (ARO-HBV)

All Patients Receiving 3 monthly Doses Achieved > 1 log Mean Reduction in HBsAg in Phase 1/2 Clinical Trial



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

Adverse Events Mostly Mild without Dose Related Pattern in Phase 1/2 Clinical Trial

AEs reported in ≥ 2 CHB patients

<u>AROHBV1001</u> <u>HBV Patients</u>	<u>Cohort</u> <u>2b</u> <u>Open</u> <u>Label</u> <u>n = 8</u>	<u>Cohort</u> <u>3b</u> <u>Open</u> <u>Label</u> <u>n = 8</u>	<u>Cohort</u> <u>4b</u> <u>Open</u> <u>Label</u> <u>n = 8</u>	<u>Cohort</u> <u>5b</u> <u>Open</u> <u>Label</u> <u>n = 8</u>	<u>Cohort 6</u> <u>Open</u> <u>Label</u> <u>n = 4</u>	<u>Cohort 7</u> <u>Open</u> <u>Label</u> <u>n = 4</u>	<u>Cohort 8</u> <u>Open</u> <u>Label</u> <u>n = 4</u>	<u>Cohort 9</u> <u>Open</u> <u>Label</u> <u>n = 4</u>	<u>Cohort</u> <u>10</u> <u>Open</u> <u>Label</u> <u>n = 4</u>	<u>Cohort</u> <u>11</u> <u>Open</u> <u>Label</u> <u>n = 4</u>	
<u>AE Reported Terms</u>											
Sore Throat, URTI	1	3	3	3	1	1	1	1	2	1	17
Injection Site Erythema/Redness, Very mild Erythema, Injection Site Rash, Injection Site Hematoma/Bruising, IS Pain			3	2		2	2	1		2	12
Headache			2	1		1			1	1	6
Raised or Elevation in Creatine Kinase			2			2	1				5
Lower Back Ache/Pain			1			2	1				4
Acne, Facial Acne							2				2
Bronchitis, Viral Bronchitis						1			1		2
Diarrhea, Intermittent Diarrhea			1	1							2
Pain in abdomen, Intermittent Right Upper Quadrant Pain		1		1							2
Insect Bites ankles, Flea Bites neck	1		1								2
Dizzy, Light headedness	1									1	2
Hot flush				1					1		2
Presence of calcium oxalate crystals in urine		1				1					2
Dry cough				1	1						2
Elevated Blood Pressure, Worsening Hypertension								1		1	2
Other all single occurring terms:											64 Total

Select Clinical Studies

Study of ARO-HBV in Normal Adult Volunteers and Patients With Hepatitis B Virus (HBV)

A Phase 1/2a Single Dose-Escalating Study to Evaluate the Safety, Tolerability and Pharmacokinetic Effects of ARO-HBV in Normal Adult Volunteers and Multiple Escalating Doses Evaluating Safety, Tolerability and Pharmacodynamic Effects in HBV Patients

ClinicalTrials.gov Identifier: [NCT03365947](https://clinicaltrials.gov/ct2/show/study/NCT03365947)

A Study of JNJ-73763989 in Healthy Japanese Adult Participants

A Double-blind, Placebo-controlled, Randomized, Parallel, Single Dose Study to Investigate Pharmacokinetics, Safety, and Tolerability of JNJ-73763989 in Healthy Japanese Adult Participants

ClinicalTrials.gov Identifier: [NCT04002752](https://clinicaltrials.gov/ct2/show/study/NCT04002752)

A Study to Evaluate the Effect of Hepatic Impairment on JNJ-73763989

A Phase 1, Single-Dose, Open-Label, Parallel-Group Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of JNJ-73763989

ClinicalTrials.gov Identifier: [NCT04208386](https://clinicaltrials.gov/ct2/show/study/NCT04208386)

A Study of Different Combination Regimens Including JNJ-73763989 and/or JNJ-56136379 for the Treatment of Chronic Hepatitis B Virus Infection (REEF-1)

A Phase 2b, Multicenter, Double-blind, Active-controlled, Randomized Study to Investigate the Efficacy and Safety of Different Combination Regimens Including JNJ-73763989 and/or JNJ-56136379 for the Treatment of Chronic Hepatitis B Virus Infection

ClinicalTrials.gov Identifier: [NCT03982186](https://clinicaltrials.gov/ct2/show/study/NCT03982186)

A Study of JNJ 73763989+JNJ 56136379+Nucleos(t)ide Analog (NA) Regimen Compared to NA Alone in e Antigen Negative Virologically Suppressed Participants With Chronic Hepatitis B Virus Infection

A Randomized, Double Blind, Placebo-controlled Phase 2b Study to Evaluate Efficacy, Pharmacokinetics, and Safety of 48-week Study Intervention With JNJ 73763989+JNJ 56136379+Nucleos(t)ide Analog (NA) Regimen Compared to NA Alone in e Antigen Negative Virologically Suppressed Participants With Chronic Hepatitis B Virus Infection

ClinicalTrials.gov Identifier: [NCT04129554](https://clinicaltrials.gov/ct2/show/study/NCT04129554)

Alpha-1 Antitrypsin Deficiency ARO-AAT



Alpha-1 Antitrypsin Deficiency

Mutation in AAT gene (Z-AAT) leads to mis-folding of the protein and poor export from hepatocytes: low levels in circulation and accumulation in liver

Pathophysiology

Lung

Tissues susceptible to damage by neutrophil proteases: COPD



Treated with AAT enzyme replacement therapy today

Liver

Accumulation of mutant Z protein causes clinical liver disease



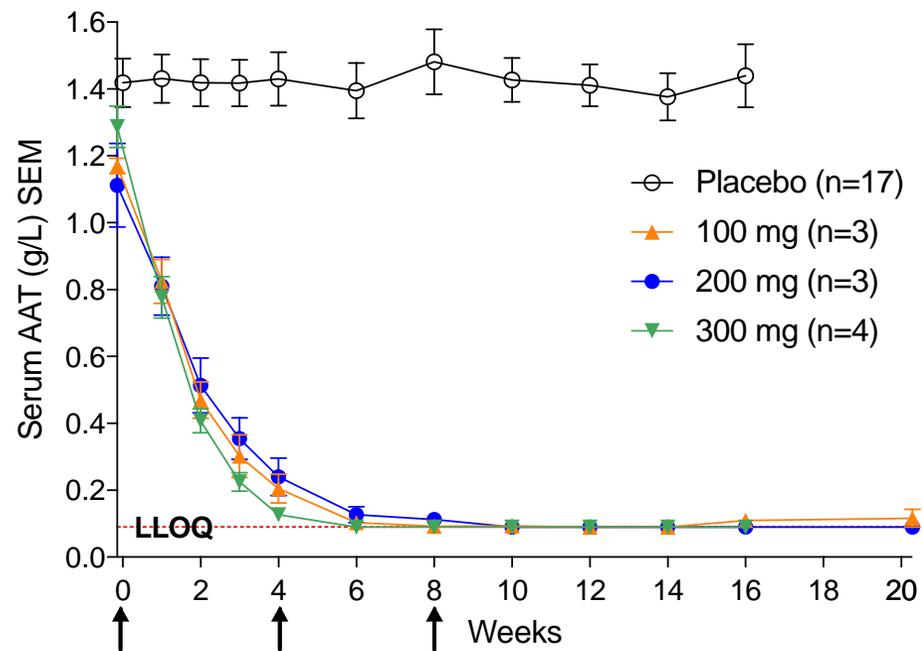
No current treatment

ARO-AAT designed to stop Z-AAT production by silencing AAT gene to:

- Prevent liver accumulation
- Allow clearance of accumulated protein
- Prevent cycles of cellular damage
- Prevent/Reverse progression of liver fibrosis

ARO-AAT Phase 1

Multiple dose ARO-AAT



Data support potential for quarterly or less frequent dosing

ARO AAT Phase 1 Safety Summary

AE Terms	SD 35 mg n = 4	MD 100 mg n = 4	SD 100 mg n = 4	MD 200 mg n = 4	SD 200 mg n = 4	MD 300 mg n = 4	SD 300 mg n = 4	Placeb o n = 17 (#/%)	ARO- AAT n = 28 (#/%)
Upper respiratory tract infection		2	1	1	1	2	4	4/24%	11/39%
Headache	2	1		2	1	1	2	2/12%	9/32%
Sore throat/throat irritation/dry throat	1	1	2		1	1		5/29%	6/21%
Rhinorrhea		1	2	1			1	3/18%	5/18%
Nausea, Dyspepsia	1			2		1	2	1/6%	6/21%
Pain/phlebitis at cannula site	2		2			1		2/12%	5/18%
AE at injection site (e.g. pain, bruising, erythema)			2	1	1	1	1	0/0%	6/21%
Cough			1			1	1	3/18%	3/11%
Abdominal Pain			1	2			2	1/6%	5/18%
Back or neck pain		2				1		2/12%	3/11%
Venipuncture bruise or tenderness		1			2			2/12%	3/11%
Sinus/nasal congestion, sinusitis							1	3/18%	1/4%
Emesis		1	1	1				1/6%	3/11%
Lightheadedness, Dizziness	1			1			1	1/6%	3/11%
Insect bites	2							1/6%	2/7%
Ankle pain, injury	1		1					0/0%	2/7%
Musculoskeletal chest pain			1					1/6%	1/4%
Laceration/Abrasion								2/12%	0/0%
Nose bleed, Blood stained nasal mucous		1		1				0/0%	2/7%
Cold sores, Scattered mouth blisters		1	1					0/0%	2/7%
Gastroenteritis								2/12%	0/0%
Feeling Feverish								2/12%	0/0%
Total AEs occurring in >1 subject	10	11	15	12	6	9	15	38	78

- **No AEs that increased in frequency or severity with dose**
- **No AEs rated as serious, or severe**
- **Most AEs were graded as mild**
- **Most frequent AEs in subjects receiving ARO-AAT were upper respiratory tract infection (39%) and headache (32%)**
- **Fifty doses of ARO-AAT were administered with 6 (12%) resulting in an AE at the injection site**

Schwabe Christian et al. AASLD 2018, LB-9

ARO-AAT SEQUOIA Pivotal Study

- SEQUOIA

- Dosing began August 2019
- Adaptive design Phase 2/3 trial (SEQUOIA) with the potential to serve as a pivotal registrational study of ARO-AAT
- 120 Patients
- The multi-dose, placebo-controlled Part A component of the study is expected to feed seamlessly into a two-arm placebo-controlled Part B component
- The primary objective for Part A is to select a single dose level for use in Part B of the study based on a combined evaluation of safety and pharmacodynamic dose response using change from baseline in soluble liver Z-AAT, insoluble liver Z-AAT, and serum AAT levels as pharmacodynamic metrics in 36 patients
- The primary objective for Part B is to evaluate efficacy, as assessed by the proportion of ARO-AAT treated patients relative to placebo achieving a 2-point improvement in a histologic grading scale of alpha-1 antitrypsin deficiency associated liver disease AND no worsening of liver fibrosis on end of study biopsy
- Patients will receive a minimum of 9 doses overall (Day 1, Day 29 and then every 12 weeks)

ARO-AAT2002 Open Label Study

AROAAT2002 Open Label

- Pilot open-label, multi-dose, Phase 2 study to assess changes in a novel histological activity scale
- 12 patients in two sequential cohorts (Cohort 1 n=4, Cohort 2 n=8)
- Patients will receive a minimum of 3 doses in Cohort 1 and 5 doses in Cohort 2 (Day 1, Day 29 and then every 12 weeks)
- Repeat biopsies 1 month after the 3rd or 5th dose, respectively
- The primary objective, to evaluate the effect of ARO-AAT on a histological liver disease activity scale, will be assessed at week 24 for cohort 1 and week 48 for cohort 2
- Patients may elect to participate in an extension cohort and receive an additional 4 doses followed by a repeat liver biopsy

Clinical Studies

Study of ARO-AAT in Normal Adult Volunteers

A Phase 1 Single and Multiple Dose-Escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Effect of ARO-AAT on Serum Alpha-1 Antitrypsin Levels in Normal Adult Volunteers

ClinicalTrials.gov Identifier: [NCT03362242](https://clinicaltrials.gov/ct2/show/study/NCT03362242)

Assessment of Changes in a Novel Histological Activity Scale in Response to ARO-AAT

A Pilot Open Label, Multi-dose, Phase 2 Study to Assess Changes in a Novel Histological Activity Scale in Response to ARO-AAT in Patients With Alpha-1 Antitrypsin Deficiency Associated Liver Disease (AATD)

ClinicalTrials.gov Identifier: [NCT03946449](https://clinicaltrials.gov/ct2/show/study/NCT03946449)

Safety, Tolerability and Effect on Liver Histologic Parameters of ARO-AAT (SEQUOIA)

SEQUOIA – A Placebo-Controlled, Multi-dose, Phase 2/3 Study to Determine the Safety, Tolerability and Effect on Liver Histologic Parameters in Response to ARO-AAT in Patients With Alpha-1 Antitrypsin Deficiency (AATD)

ClinicalTrials.gov Identifier: [NCT03945292](https://clinicaltrials.gov/ct2/show/study/NCT03945292)

Cardiometabolic Diseases

ARO-APOC3, ARO-ANG3



Building Cardiometabolic Pipeline with TRiM™

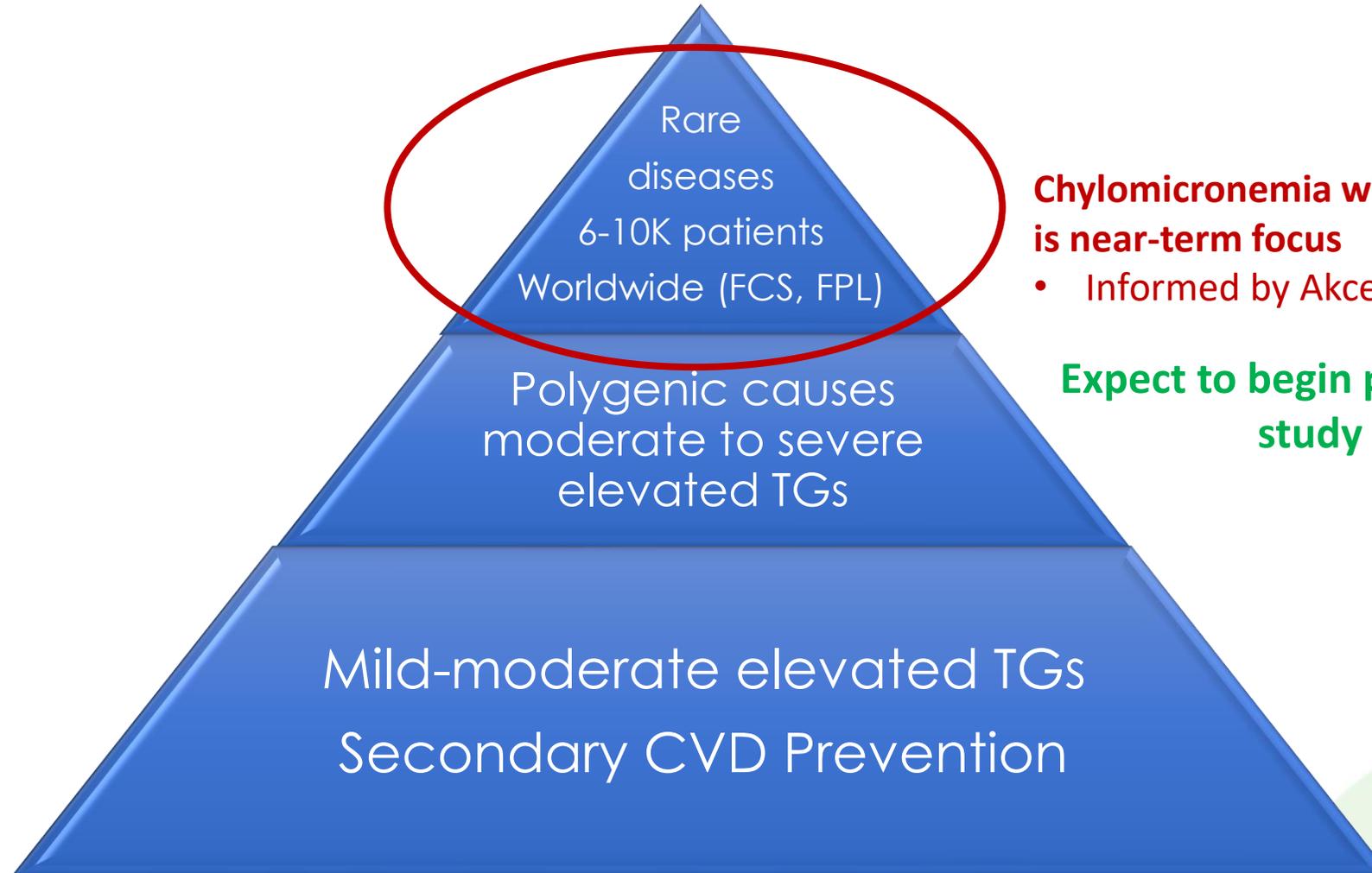
ARO-ANG3

- AROANG1001 Phase 1 single and multiple dose study
- To evaluate the safety, tolerability, pharmacokinetic, and pharmacodynamics
- Up to 70 subjects including adult healthy volunteers with elevated triglycerides as well as patients with various types of dyslipidemia

ARO-APOC3

- AROAPOC31001 Phase 1 single and multiple dose study
- To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics
- Up to 63 adult healthy volunteers with elevated triglycerides and patients with severe hypertriglyceridemia and familial chylomicronemia syndrome.

Clinical Indications for APOC3: Tiered by Size and Regulatory Complexity



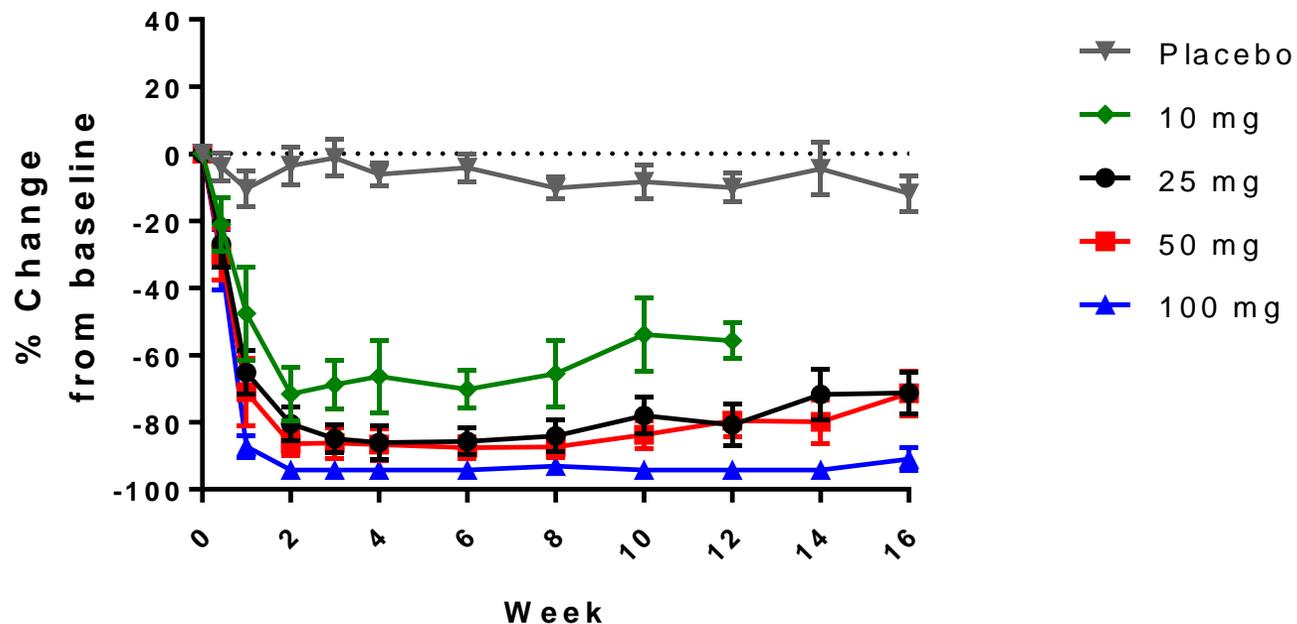
Chylomicronemia with pancreatitis risk is near-term focus

- Informed by Akcea experience

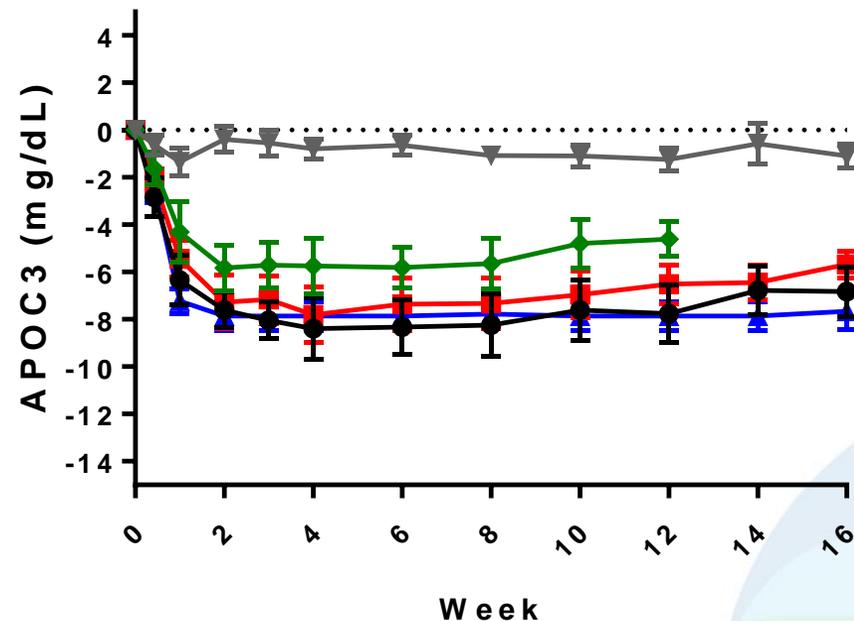
Expect to begin potentially pivotal study in 2020

Mean Reduction of APOC3 after Single Dose of ARO-APOC3 in Phase 1 Trial

APOC3

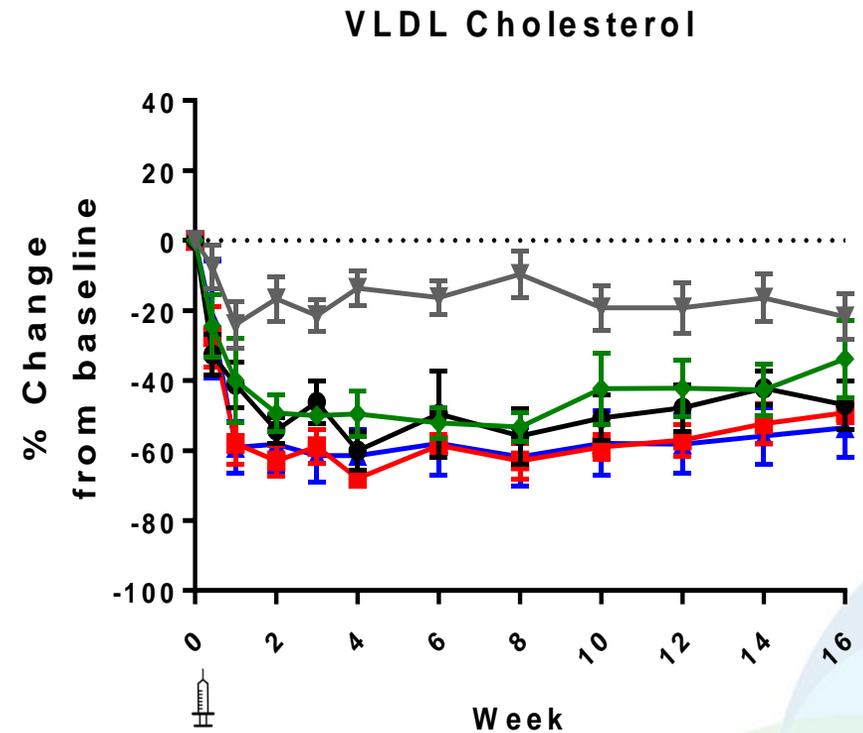
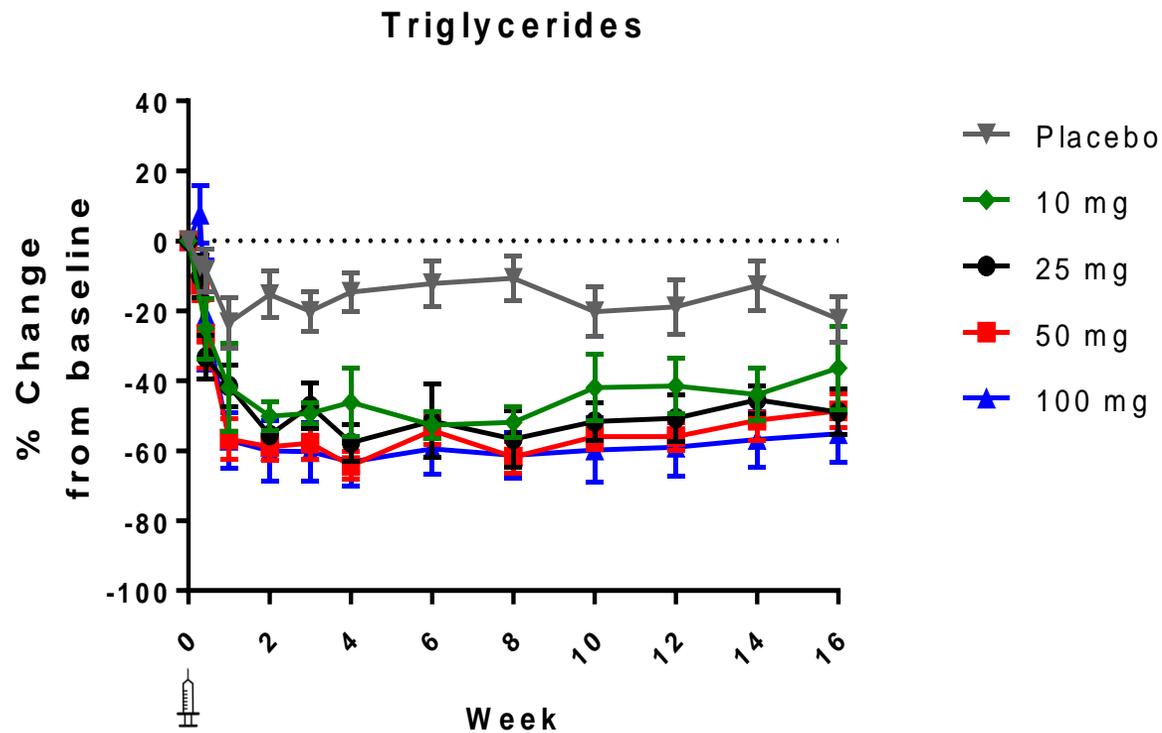


Absolute Change from Day 1



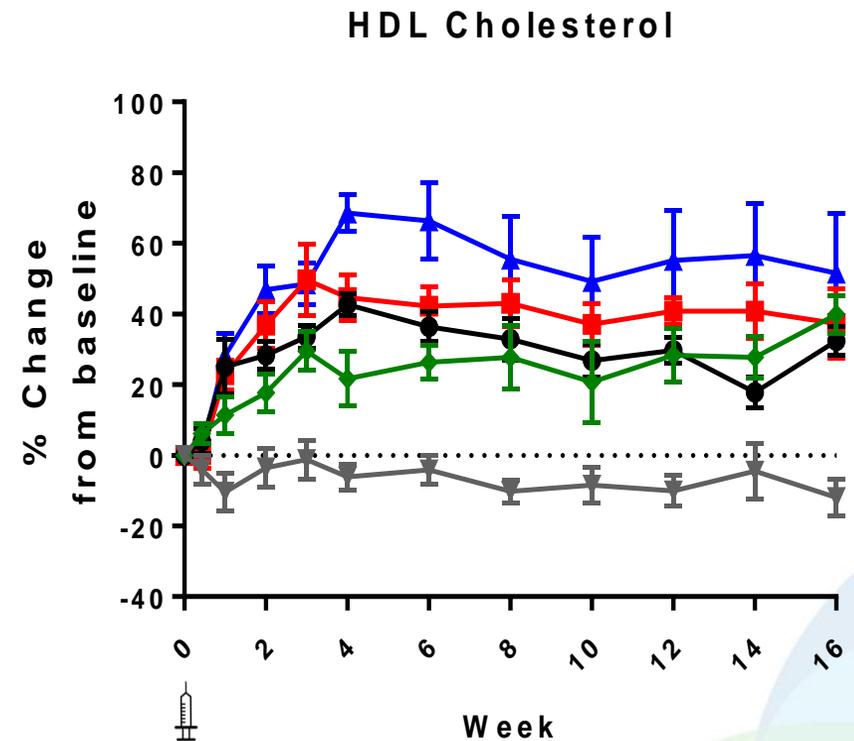
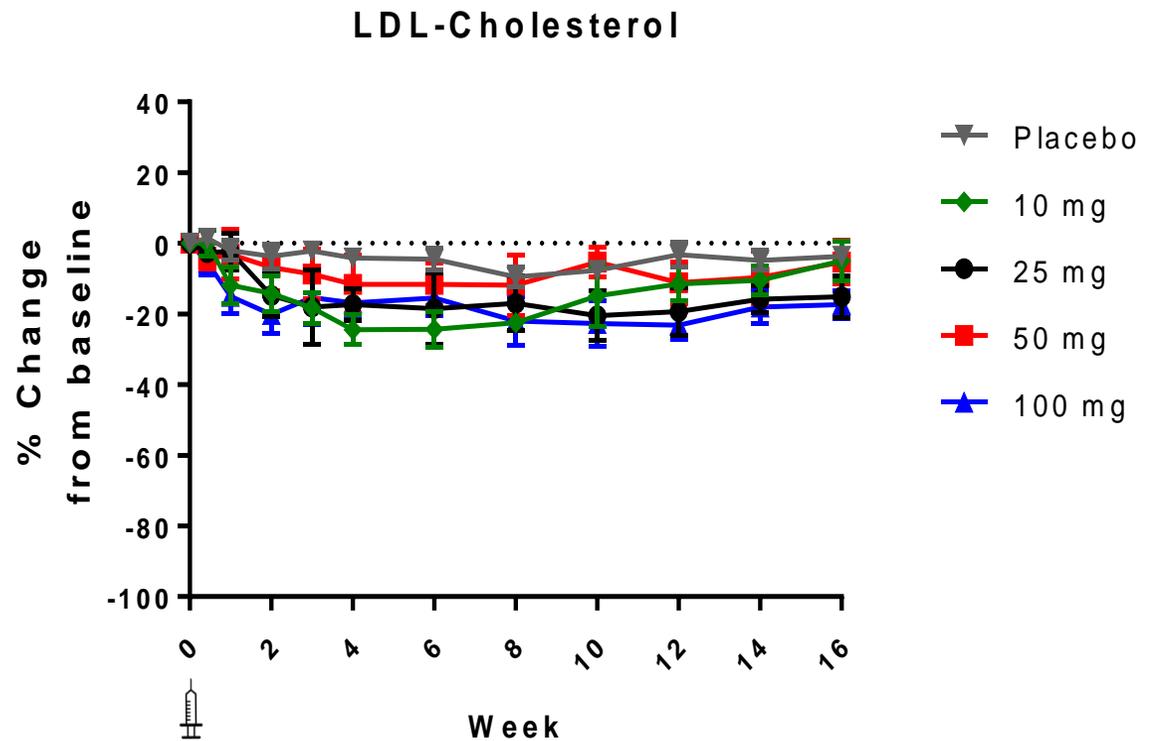
Data as of November 5, 2019; Presented at AHA
Scientific Sessions 2019

Mean Reductions in Triglycerides and VLDL-C after Single Dose of ARO-APOC3 in Phase 1 Trial



Data as of November 5, 2019; Presented at AHA Scientific Sessions 2019

Mean Changes in LDL-C and HDL-C after Single Dose of ARO-APOC3 in Phase 1 Study



Data as of November 5, 2019; Presented at AHA Scientific Sessions 2019

ARO-APOC3 Interim Safety Results from Phase 1 Trial

- 40 subjects enrolled and dosed (24 active, 16 placebo)
- No Serious AEs reported
- No Severe AEs reported
- One AE of moderate transient ALT elevation (peak of 210 U/L) in subject receiving ARO-APOC3 who had elevated ALT at baseline (65 U/L), with return to baseline by end-of-study (Day 113, 45 U/L).
- No other AEs from lab abnormalities observed in subjects receiving drug
- 8 Local Injection Site Reactions (LISRs) – all rated mild, more common at higher doses
 - LISR defined based on specific MedDRA preferred terms with duration of at least 48 hours.

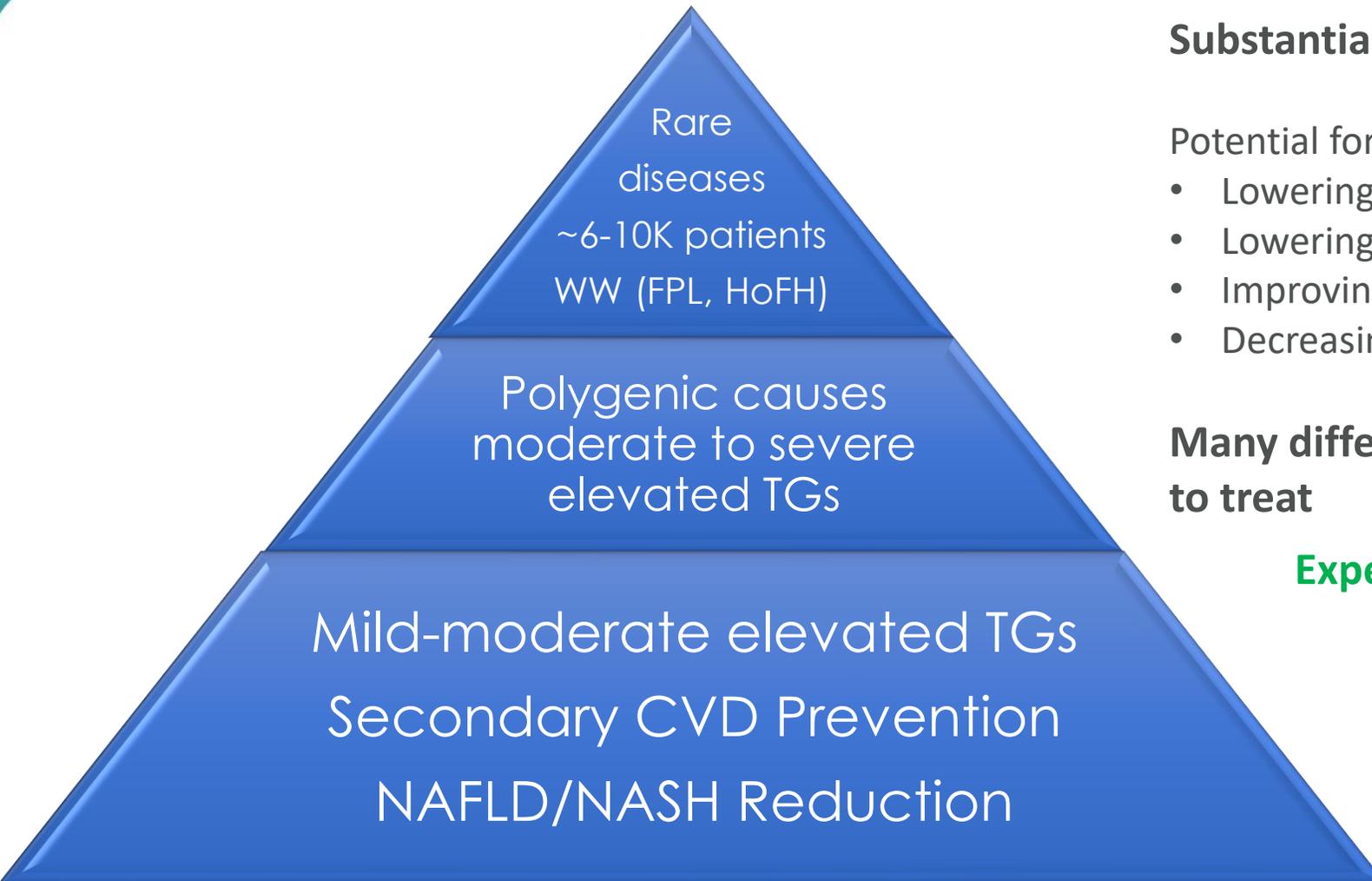
Clinical Studies

Study of ARO-APOC3 in Healthy Volunteers, Hypertriglyceridemic Patients and Patients With Familial Chylomicronemia Syndrome (FCS)

A Phase 1 Single and Multiple Dose-Escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Effects of ARO-APOC3 in Adult Healthy Volunteers as Well as in Severely Hypertriglyceridemic Patients and Patients With Familial Chylomicronemia Syndrome

ClinicalTrials.gov Identifier: [NCT03783377](https://clinicaltrials.gov/ct2/show/study/NCT03783377)

Clinical Indications for ANG3: Tiered by Size and Regulatory Complexity



Rare
diseases
~6-10K patients
WW (FPL, HoFH)

Polygenic causes
moderate to severe
elevated TGs

Mild-moderate elevated TGs
Secondary CVD Prevention
NAFLD/NASH Reduction

Substantial Promise for ANGPTL3 Target

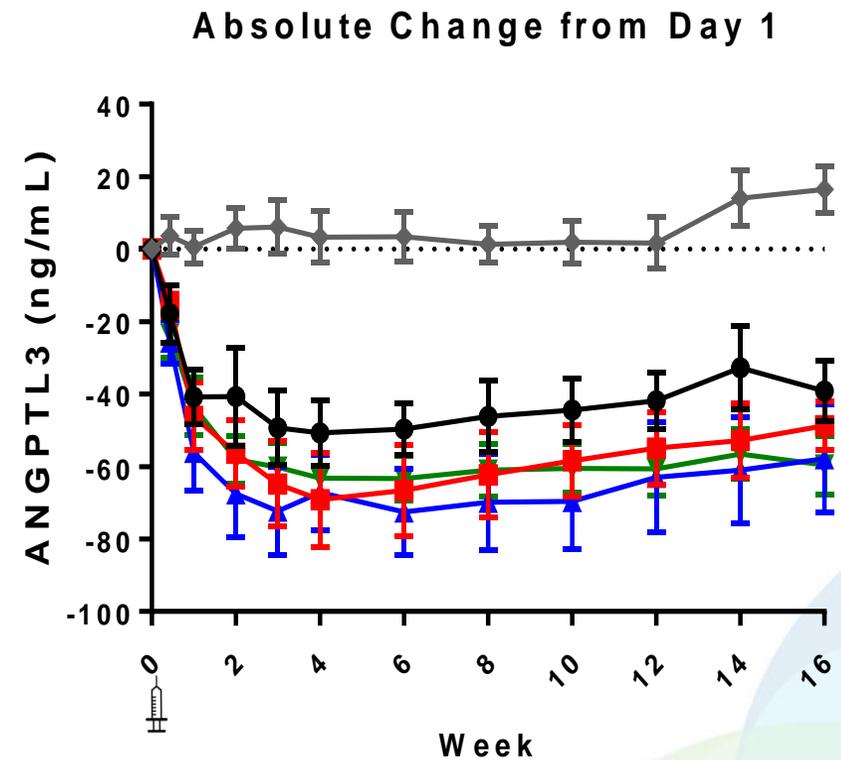
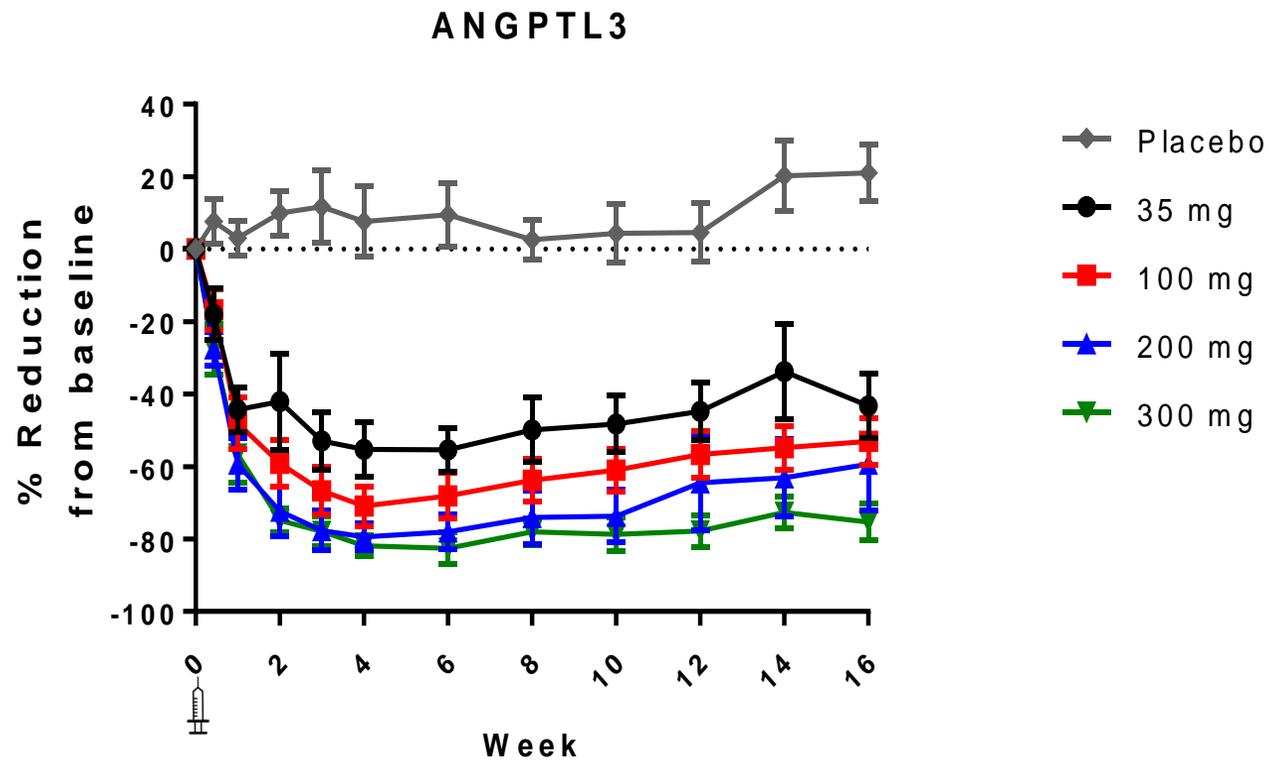
Potential for:

- Lowering triglycerides
- Lowering LDL-C
- Improving of Insulin Sensitivity
- Decreasing liver fat

Many different populations of potential patients to treat

Expect to begin potentially pivotal study in 2020

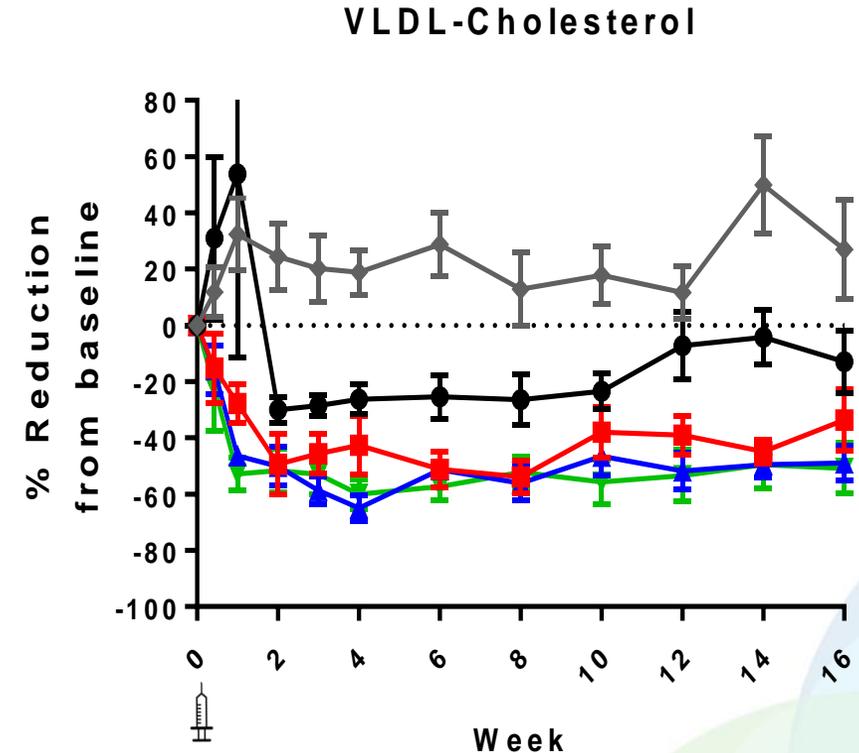
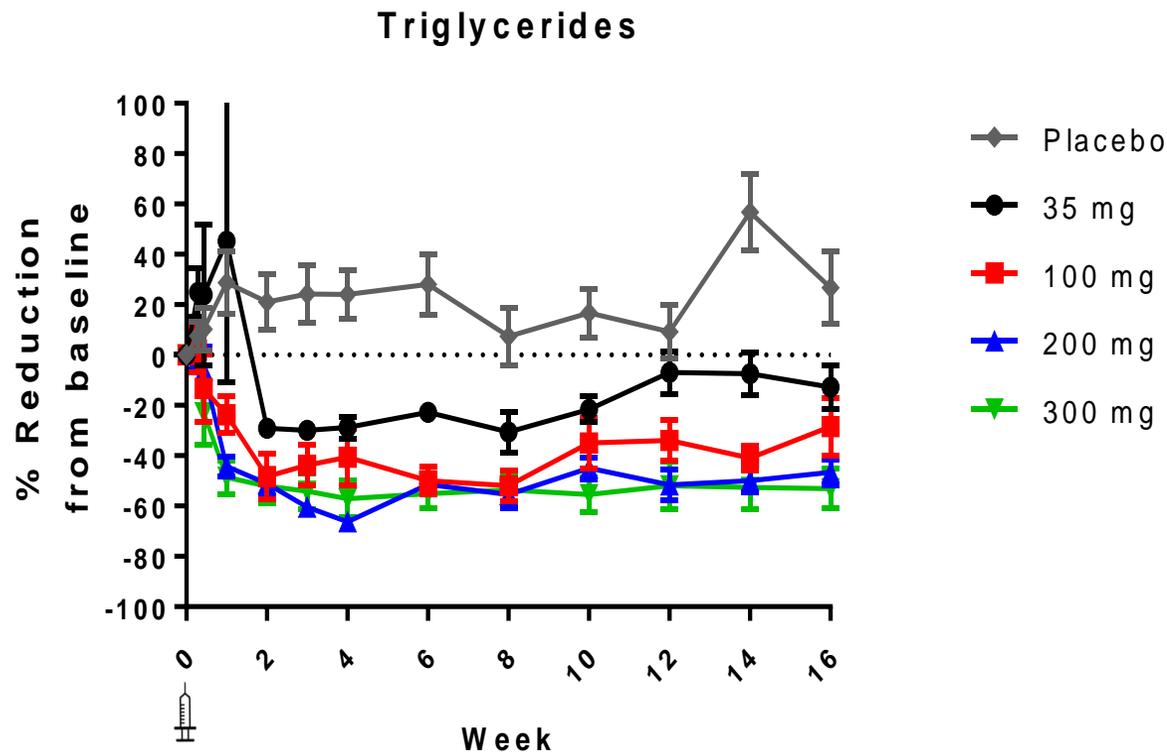
Mean Reduction of ANGPTL3 after Single Dose of ARO-ANG3 in Phase 1 Study



Data as of November 5, 2019; Presented at AHA Scientific Sessions 2019

Mean Reductions in Triglycerides and VLDL-C after Single Dose of ARO-ANG3 in Phase 1 Trial

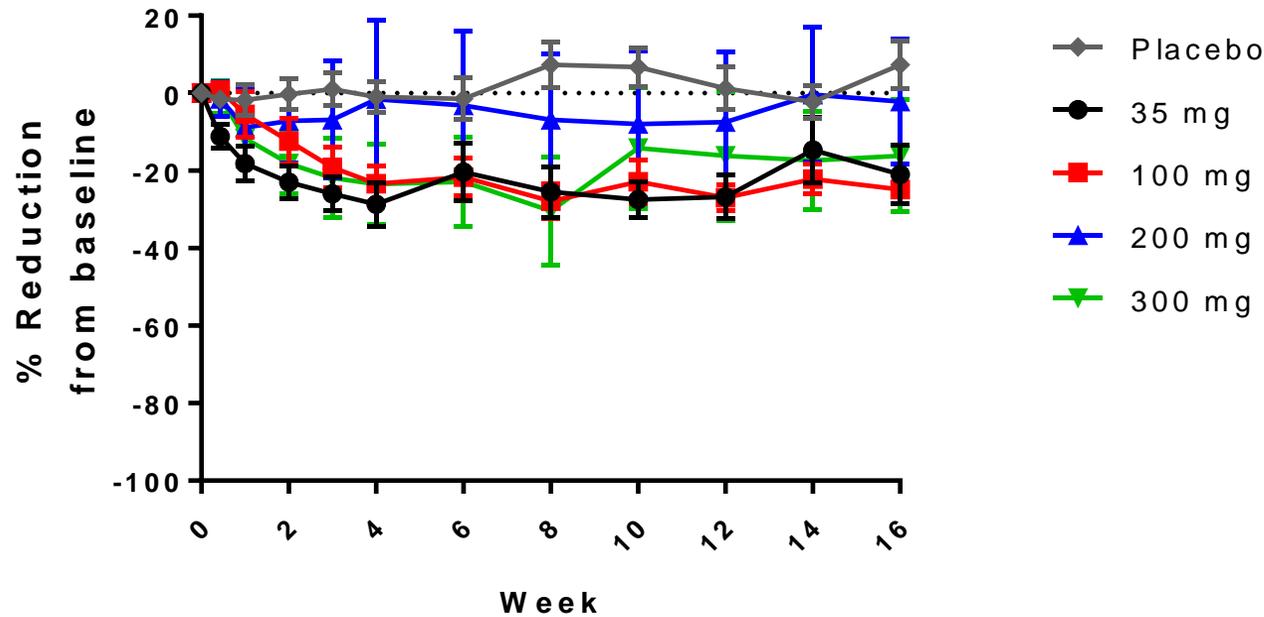
ARO-ANG3 or Placebo on Day 1



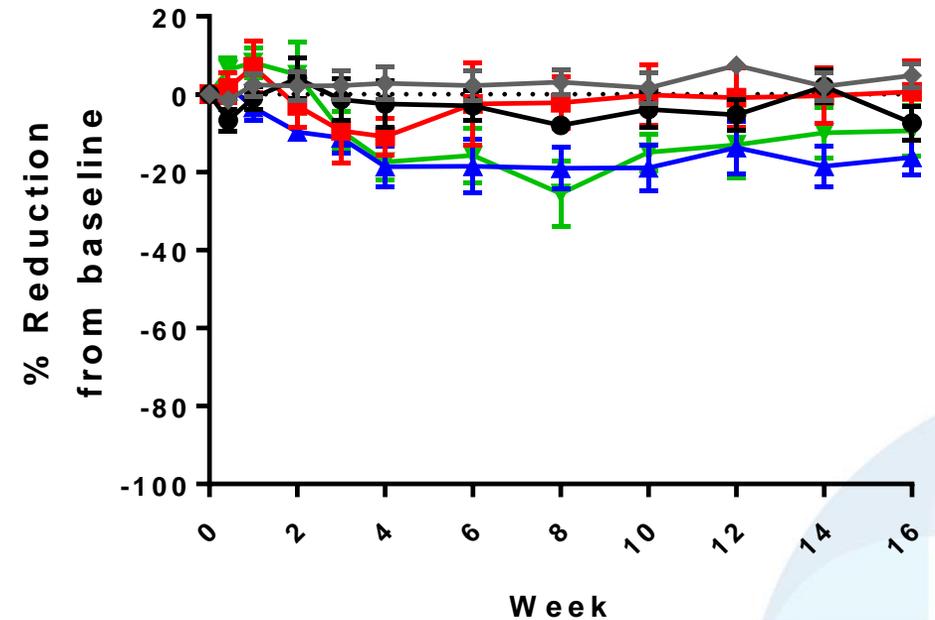
Data as of November 5, 2019; Presented at AHA Scientific Sessions 2019

Mean Reductions in LDL-C and HDL-C after Single Dose of ARO-ANG3 in Phase 1 Trial

LDL-Cholesterol



HDL-Cholesterol



Data as of November 5, 2019; Presented at AHA Scientific Sessions 2019

ARO-ANG3 Interim Safety Results from Phase 1 Trial

- 40 subjects enrolled received single ascending doses (24 active, 16 placebo)
- **No Serious AEs or drop outs** in subjects on drug
- No significant abnormalities observed in platelet counts or renal biochemistry
- **Two AEs** of mild transient elevations in ALT (one active, one placebo). No other AEs from lab abnormalities in subjects on drug
 - ALT elevation in one subject on ARO-ANG3 confounded by concomitant ingestion of herbal supplement with known liver toxicity (Peak ALT 192 U/L Day 99, normal by Day 113).
- **1 mild** drug related Local Injection Site Reaction
 - LISR defined based on MedDRA; erythema resolved after 48 hours.

Clinical Studies

Study of ARO-ANG3 in Healthy Volunteers and in Dyslipidemic Patients

A Phase 1 Single and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Effects of ARO-ANG3 in Adult Healthy Volunteers and in Dyslipidemic Patients

ClinicalTrials.gov Identifier: [NCT03747224](https://clinicaltrials.gov/ct2/show/study/NCT03747224)

Novel NASH Target ARO-HSD



ARO-HSD

- HSD17B13 is involved in the metabolism of hormones, fatty acids and bile acids
- Genetic studies found **loss-of-function mutations were protective** against development of both alcohol related and non-alcohol related liver disease
 - 30-50% risk reduction compared to non-carriers
- ARO-HSD expected to be the **first** clinical candidate using **any modality** against HSD17B13 target

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Protein-Truncating *HSD17B13* Variant and Protection from Chronic Liver Disease

N.S. Abul-Husn, X. Cheng, A.H. Li, Y. Xin, C. Schurmann, P. Stevis, Y. Liu, J. Kozlitina, S. Stender, G.C. Wood, A.N. Stepanchick, M.D. Still, S. McCarthy, C. O'Dushlaine, J.S. Packer, S. Balasubramanian, N. Gosalia, D. Esopi, S.Y. Kim, S. Mukherjee, A.E. Lopez, E.D. Fuller, J. Penn, X. Chu, J.Z. Luo, U.L. Mirshahi, D.J. Carey, C.D. Still, M.D. Feldman, A. Small, S.M. Damrauer, D.J. Rader, B. Zambrowicz, W. Olson, A.J. Murphy, I.B. Borecki, A.R. Shuldiner, J.G. Reid, J.D. Overton, G.D. Yancopoulos, H.H. Hobbs, J.C. Cohen, O. Gottesman, T.M. Teslovich, A. Baras, T. Mirshahi, J. Gromada, and F.E. Dewey

CTA Filed December 2019

Clinical Studies

Study of ARO-HSD in Healthy Volunteers and Patients With Non-Alcoholic Steatohepatitis (NASH) or Suspected NASH

A Phase 1 Single and Multiple Dose-Escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Effects of ARO-HSD in Normal Healthy Volunteers as Well as in Patients With NASH or Suspected NASH

ClinicalTrials.gov Identifier: [NCT04202354](https://clinicaltrials.gov/ct2/show/study/NCT04202354)

Extra-hepatic Programs ARO-HIF2, ARO-ENaC, Muscle-targeting

ARO-HIF2

- Targeting HIF2a for treatment of clear cell renal cell carcinoma
- Majority of ccRCC tumors express mutant Von Hippel-Landau protein that is unable to degrade HIF-2 alpha
- HIF-2a linked to tumor progression and metastasis
- Substantial interest in target
 - Peloton Therapeutics acquired by Merck in 2019 for up to \$2.2B
- First TRiM™ enabled extra-hepatic candidate

IND Filed December 2019

Clinical Studies

Study of ARO-HIF2 in Patients With Advanced Clear Cell Renal Cell Carcinoma

A Phase 1b Adaptive Dose-Finding Study of ARO-HIF2 in Patients With Advanced Clear Cell Renal Cell Carcinoma

ClinicalTrials.gov Identifier: [NCT04169711](https://clinicaltrials.gov/ct2/show/study/NCT04169711)

Targeting New Tissues Using TRiM™ Platform

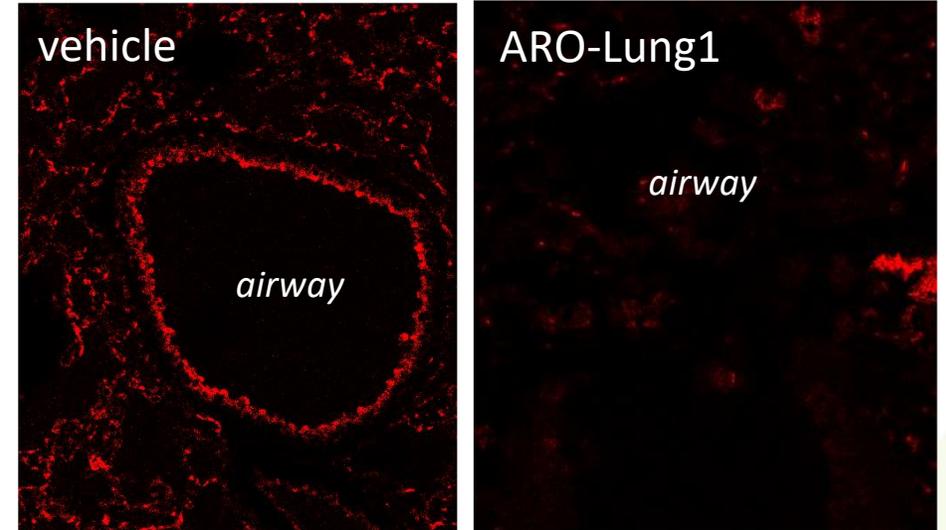
ARO-ENaC

- Targeting the epithelial sodium channel (ENaC) alpha subunit for treatment of cystic fibrosis
- Validated CF target: historically undruggable
- Inhaled administration

CTA Submission Planned First Half of 2020

After clinical PoC, we expect rapid expansion into other targets/indications

Red: lung target protein expression by IHC



Muscle Targeting

- Skeletal muscle is the next cell type we plan to target
- Demonstrated in multiple animal models
- First target/and potential indication undisclosed

First CTA Submission Planned in 2020

Looking through 2020

We expect the near term to be productive

- **We expect to begin clinical studies for:**
 - ARO-HIF2
 - ARO-HSD
- **We expect to submit 3 new CTAs in 2020, including:**
 - ARO-ENaC
 - First muscle-targeting program
- **We expect to initiate or continue potentially pivotal studies with 3 wholly-owned candidates in 2020**
 - ARO-AAT, ARO-ANG3, ARO-APOC3
- **We expect progress with partnered clinical candidates**
 - JNJ-3989 (ARO-HBV), AMG 890
- **We expect 10 TRiM™ – enabled clinical programs by end of 2020 targeting 4 different cell types**