Glaucienne
Diagnosed with AHP (Brazil)

Liver-Directed RNAi Pipeline Programs

RNAi ROUNDTABLE 2021

September 20, 2021

Alnylam® PHARMACEUTICALS

Agenda

Welcome
- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction
- Eric Green – Senior Vice President, Development Programs

Clinical and Pre-clinical Liver-Directed Programs
- Tanya Fischer, M.D., Ph.D. – Vice President, Clinical Development
- Josh Friedman, M.D., Ph.D. – Senior Director, Clinical Research

Q&A Session

Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface

Replay, slides and transcript available at www.alnylam.com/capella

Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including expectations regarding our aspiration to become a leading biotech company, and the planned achievement of our "*Alnylam P^{5}x25*" strategy, plans for additional global regulatory filings and the continuing product launches of our approved products and the approved product of our partner, the potential therapeutic benefit of, and the expected achievement of additional pipeline and regulatory milestones for, Alnylam's liver-directed RNAi therapeutics, including ALN-HBV02 (in development with Vir), cemdisiran and cemdisiran plus pozelimab (in development with Regeneron), ALN-HSD and ALN-PNP (in development with Regeneron), ALN-XDH and ALN-KHK, and the potential opportunity to advance additional liver-directed RNAi therapeutics for both rare and prevalent diseases. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including lumasiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO (and potentially vutrisiran) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

Save the date!

Alnylam® R&D Day

November 19, 2021

A VIRTUAL EVENT

Registration information coming soon.

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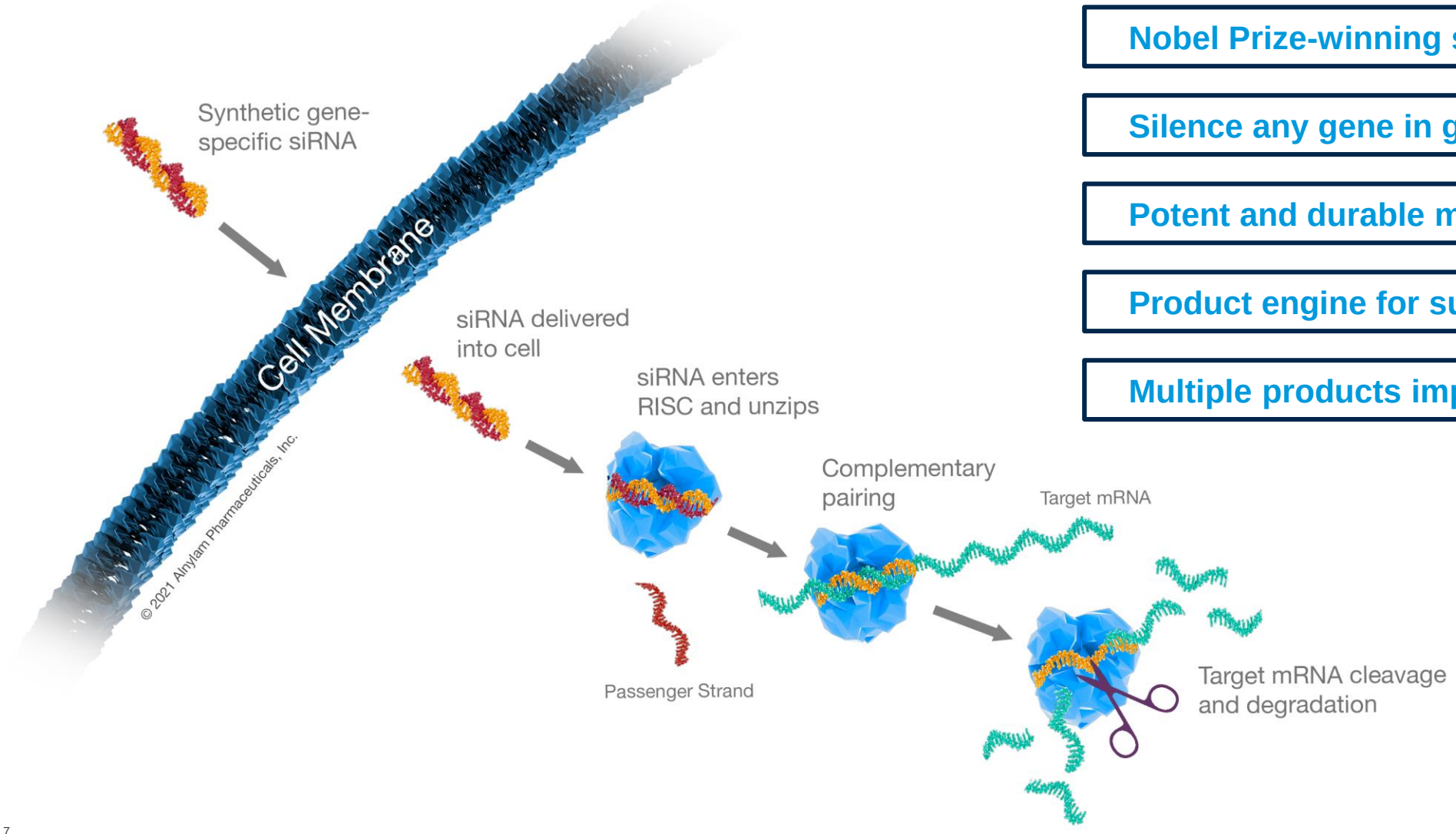
RNAi Therapeutics: New Class of Innovative Medicines

Clinically and Commercially Established Approach with Transformational Potential



- **Nobel Prize-winning science**
- **Silence any gene in genome with siRNAs**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products impacting patients globally**

RNAi Therapeutics: Transformational Medicines for Rare & Prevalent Diseases

Four Global Approvals in Just Over 2 Years

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

Hereditary ATTR Amyloidosis with Polyneuropathy

U.S.
EU
Canada
Japan

Switzerland
Brazil
Israel
Taiwan

2018

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Acute Hepatic Porphyria

U.S.
EU
Brazil

Canada
Switzerland
Japan

2019

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

Primary Hyperoxaluria Type 1

EU
U.S.
Brazil

2020

Leqvio® (inclisiran)

Hypercholesterolemia

NOVARTIS

EU
Canada
Israel

2020

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Kidney Stones*	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6*]	*Complement-Mediated Diseases*	●			Milestone/Royalty
Belcesiran[7*]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8*]	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of August 2021

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As of August 2021

Over 25 Preclinical Programs in Four Tissues Feeding Sustainable Innovation

Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

Alnylam
- ALN-TTRoc

Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

Alnylam/Vir
- ALN-COV
  - *discontinued*
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

2-4 *INDs planned per year from organic product engine (4+ planned by end-'25)*

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Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

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- ALN-APP
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- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

Alnylam
- ALN-TTRoc

Alnylam/Regeneron
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- ALN-REGN-E2
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  - *discontinued*
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

2-4 *INDs planned per year from organic product engine (4+ planned by end-'25)*

Potential RNAi Therapeutics Profile Supports Expansion to Prevalent Diseases

- Durability
- Clamped pharmacology
- Safety profile evaluated in clinical trials
- Improved access

RARE

ONPATTRO: hATTR-PN[1]
GIVLAARI
OXLUMO
Vutrisiran: hATTR-PN[3]
Fitusiran
Belcesiran
ALN-APP
ALN-HTT

SPECIALTY

Patisiran: ATTR-CM[2]
Vutrisiran: ATTR-CM[3]
Cemdisiran

PREVALENT

Leqvio® (inclisiran)[4]
ALN-HBV02 (VIR-2218)
Zilebesiran (ALN-AGT)
ALN-HSD
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ALN-KHK

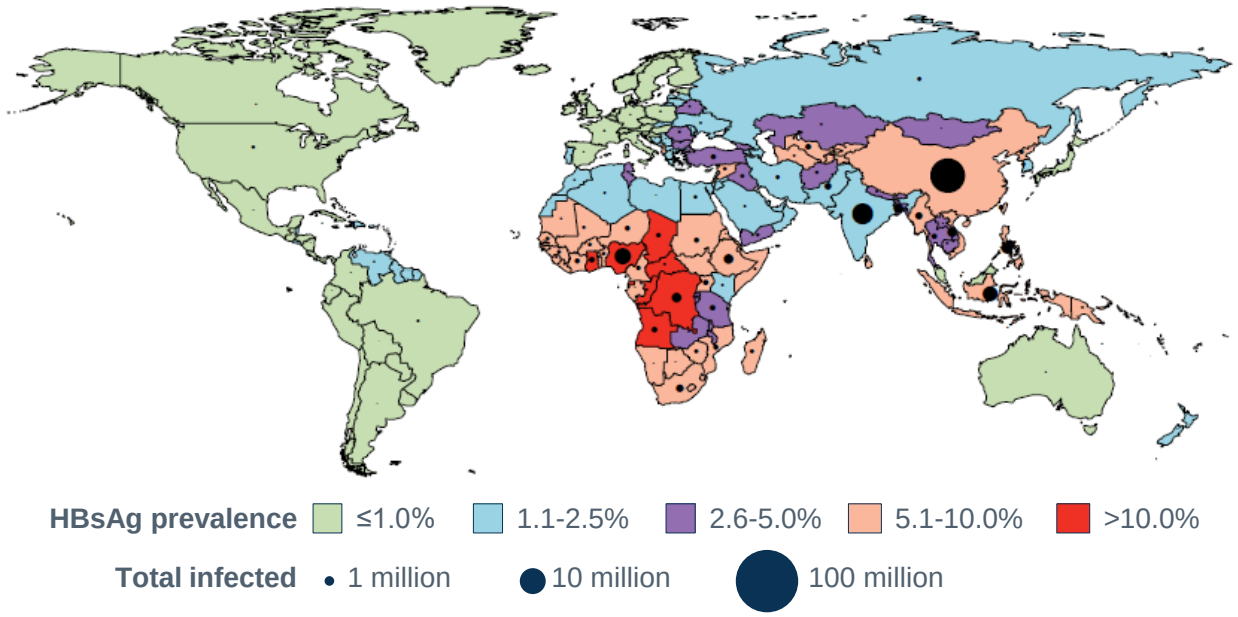
[1] ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; [2] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population; [3] Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; NDA submitted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing; [4] Leqvio is approved in the EU for the treatment of adults with hypocholesterolemia or mixed dyslipidemia; in the U.S., Novartis re-submitted the NDA in response to a Complete Response Letter and have a PDUFA date of January 1, 2022. None of the investigative therapeutics referenced herein has been reviewed by EMA, FDA or any other regulatory agency and no conclusions can or should be drawn regarding their respective safety or efficacy.

ALN-HBV02 (VIR-2218) for HBV Infection

Alnylam PHARMACEUTICALS

HBV: Global Health Problem Impacting Developed and Developing Countries

HBV Prevalence Estimate: ~290 M
(diagnosed + undiagnosed)



~24M diagnosed patients
in top high-/middle-income countries*

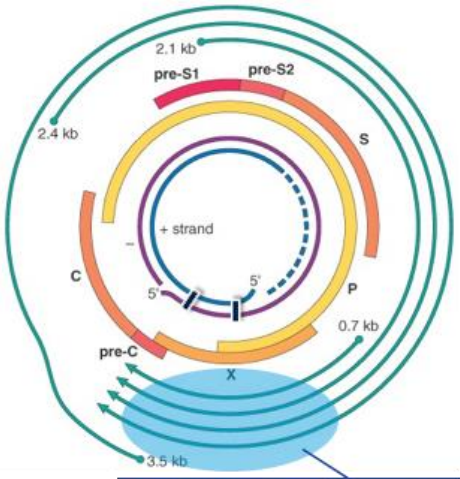
ALN-HBV02 (VIR-2218)
Investigational RNAi Therapeutic for Treatment of Chronic HBV Infection

Targets conserved region in X gene, upstream of integration hotspot, allowing for

- Single siRNA to suppress HBsAg from both intDNA and cccDNA
- Suppression of all HBV mRNAs, which overlap in this region

GalNAc-conjugated ESC+ siRNA

- Subcutaneous administration with GalNAc ligand for targeted delivery to liver and prolonged pharmacodynamic effect
- ESC+ technology: improved specificity of RNAi activity



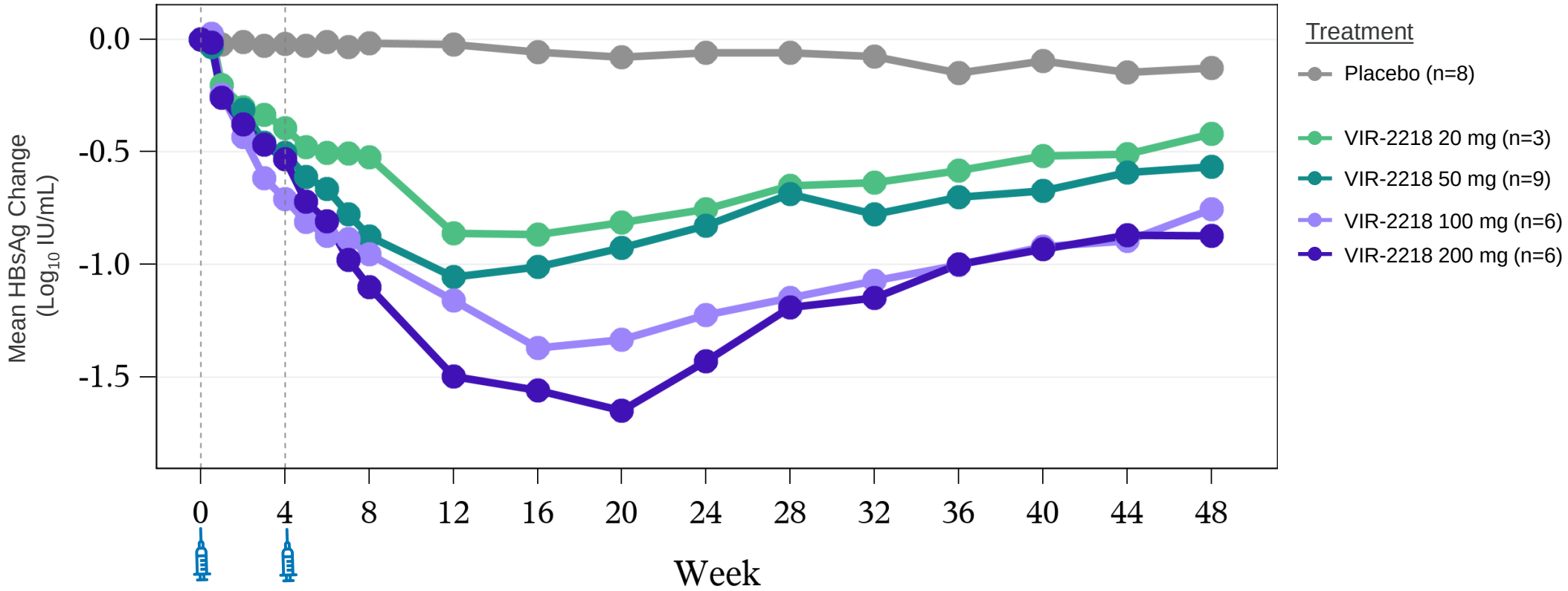
siRNA targeting an overlapping region can silence all transcripts

*Main high-income countries (HICs) outside US/EU with high prevalence are S Korea, Taiwan, Canada, and Australia; HIC is defined per World Bank designations.

The Polaris Observatory Collaborators. Lancet Gastroenterol Hepatol 2018

VIR-2218 Phase 2 Study Results

Safety and Antiviral Activity Support Continued Development in Combination Regimens Targeting Functional Cure

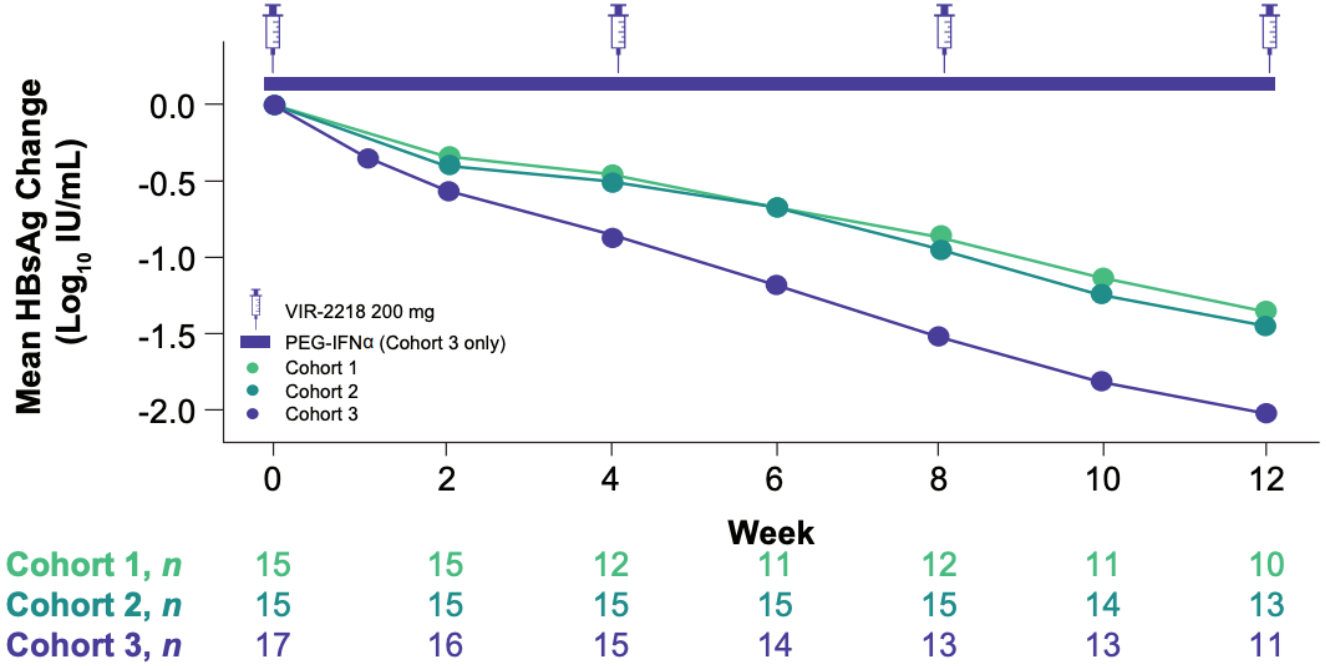


- Two doses of VIR-2218 at 20-200 mg given 4 weeks apart was generally well tolerated with no treatment discontinuations; adverse events were generally mild
- ≥ 1 log reductions in HBsAg were observed in both HBeAg-negative and HBeAg-positive participants across all dose levels and sustained in higher dose cohorts

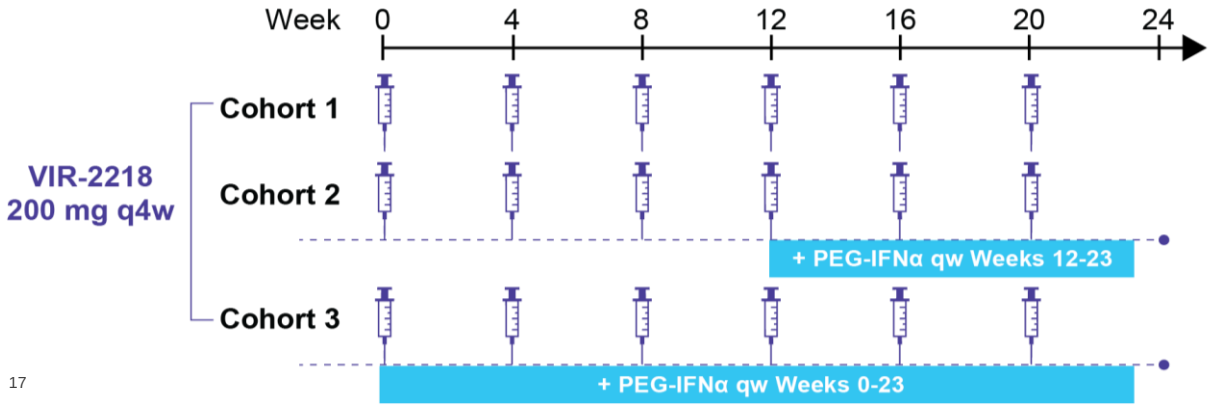
Edward Gane, Young-Suk Lim, Daniel Cloutier, Ling Shen, Andrea Cathcart, Xiao Ding, Phil Pang, Stephen A. Huang, Man-Fung Yuen. "Safety and Antiviral Activity of VIR-2218, An X-Targeting RNAi Therapeutic, In Participants With Chronic Hepatitis B Infection: Week 48 Follow-Up Results". The International Liver Congress™; EASL - European Association for the Study of the Liver; June 23-26 2021.

VIR-2218 + PEG-IFNα Preliminary Phase 2 Study Results

Preliminary Data Support Hypothesis that Activity of VIR-2218 can be Potentiated by PEG-IFNα Immunomodulator



Cohort 1, *n*	15	15	12	11	12	11	10
Cohort 2, *n*	15	15	15	15	15	14	13
Cohort 3, *n*	17	16	15	14	13	13	11



- Administration of VIR-2218 alone or in combination with PEG-IFNα generally well tolerated
- Preliminary antiviral data demonstrate that combination of VIR-2218 and PEG-IFNα resulted in more rapid and substantial HBsAg decline compared to VIR-2218 alone

Man-Fung Yuen, Young-Suk Lim, Daniel Cloutier, Ling Shen, Andre Arizpe, Phillip S. Pang, Chin Tay, Vaidehi Thanawala, Sneha V. Gupta, Andrea L. Cathcart, and Edward Gane. “Preliminary On-Treatment Data From a Phase 2 Study Evaluating VIR-2218 in Combination With Pegylated Interferon Alfa-2a in Patients With Chronic Hepatitis B Infection”. The International Liver Congress™; EASL - European Association for the Study of the Liver; June 23-26 2021.

ALN-HBV02 (VIR-2218) Next Steps

Robust Clinical Development Plan with Multiple Combinations and Potential Best-In-Class siRNA as Backbone

Vir Sponsored Studies

ALN-HBV02[a]

- Phase 2 one-year response durability study complete

ALN-HBV02 + PEG-IFNα combo[b]

- Phase 2 initial data presented; study ongoing

ALN-HBV02 + VIR-3434 (HBV Mab) combo[c]

- Phase 2 MARCH study initiated in July 2021

Additional Vir Partnered Studies

ALN-HBV02 + Selgantolimod combo (Gilead)[d]

- Phase 2 study start in Q3 2021

ALN-HBV02 (Brii)[e]

- Phase 2 trial in mainland China on-going

ALN-HBV02 + BRII-179 combo (Brii)[f]

- Phase 2 trial in mainland China on-going

Alnylam Opt-in Right Prior to Phase 3

[a]NCT03672188; [b]NCT04412863; [c]NCT04856085; [d]NCT04891770; [e]NCT04507269; [f]NCT04749368

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Cemdisiran for Complement-Mediated Diseases

Alnylam PHARMACEUTICALS

Complement C5 and Cemdisiran Program

Complement C5 is *genetically* validated target

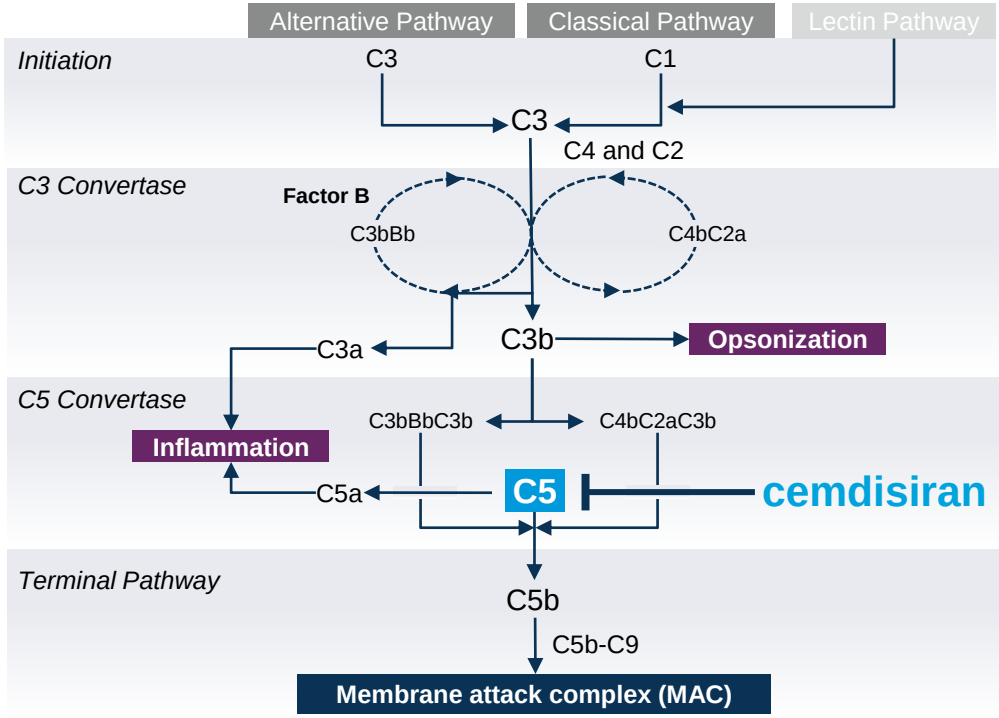
- Key component of terminal pathway
- Human C5 deficiency associated with minimal complications
- Majority expressed in liver; circulates in plasma

Complement C5 is *clinically* validated target

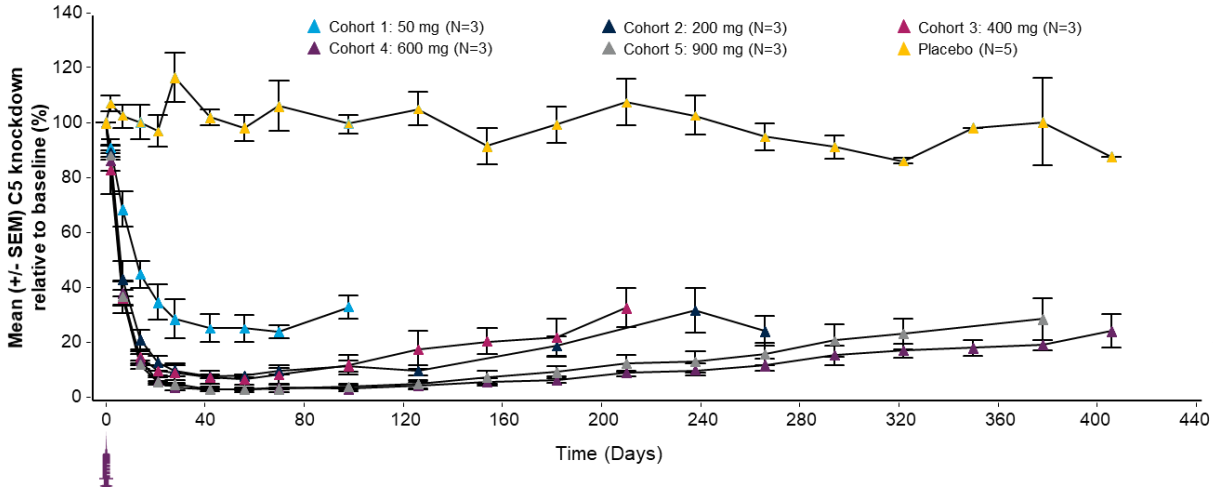
- Eculizumab is anti-C5 Mab approved in PNH and aHUS
  - In PNH, >80% inhibition of hemolytic activity associated with clinical benefit[1]
- Potential advantages of synthesis inhibition vs. protein binding approach

Deep and durable C5 inhibition observed with single doses of cemdisiran in healthy volunteers

- Maximum C5 knockdown relative to baseline up to 99%
- Mean maximum (± SEM) C5 knockdown: 98 ± 0.9% (600mg)



Healthy Volunteer Study



[1]Hillmen *et al., NEJM*; 350:552-9 (2004)

Complement-Mediated Disorders

Numerous Debilitating Diseases

REGENERON

IgA Nephropathy
Prevalence ~300-450K
Reduce proteinuria, and improve kidney function

Evaluating Role for Cemdisiran Monotherapy

- Sub-maximal levels of complement inhibition may be effective
- Phase 2 study underway
- Opportunity to expand to other renal diseases involving complement (e.g., membranoproliferative glomerulonephritis)

Myasthenia Gravis
Prevalence ~175K
Improve Motor Function & Activities of Daily Living

PNH
Prevalence ~25K
Reduce RBC hemolysis

Evaluating Role for Combination Therapy with Cemdisiran + Pozelimab*

- Potent inhibition of C5 required
- Phase 2 studies for PNH underway
- Opportunity to expand to other complement-driven diseases

* Pozelimab is an anti-C5 monoclonal antibody in development by Regeneron

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IgA Nephropathy

Immune-Mediated Disease Characterized by Proteinuria and Progressive Kidney Failure

Epidemiology

- Most common cause of glomerulonephritis worldwide

Pathophysiology

- ~6% have family history of disease
- Abnormally galactosylated IgA1 is antigenic leading to autoantibody formation, glomerular immune complex deposition and complement activation (C3, C5, MAC) causing inflammation

Clinical Features

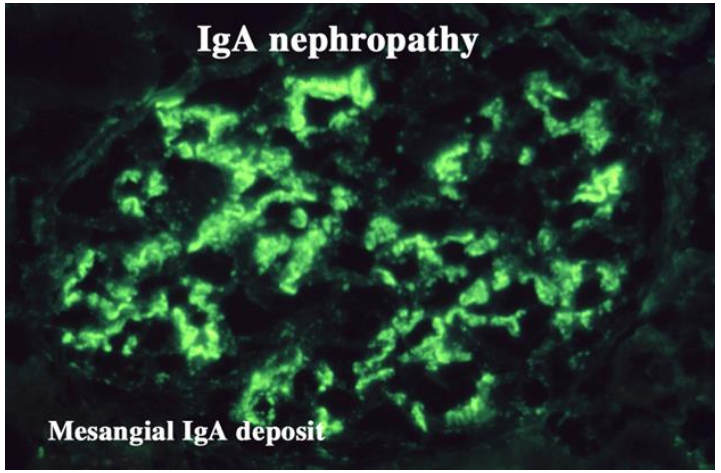
- Often presents after respiratory or GI infection with hematuria and variable degree of proteinuria
- Symptoms can be recurrent
- 30-40% can evolve to chronic renal failure
- Rarely presents with rapid deterioration to end-stage renal disease

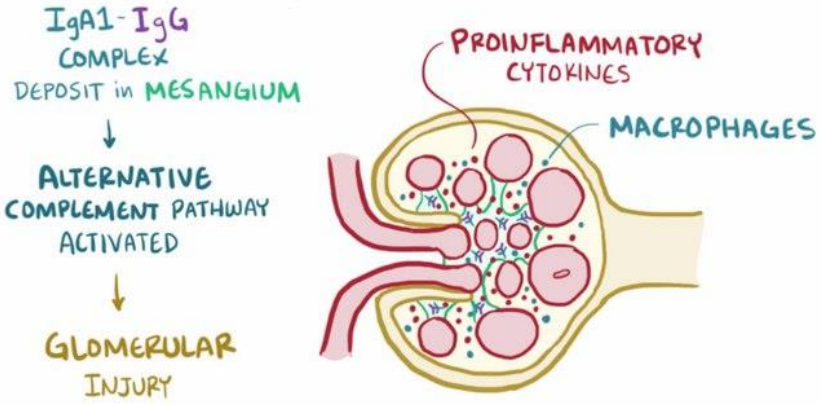
Treatment

- No disease-specific therapy; ACE-inhibitors and ARBs are standard of care in US / EU
- Steroids and immunosuppressive drugs sometimes used with variable results

Unmet Need

- Only definitive therapy is renal transplantation, but disease can recur in graft

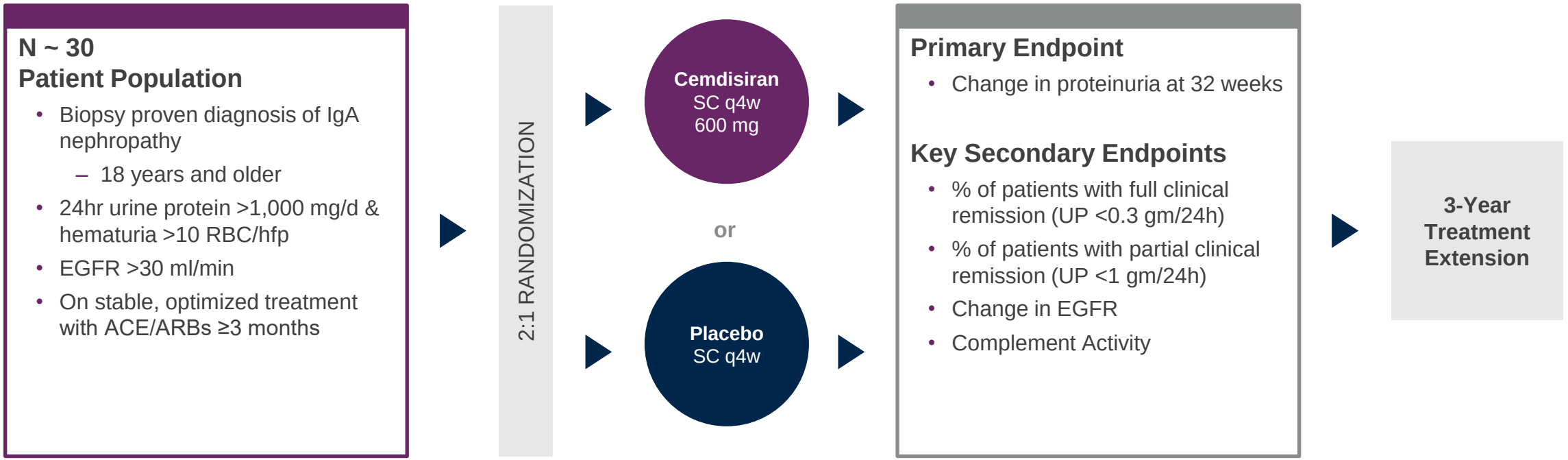




ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker

Cemdisiran Phase 2 Study*

Randomized, Double-Blind Study in Patients with IgA Nephropathy



Enrollment **completed**

Initial data expected **2021**

* NCT03841448

Complement-Mediated Disorders

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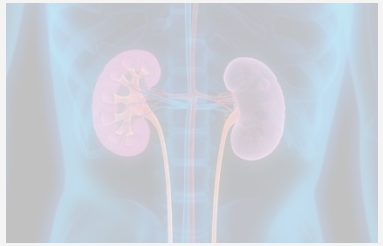

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Improve Motor Function & Activities of Daily Living

PNH
Prevalence ~25K
Reduce RBC hemolysis

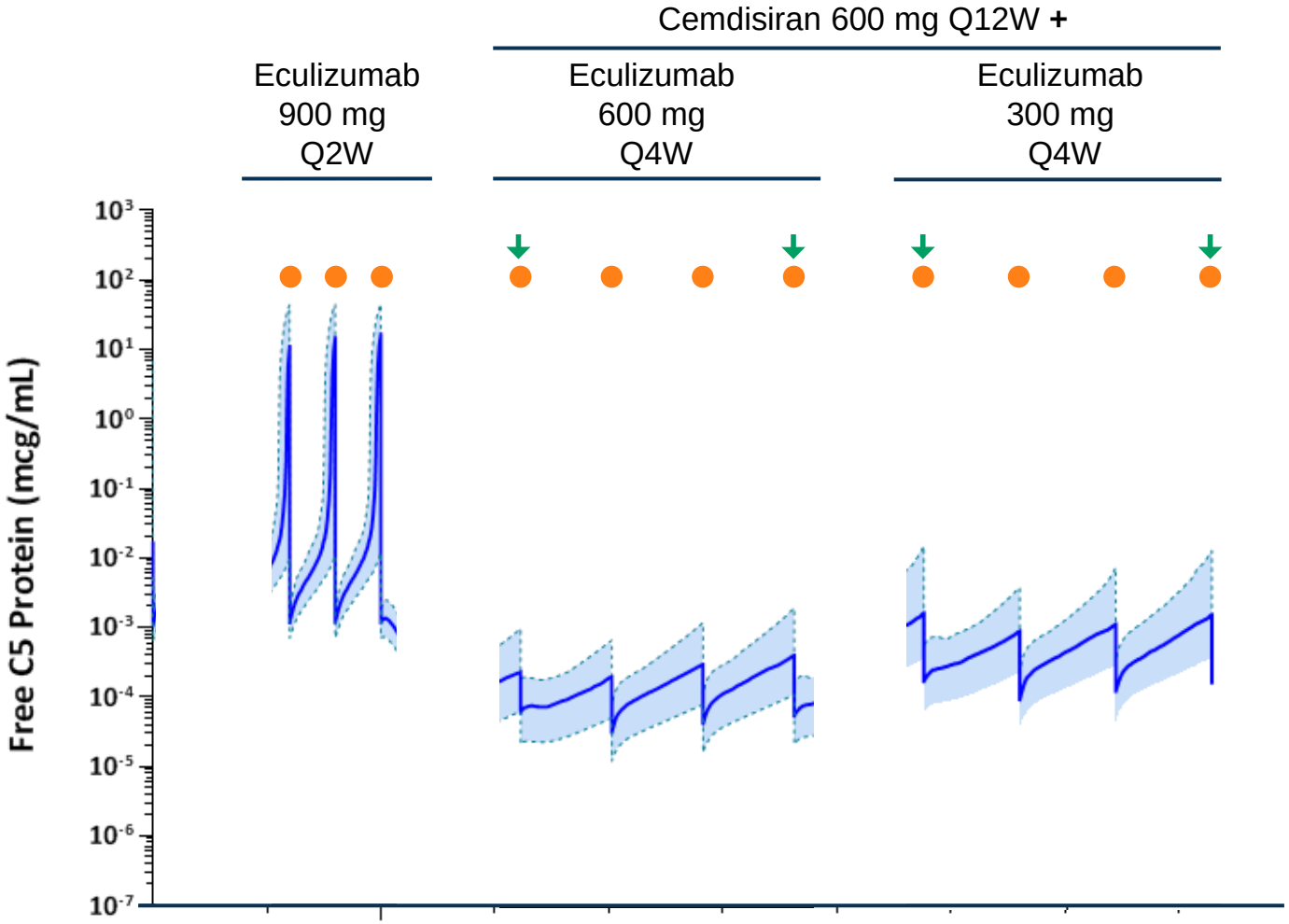
Evaluating Role for Combination Therapy with Cemdisiran + Pozelimab*

- Potent inhibition of C5 required
- Phase 2 studies for PNH underway
- Opportunity to expand to other complement-driven diseases

* Pozelimab is an anti-C5 monoclonal antibody in development by Regeneron

Combination of Cemdisiran and Anti-C5 Mab Offers Potential for Highly Potent C5 Inhibition with Monthly SC Dosing

Results of PK/PD Modeling with Eculizumab*



Prior Experience in PNH

- Co-treatment with cemdisiran + eculizumab studied in PNH patients in prior Phase 1/2 study**
- Combination resulted in lower free C5 levels than either therapy alone
- Enabled monthly dosing of Mab with quarterly cemdisiran

Potential Role in Diseases Requiring Potent C5 Inhibition

- PNH
- Myasthenia Gravis
- aHUS
- Others

* 100 subjects were simulated to obtain 95th percentiles. Figure depicts three independent simulations and does not represent actual clinical results. X-axis tick marks indicate Q4W intervals.

** NCT02352493

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Progressive Disease of Unregulated Complement Activity

Epidemiology

- Rare disease, incidence of 1 to 10 cases per million
- Affects mostly adults, median age of onset in 30s

Pathophysiology

- Bone marrow defect due to acquired PIG-A gene mutation
- Deficiency of glycophosphatidylinositol (GPI)-anchored surface proteins that protect red blood cells against complement-mediated cell lysis

Clinical Features

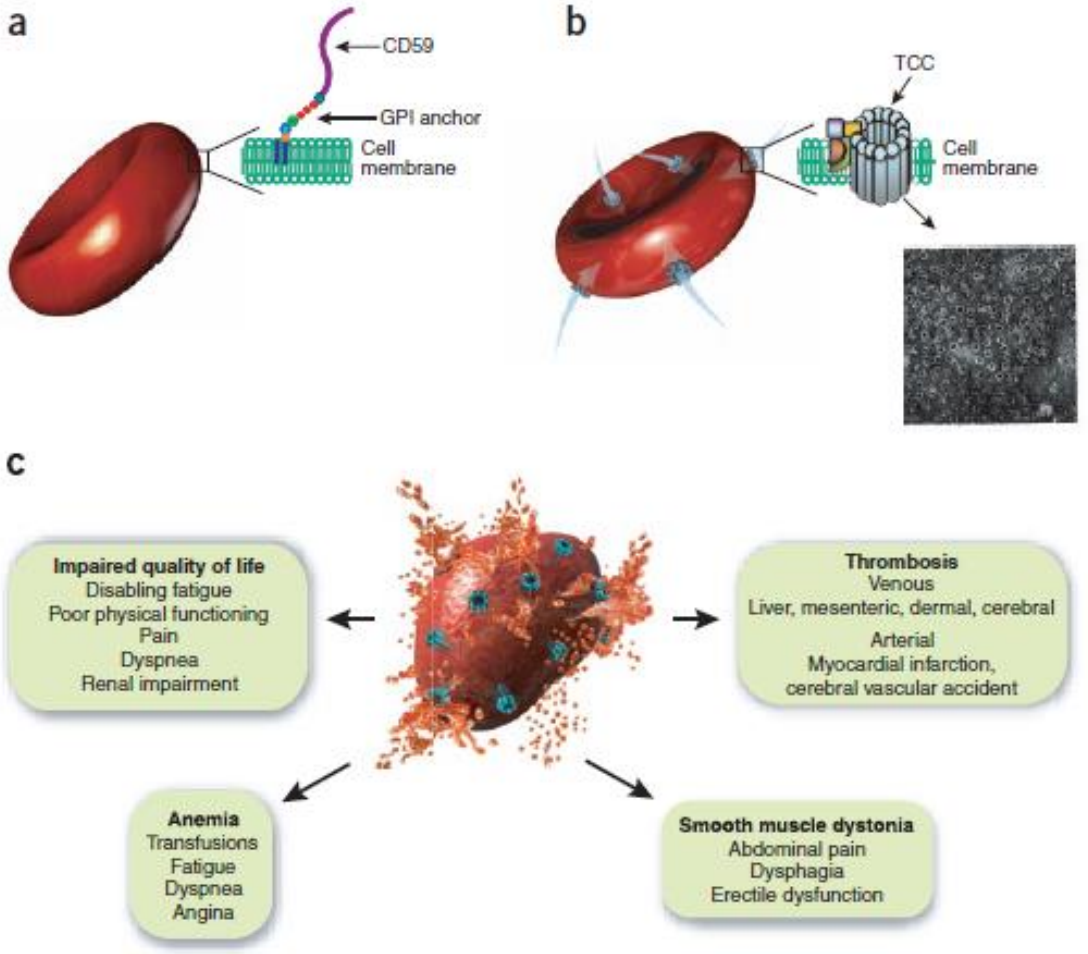
- Concomitant bone marrow failure in ~50% of patients with anemia and increased risk of infection
- Presentation is variable, may be non-specific; complication risk highest during inflammation (e.g., infection)
- Life threatening complications include arterial or venous thromboembolism, kidney failure, pulmonary hypertension

Unmet Need

- Requires high-grade suppression of C5, which can fluctuate up to ~100%[1]
- Many PNH patients on Eculizumab experience breakthrough hemolysis[2]
- Infrequent SC administration desirable

Treatment

- Eculizumab and ravulizumab
- Wide inter-individual variation in pharmacodynamics and clearance of eculizumab[2-4]



[1] Int Archs Allergy Appl Immun; 48: 706-720 (1975), [2]de Latour RP, et al, Blood;125:775-83 (2015)
[3]Jodele S, et al. BBMT (2015), [4]Gatault P, et al, mAbs; 7:1205-11 (2015)

Myasthenia Gravis (MG)

Autoimmune Disease Characterized by Muscle Weakness and Fatigability

Epidemiology

- Worldwide prevalence of 50-300 per million people.
- U.S. prevalence of 20 per 100,000 and total of ~68,000 patients.
- Generalized MG is more severe form of disease, affecting multiple organs, whereas ocular MG only causes weakness in eye muscles.

Pathophysiology

- Autoantibodies block signals from nerves and complement activation destroys neuromuscular junction (NMJ).

Clinical Presentation

- Clinical hallmark of MG consists of fluctuating fatigability and weakness affecting ocular, bulbar and (proximal) limb skeletal muscle groups.
- Course of disease is variable, but progression to maximum severity typically occurs within first 2 years of onset.
- Spontaneous long-lasting remissions are uncommon.

Diagnosis

- Established by history and typical examination and confirmed with serology.

Treatment

- Symptomatic therapy with cholinesterase inhibitors; immunosuppression, including Mabs; plasmapheresis or IVIg; surgical treatment (thymectomy).

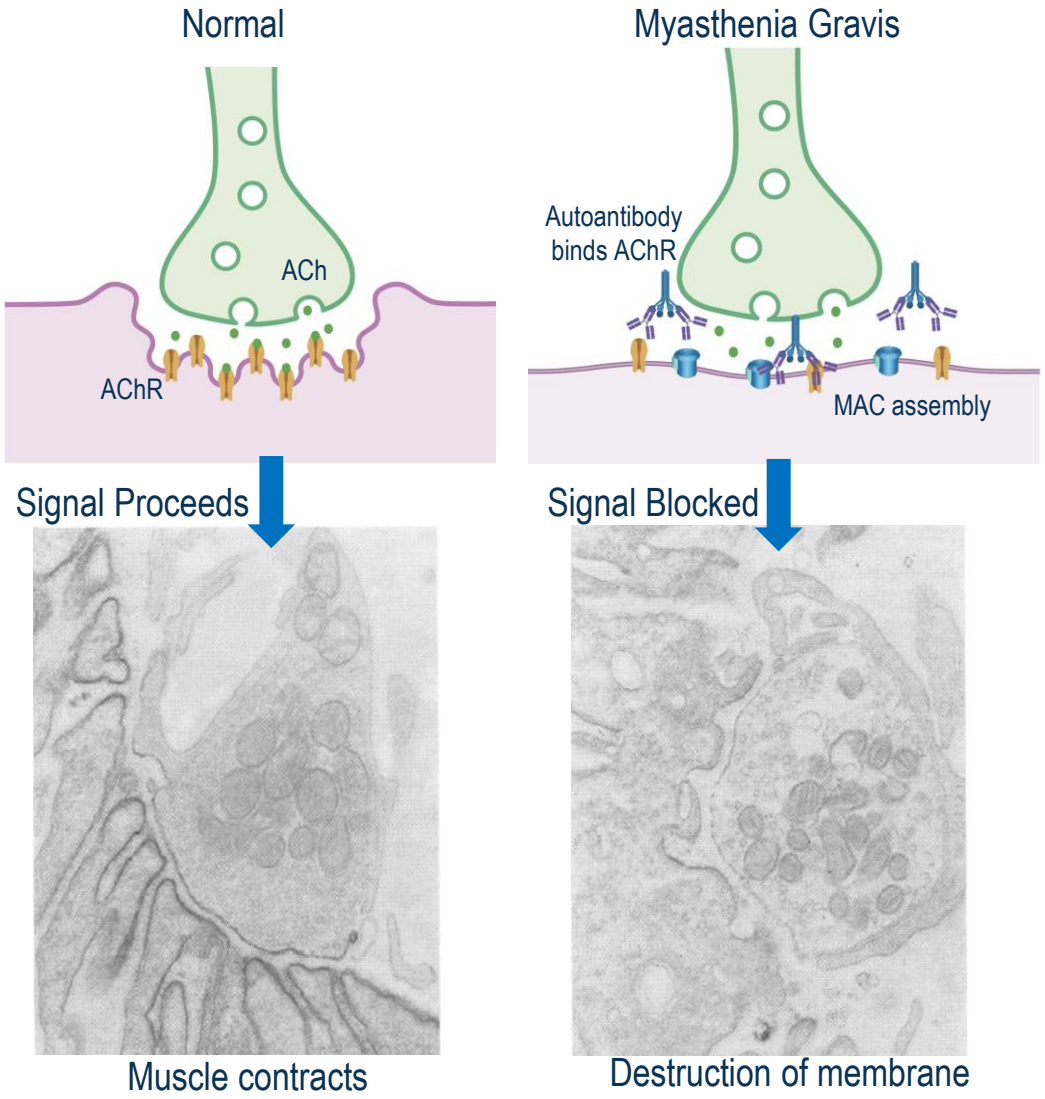


Figure adapted from DOI: 10.5772/intechopen.85761
Neurology 1977; 27:307-15.

Clinical Plan with Cemdisiran/Pozelimab Combination

REGENERON

Clinical Activities Led by Regeneron

NORMAL HEALTHY VOLUNTEERS

Phase 1 study[1]

Study in healthy adult volunteers evaluating safety, tolerability, PK, and PD of pozelimab in combination with cemdisiran administered on either same day or 28 days apart

Study underway

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Phase 2 study[2]

Study in adult participants with PNH evaluating safety and tolerability of two dosing regimens of combination therapy

Phase 2 study[3]

Study of pozelimab and cemdisiran combination therapy in adult participants with PNH who switch from eculizumab therapy

Studies underway

MYASTHENIA GRAVIS

Phase 3 study

Study in adult participants with Myasthenia Gravis

Study initiation planned for **late 2021**

[1]NCT04601844; [2]NCT04811716; [3]NCT04888507

ALN-HSD and ALN-PNP for NASH

Alnylam

Nonalcoholic Fatty Liver Disease (NAFLD)

Disorder of Over-Nutrition Leading to Accumulation of Hepatic Fat

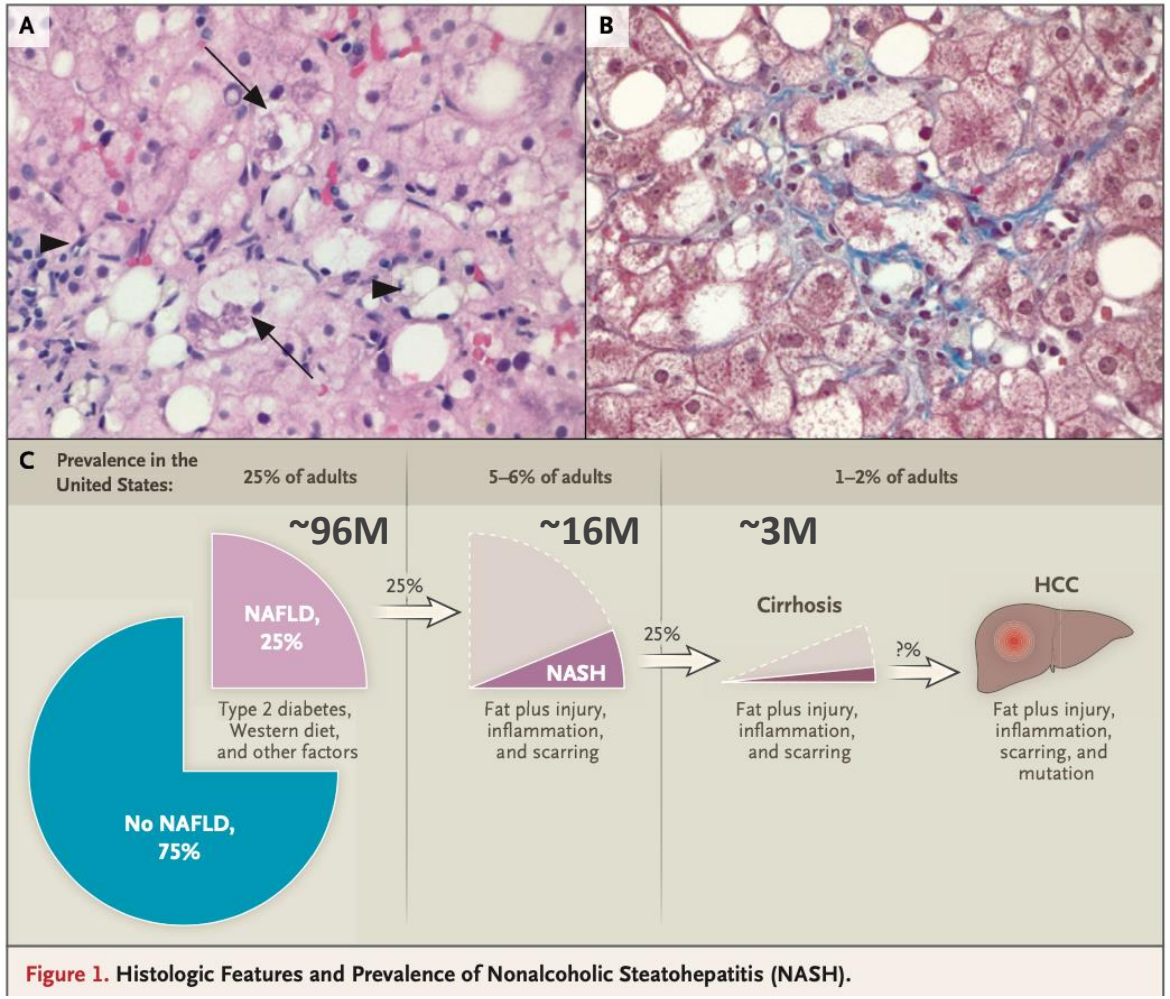


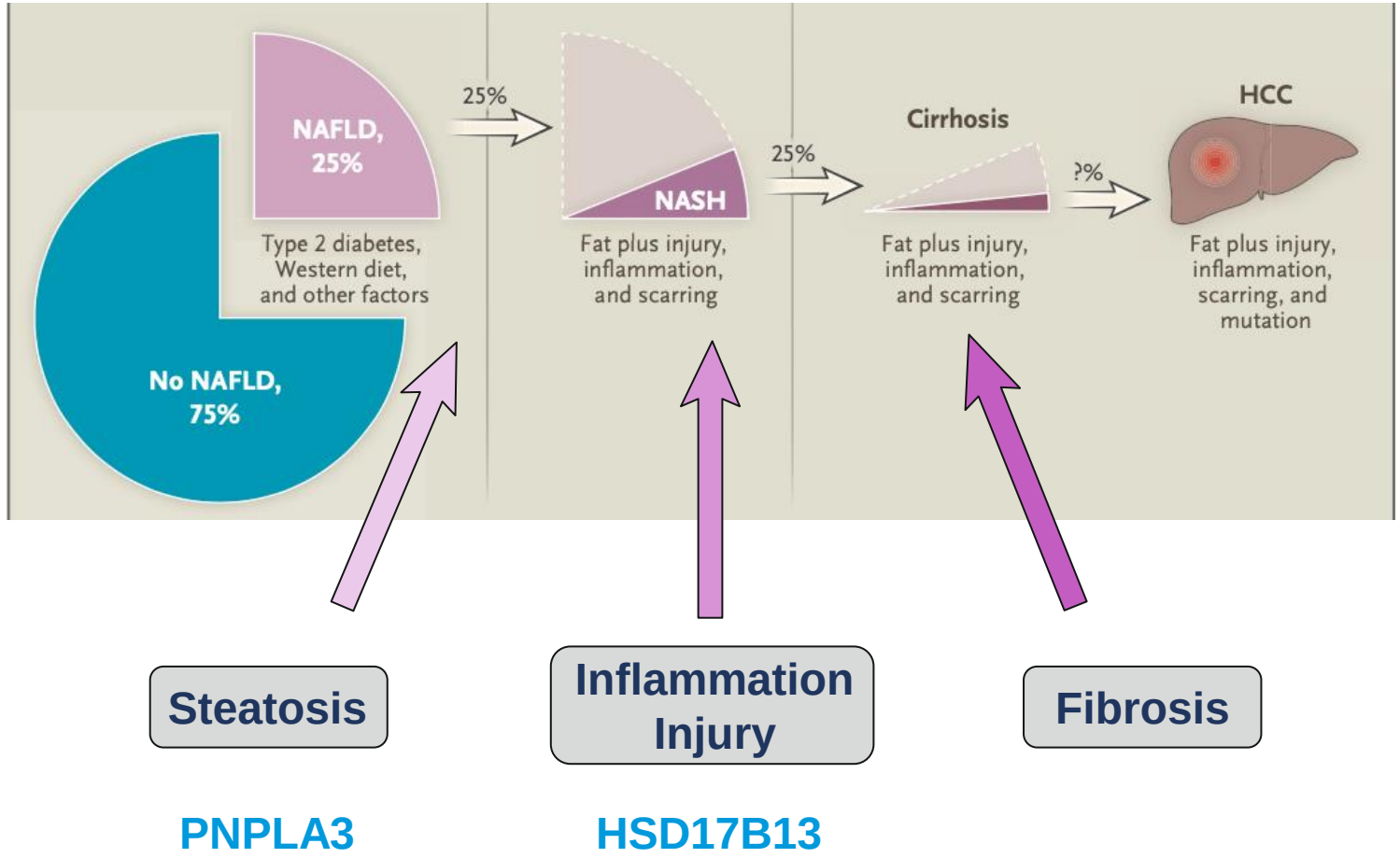
Figure 1. Histologic Features and Prevalence of Nonalcoholic Steatohepatitis (NASH).

- **Nonalcoholic steatohepatitis (NASH)**
  - Subset of NAFLD defined by presence of liver cell injury and inflammation
  - Associated with progressive fibrosis, cirrhosis, and hepatocellular carcinoma
  - Co-morbidities include obesity, metabolic syndrome, and type 2 diabetes
- **NASH treatment**
  - No approved medical therapies
  - Weight loss is effective but difficult to achieve and generally not durable

Adapted from *Diehl, A., Day, C.* (2017). NEJM 377(21), 2063-2072.

Therapeutic Strategies for Nonalcoholic Fatty Liver Disease (NAFLD)

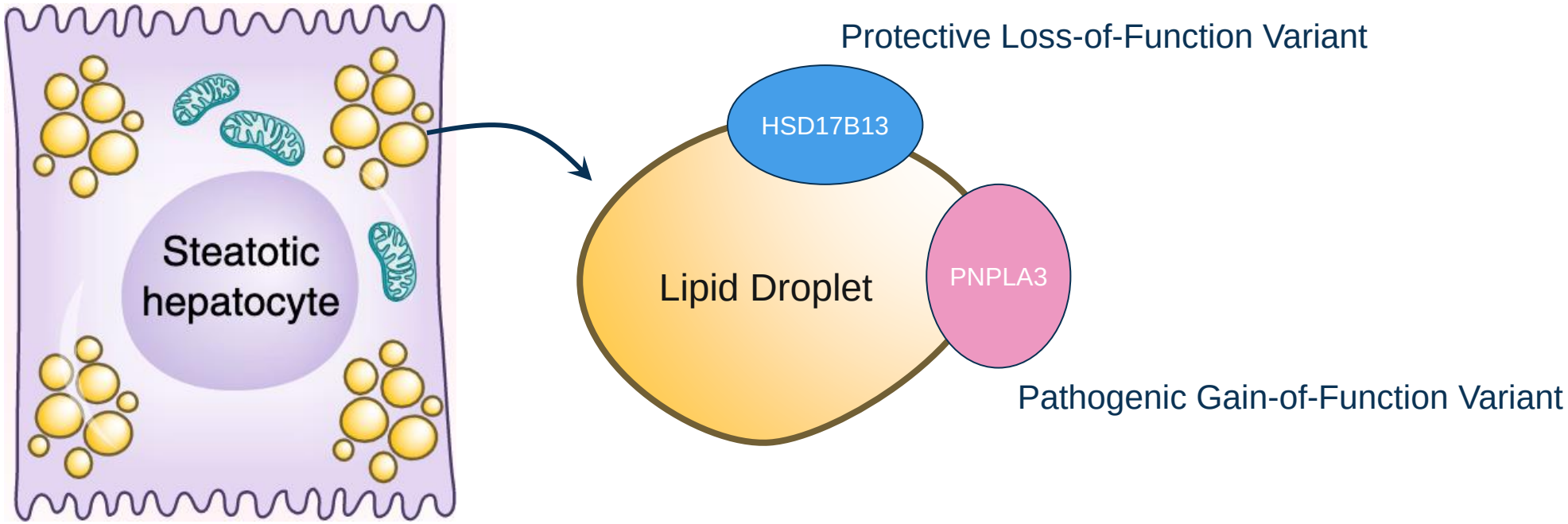
Each Stage of NASH Pathogenesis is Candidate for Intervention



Adapted from *Diehl, A., Day, C.* (2017). NEJM 377(21), 2063-2072.

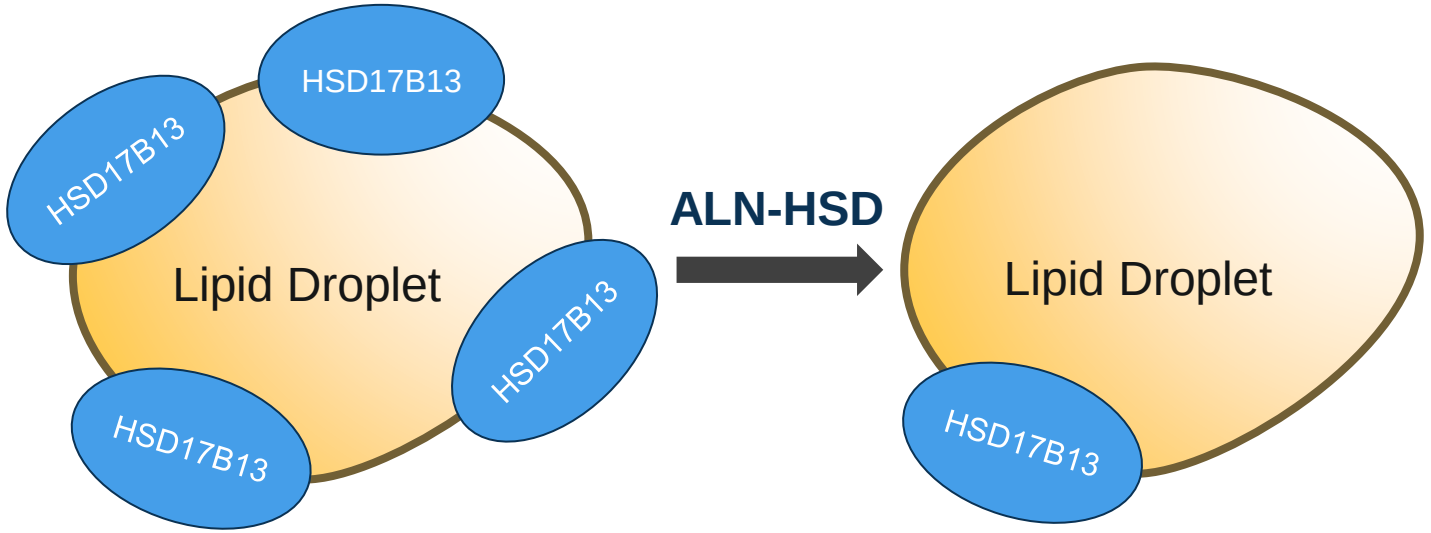
Genetic Variation: Natural Experiment to Identify Liver Disease Targets

Several Candidates are Lipid Droplet Proteins

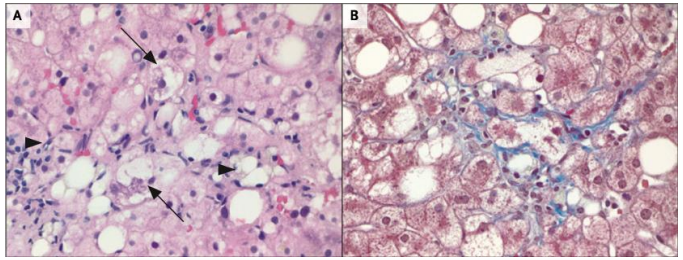


Friedman, S., Neuschwander-Tetri, B., Rinella, M., Sanyal, A. (2018). **Mechanisms of NAFLD development and therapeutic strategies** Nature Medicine 24(7), 908-922. https://dx.doi.org/10.1038/s41591-018-0104-9

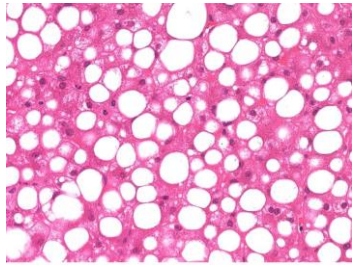
Therapeutic Hypothesis: siRNA-mediated knockdown of HSD17B13 will mimic genetic loss of function, reducing hepatic inflammation, injury, and fibrosis in NASH patients



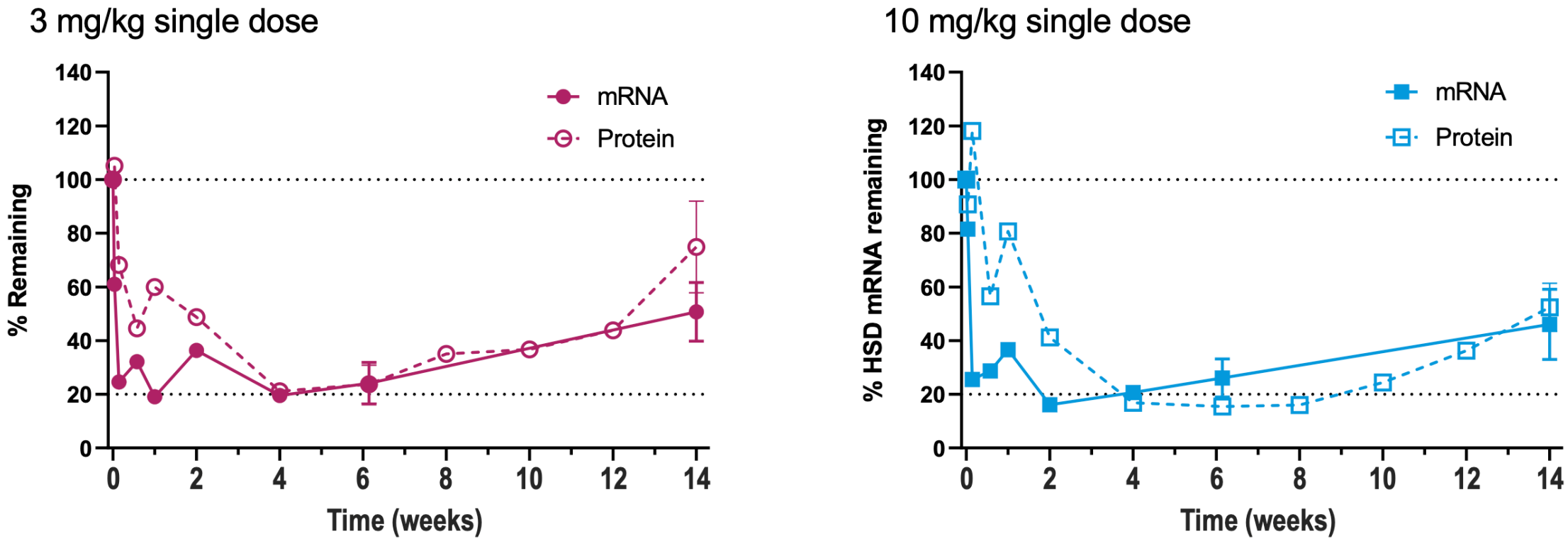
Hepatocyte injury
Inflammation
Fibrosis



Resolution of inflammation
Reduction of fibrosis
Increased phospholipids

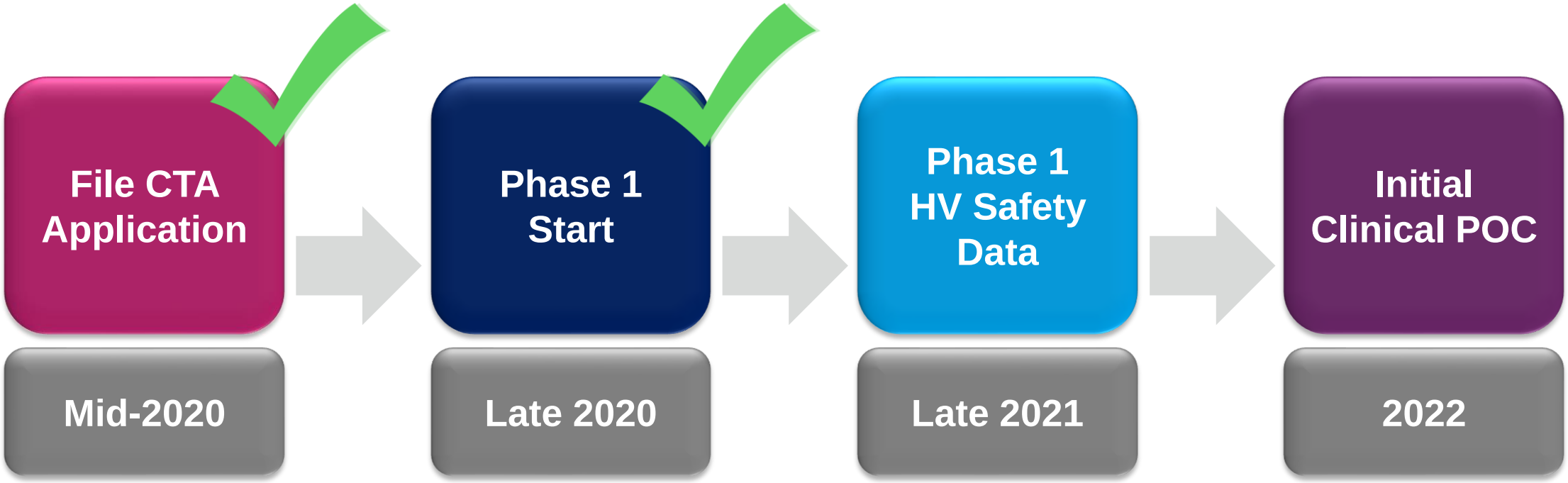


ALN-HSD Results in Potent mRNA and Protein HSD17B13 Knockdown in NHP Liver



- ALN-HSD suppresses HSD17B13 with high specificity *in vitro* and *in vivo* (rodents and healthy and obese NHPs)
- Preliminary evidence suggesting highly durable pharmacodynamic profile
- No pre-clinical toxicity of concern observed, with high safety margins demonstrated

Planned Next Steps for ALN-HSD



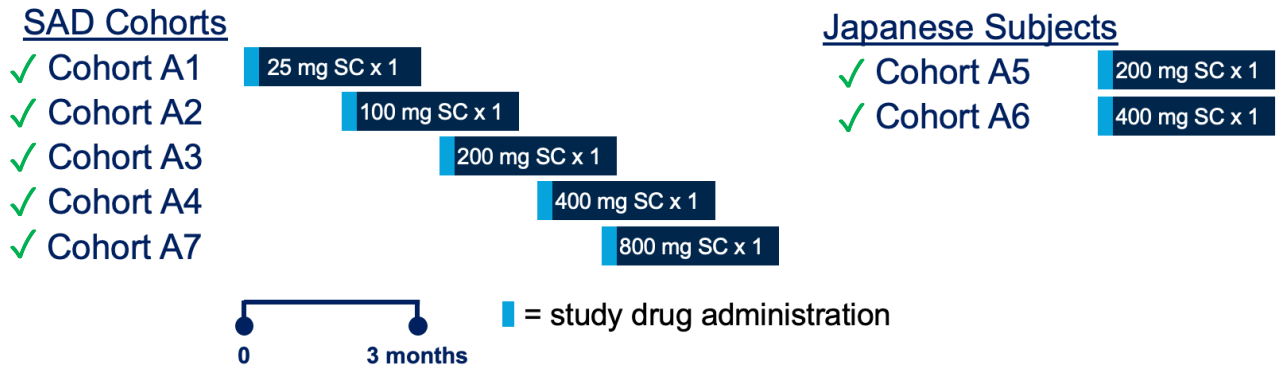
ALN-HSD Phase 1 Design Highlights

Part A: Healthy Volunteers

Primary Endpoint: Safety and tolerability of ALN-HSD

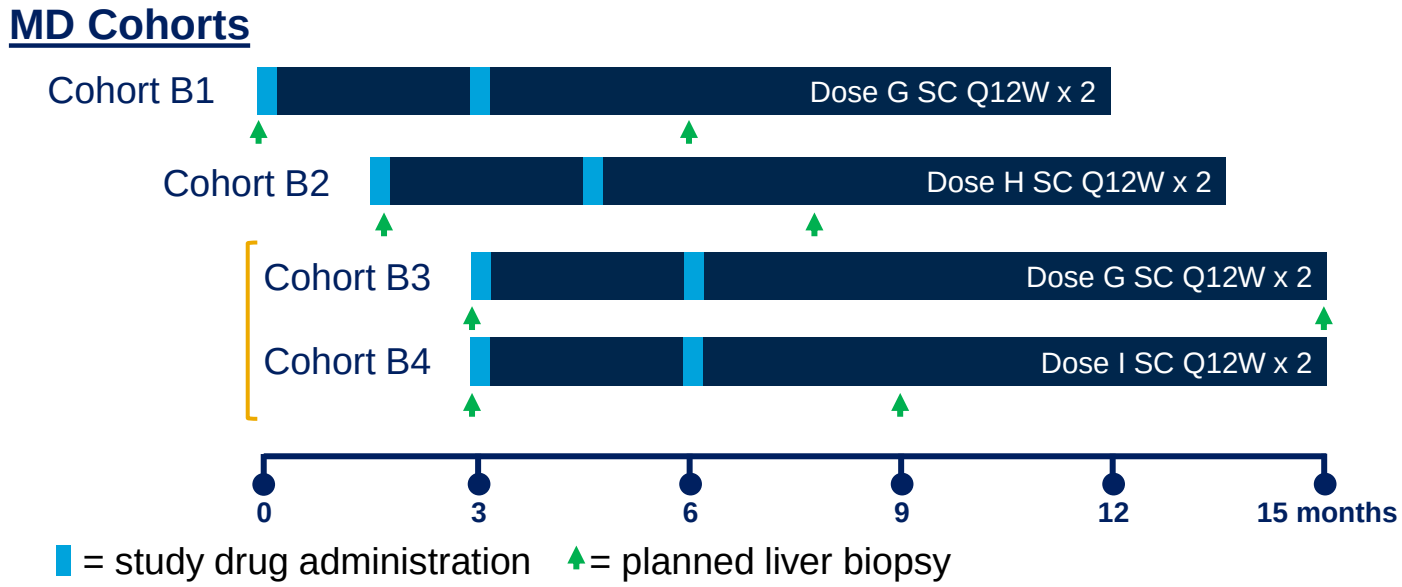
Key Secondary Endpoints: ALN-HSD PK/PD

Exploratory Endpoints: Identify potential biomarkers of HSD; Assess effects of ALN-HSD on histologic and circulating biomarkers of NASH



Part B: NASH Patients

- Multiple-dose (2 doses)
- Baseline and post-dose liver biopsies
- Designed to:
  - Test doses predicted to result in 50, 80, and 90% maximal KD
  - Assess kinetics of recovery from maximal KD



NCT04565717

ALN-HSD Summary

Nonalcoholic steatohepatitis (NASH) is subset of nonalcoholic fatty liver disease (NAFLD) that can lead to progressive fibrosis, cirrhosis, and hepatocellular carcinoma

- Significant unmet need: Approximately 16M people in U.S. live with NASH, with about 3M progressing to liver cirrhosis
- No medical therapies currently approved to treat NASH

HSD17B13 identified as novel target for treatment of NASH

- Loss-of-function variants in HSD17B13 associated with reduced risk of elevated ALT, non-alcoholic and alcoholic liver disease, cirrhosis, inflammation, and liver injury among patients with NAFLD

ALN-HSD is an investigational ESC+ GalNAc-siRNA conjugate targeting HSD17B13

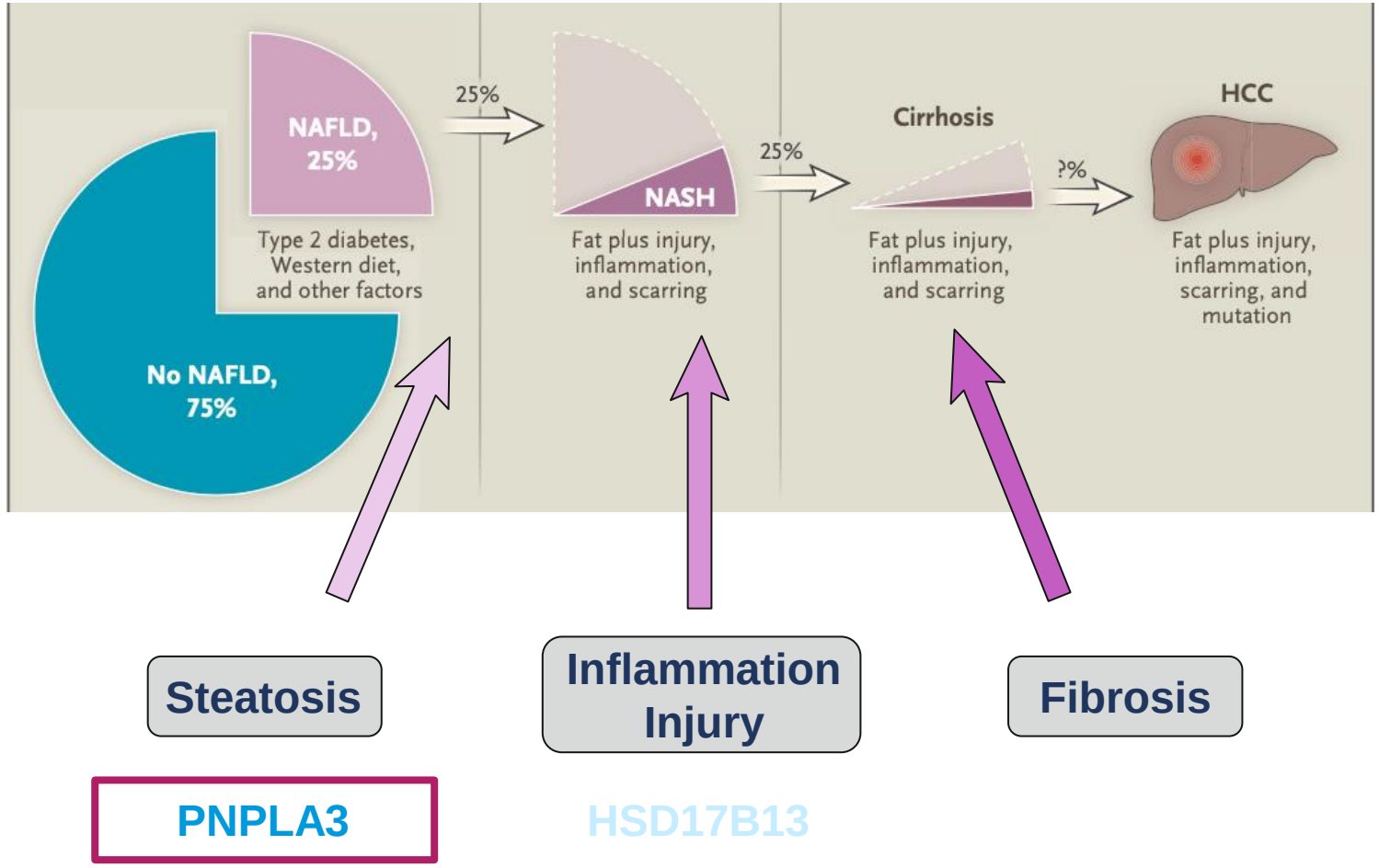
No pre-clinical toxicity of concern observed, with high safety margins demonstrated

Phase 1 trial initiated; Phase 1 HV safety results expected late 2021; POC expected in 2022

IP filed by Alnylam and Regeneron provides strong patent protection for HSD17B13 target, ALN-HSD molecule, and program going forward

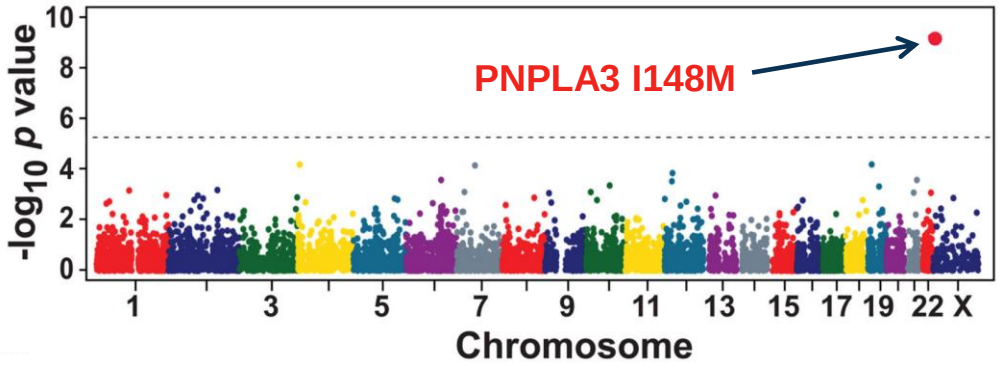
Therapeutic Strategies for Nonalcoholic Fatty Liver Disease (NAFLD)

Each Stage of NASH Pathogenesis is Candidate for Intervention

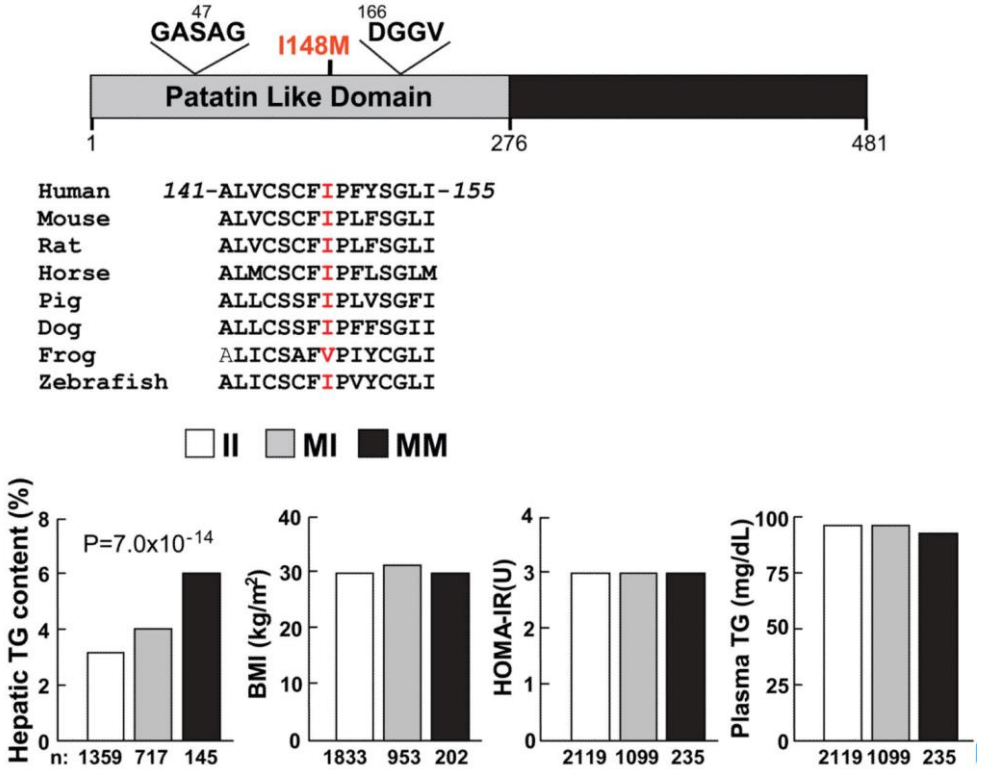


Adapted from *Diehl, A., Day, C.* (2017). NEJM 377(21), 2063-2072.

PNPLA3 Variant (I148M) Associated with Higher Hepatic Triglyceride Levels



Genome-wide scan of liver TG measured by H-MRI in the Dallas Heart Study (n=2,111)



C>G I148M variant is associated with elevated hepatic TG

Hobbs et al. 25 Nature Genetics September 2008; doi:10.1038/ng.257

PNPLA3 I148M Associated with Spectrum of Liver Diseases

Genetic Variation in the *PNPLA3* Gene Is Associated with Alcoholic Liver Injury in Caucasians

Felix Stickel,[1]* Stephan Buch,[2]* Katharina Lau,[3] Henriette Meyer zu Schwabedissen,[4] Thomas Berg,[5] Monika Ridinger,[6] Marcella Rietschel,[7] Clemens Schafmayer,[8] Felix Braun,[8] Holger Hinrichsen,[2] Rainer Günther,[2] Alexander Arlt,[2] Marcus Seeger,[2] Sebastian Müller,[9] Helmut Karl Seitz,[9] Michael Soyka,[10] Markus Lerch,[11] Frank Lammert,[12] Christoph Sarrazin,[13] Ralf Kubitz,[14] Dieter Häussinger,[14] Claus Hellerbrand,[15] Dieter Bröring,[8] Stefan Schreiber,[2] Falk Kiefer,[7] Rainer Spanagel,[7] Karl Mann,[7] Christian Datz,[16] Michael Krawczak,[17] Norbert Wodarz,[6] Henry Völzke,[3] and Jochen Hampe[2]

Homozygosity for the Patatin-Like Phospholipase-3/ Adiponutrin I148M Polymorphism Influences Liver Fibrosis in Patients with Nonalcoholic Fatty Liver Disease

Luca Valenti,[1] Ahmad Al-Serri,[3] Ann K. Daly,[3] Enrico Galmozzi,[1] Raffaela Rametta,[1] Paola Dongiovanni,[1] Valerio Nobili,[4] Enrico Mozzi,[2] Giancarlo Roviaro,[2] Ester Vanni,[5] Elisabetta Bugianesi,[5] Marco Maggioni,[6] Anna Ludovica Fracanzani,[1] Silvia Fargion,[1] and Christopher P. Day[3]

PNPLA3 I148M polymorphism and progressive liver disease

Paola Dongiovanni, Benedetta Donati, Roberta Fares, Rosa Lombardi, Rosellina Margherita Mancina, Stefano Romeo, Luca Valenti

PNPLA3 I148M variant and hepatocellular carcinoma: A common genetic variant for a rare disease

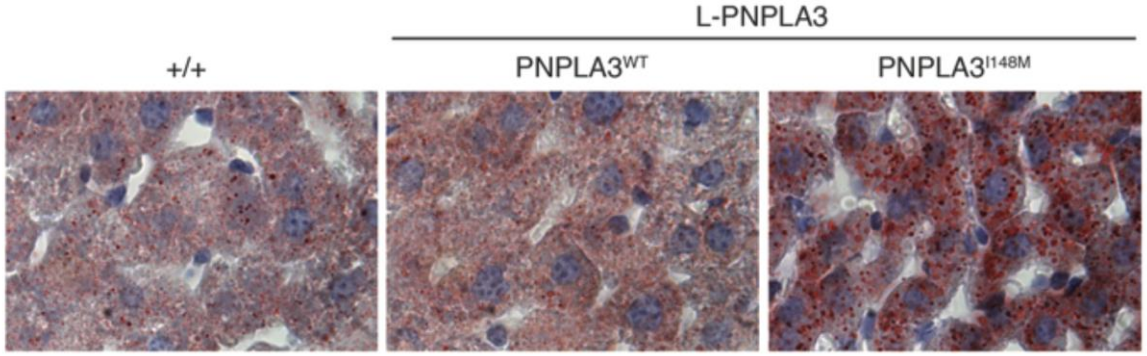
Luca Valenti[a,*], Paola Dongiovanni[a], Stefano Ginanni Corradini[b], Maria Antonella Burza[c], Stefano Romeo[c,d,**]

Stickel et al. Heatology, Vol. 53, No. 1, 2011
Vaelnti et al. Hepatology, Vol. 51, No. 4, 2010
Dongiovanni et al. PNPLA3 and Liver Disease, World J Gastroenterol 2013; 19(41): 6969-6978
L. Valenti et al. Digestive and Liver Disease, 45 (2013) 619–62

PNPLA3 I148M Variant Leads to Hepatic TG Accumulation

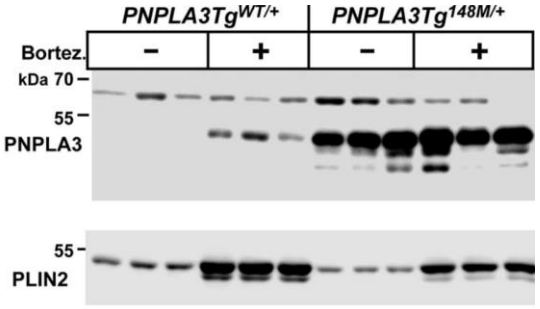
PNPLA3 I148M Resists Degradation and Competes with Triglyceride Lipase for Co-factor CGI-58

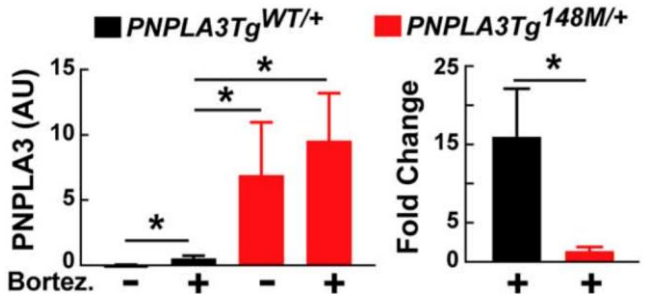
- Liver-specific hPNPLA3 WT and I148M transgenic mice



Oil Red O

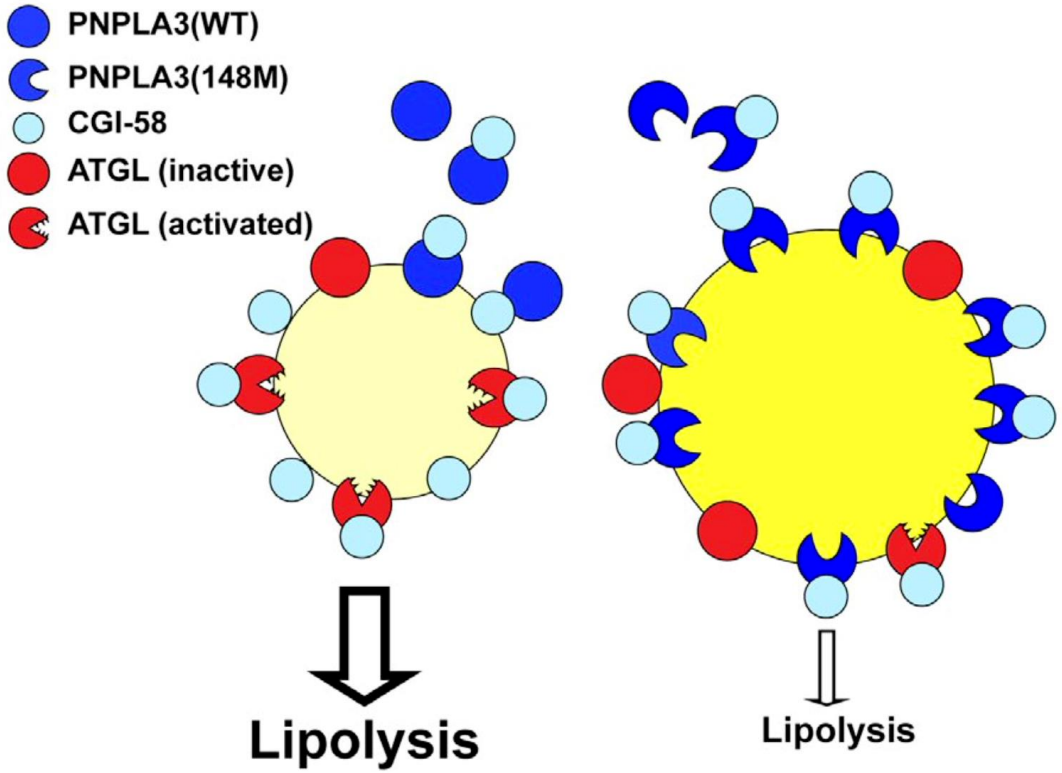
- PNPLA3 I148M variant renders protein resistant to proteasome-mediated degradation





Bortezomib: proteasome inhibitor

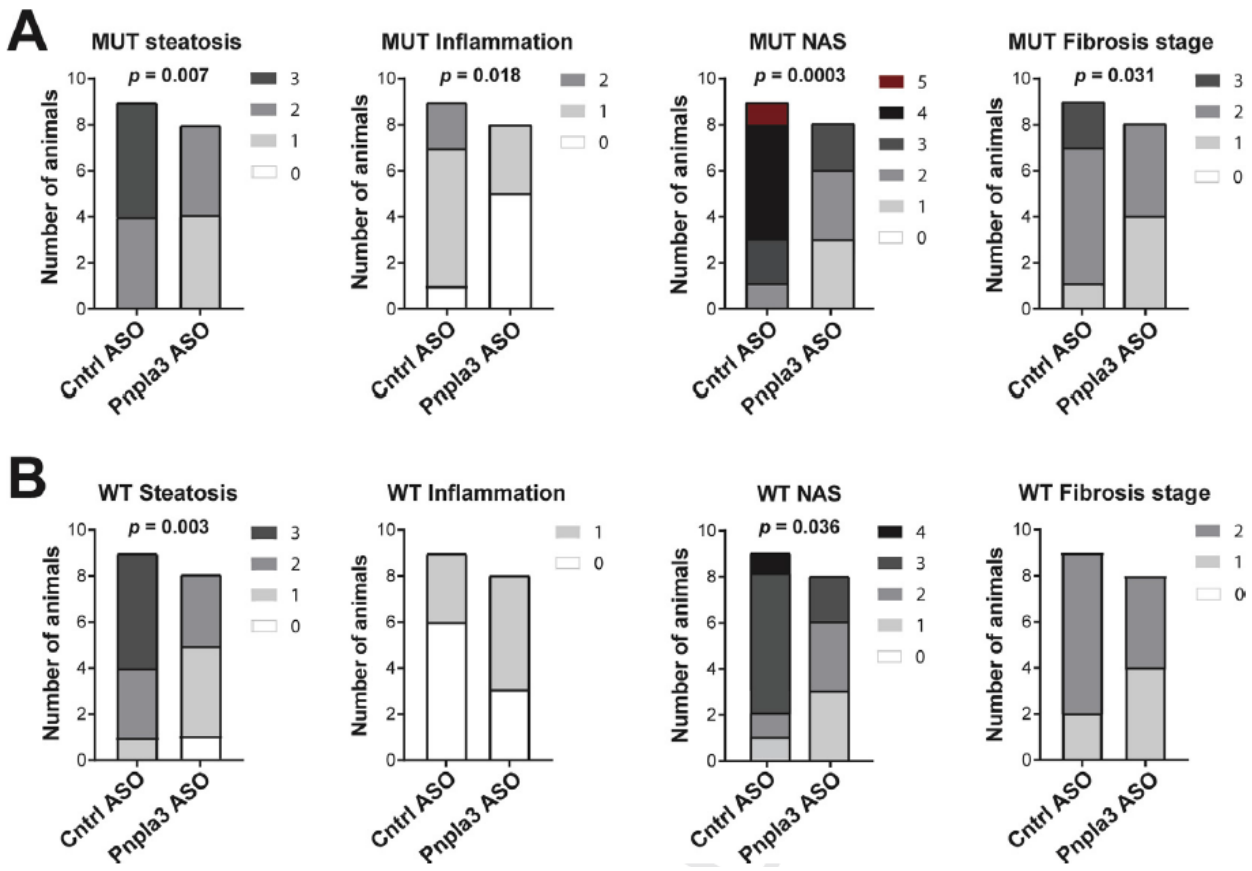
Excess PNPLA3 inhibits lipolysis by competing with ATGL for CGI-58



Li et al, (2012) JCI, BasuRay et al, (2017) Hepatology; Wang et al, (2019) Hepatology

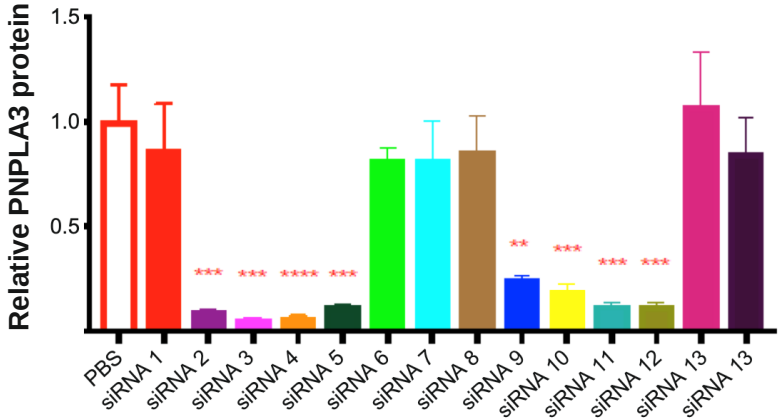
Silencing Hepatic PNPLA3 as a Potential Mechanism to Treat NASH

ASO-mediated lowering of PNPLA3 reduces steatosis and NASH activity in mouse model



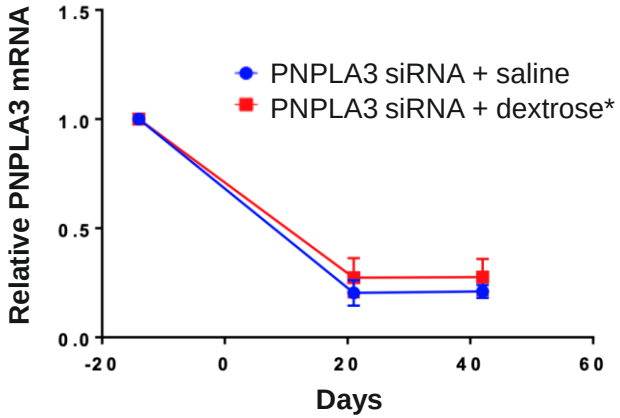
Efficient KD of PNPLA3 protein by candidate siRNAs

Human PNPLA3 I148M knock-in mice



Durable RNAi-mediated silencing of PNPLA3 in NHPs

Following single SC injection



*PNPLA3 is induced by elevated blood glucose

Lindén, D., et al. (2019). Molecular Metabolism 22(), 49-61. https://dx.doi.org/10.1016/j.molmet.2019.01.013

PNPLA3 Summary

PNPLA3 identified as novel target for treatment of NASH

- Gain-of-function variant associated with liver disease, including NAFLD spectrum from steatosis to fibrosis

PNPLA3 reduction protective in animal models of NAFLD, even in absence of I148M variant

Drug candidates show potent PNPLA3 protein knockdown

IP for broadly targeting PNPLA3 with RNAi filed Dec 2015

ALN-PNP Development Candidate selected mid-2021

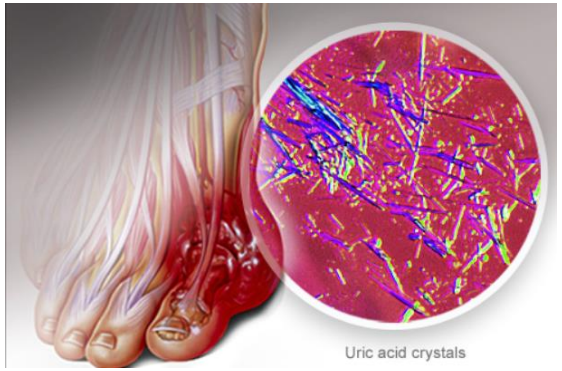
ALN-XDH for Gout

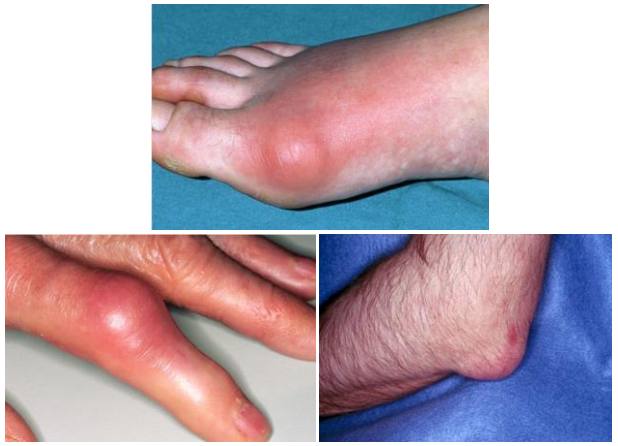
Alnylam PHARMACEUTICALS

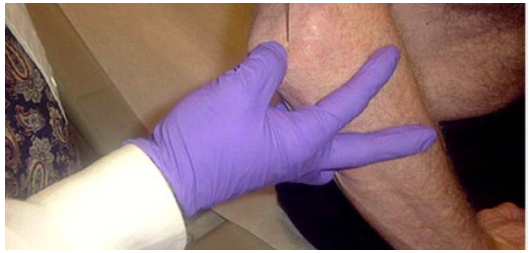
Gout

Arthritis Caused by Uric Acid Crystal Accumulation in Joints

- The most common inflammatory arthritis globally
  - Adult prevalence <1% - 6.8%
  - 14-18M individuals in US, EU5 and Japan
  - Risk factors include, increasing age, obesity, poor diet and comorbid metabolic conditions (CKD, HTN, CVD, etc.)
- Debilitating symptoms
  - Pain, edema, inflammatory arthropathy
  - Tophi, joint destruction
  - Accompanied by chronic urate nephropathy in some patients
- Diagnosis by detection of monosodium urate crystals (MSU) in aspirated joint fluid
- Urate lowering therapy essential to prevent attacks
- Targeting hepatic XDH may offer potent urate-lowering and disease control



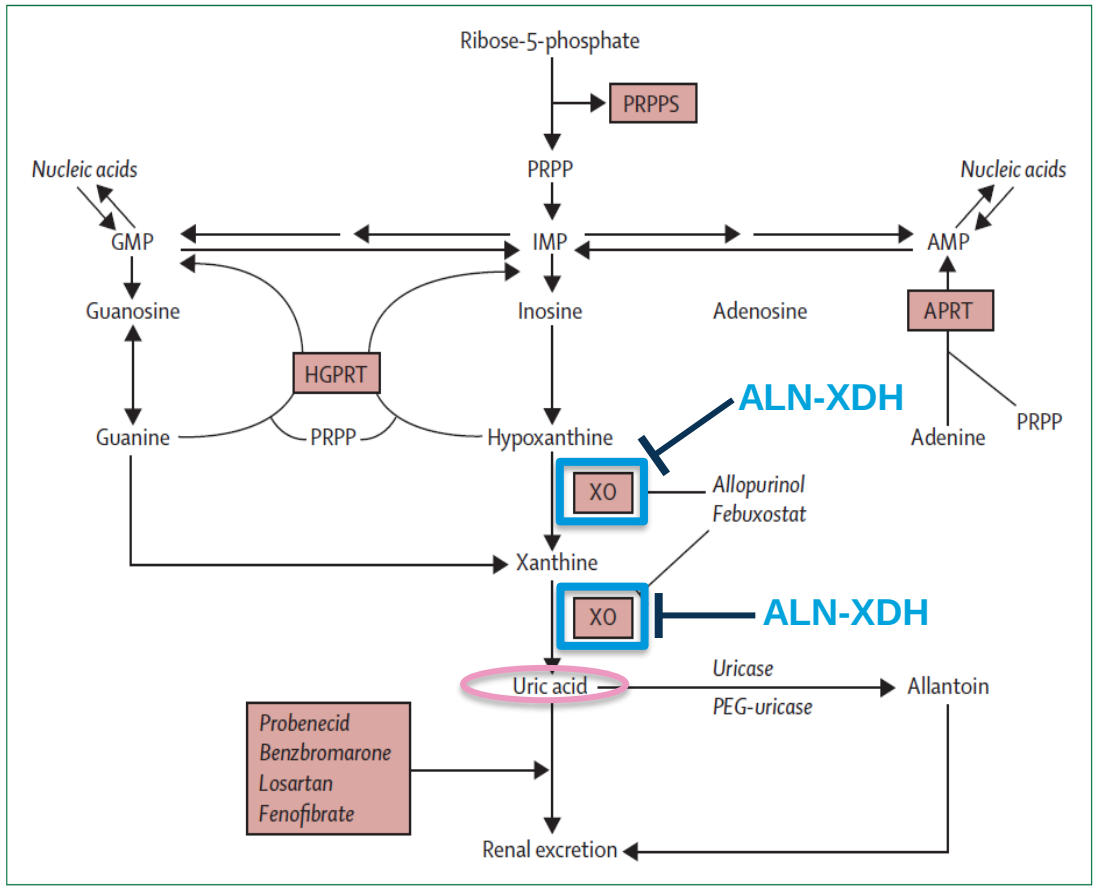




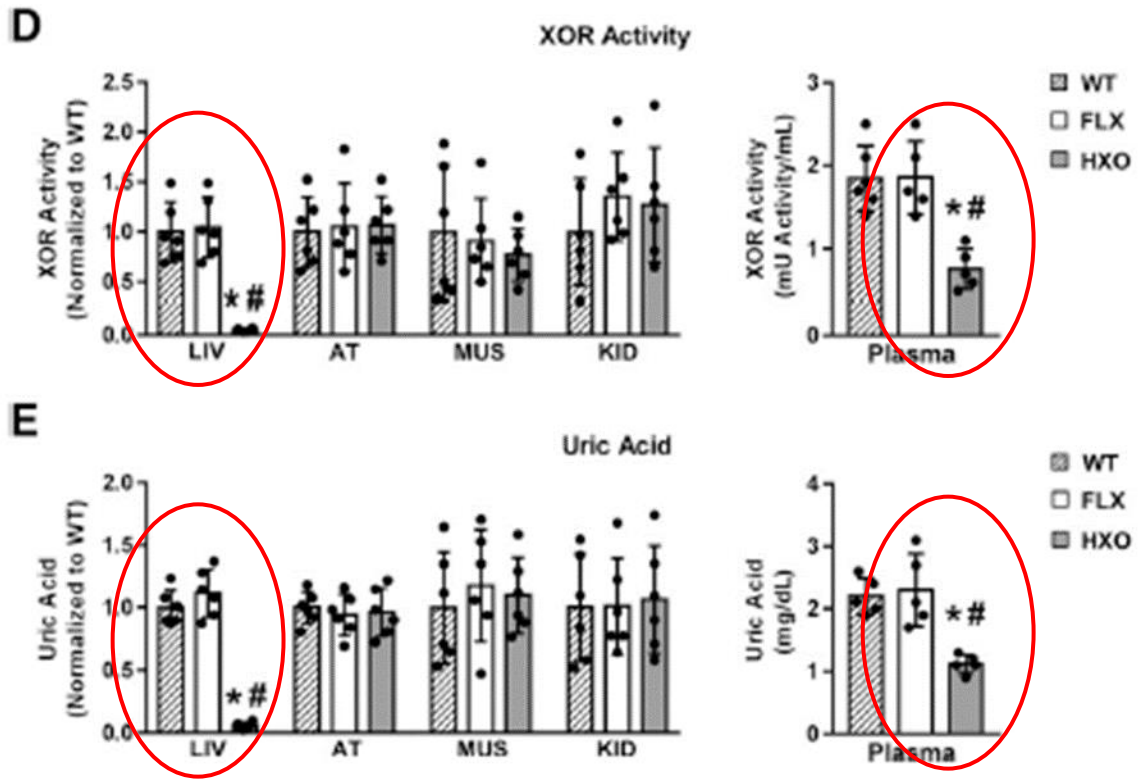
Dehlin et al. *Nature Reviews Rheumatology* 16(7):380-390 (2020); Chen-Xu et al. *Arthritis & Rheumatology* 71(6): 991-999 (2019); Koto et al. *Modern Rheumatology* 20:1-9 (2020); Kuo et al. *Nature Reviews Rheumatology 11*(11):649-662 (2015); GlobalData Disease Analysis

Targeting Xanthine Dehydrogenase (XDH)

Enzyme in Purine Metabolism Pathway*



Liver-specific Knockout of XDH in Mice Lowered Circulating Uric Acid*



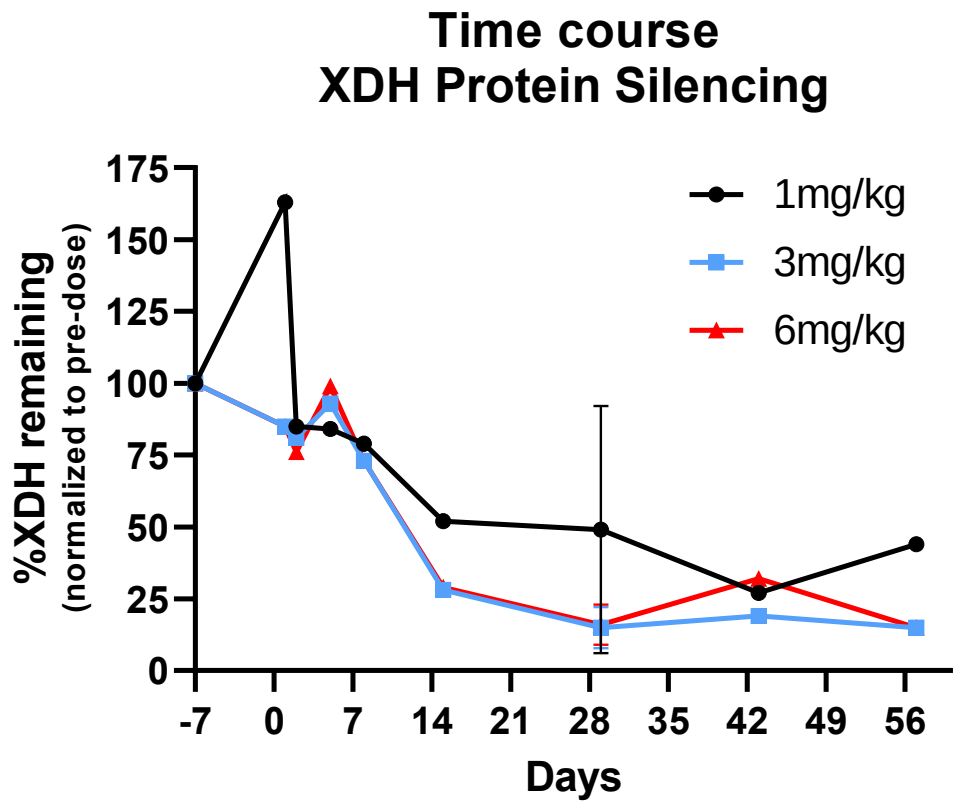
*Xanthine dehydrogenase (XDH) and xanthine oxidase (XO) are enzymatic forms of the protein xanthine oxidoreductase (XOR); the target gene is XDH

Harmon DB, et al Diabetes, 68:1221–1229 (2019); Schumacher HR, et. al, Arth Care Res, 59:1540-48 (2008)

ALN-XDH Achieves Robust Silencing in NHP

Supports Potential for Infrequent Dosing in Humans

- Single dose treatment of cynomolgus monkeys
- Robust and sustained XDH suppression
  - >90% liver XDH protein silencing, with maximum average at ~85% silencing at day 29
  - Suppression maintained up to day 56
- Based on allometric principles, extended XDH suppression (>90 days) expected in humans
  - Nonclinical PD profile supports quarterly and potentially biannual dosing



Sparse biopsy, N=3 on Day 29

Potential to Improve Gout Control with ALN-XDH

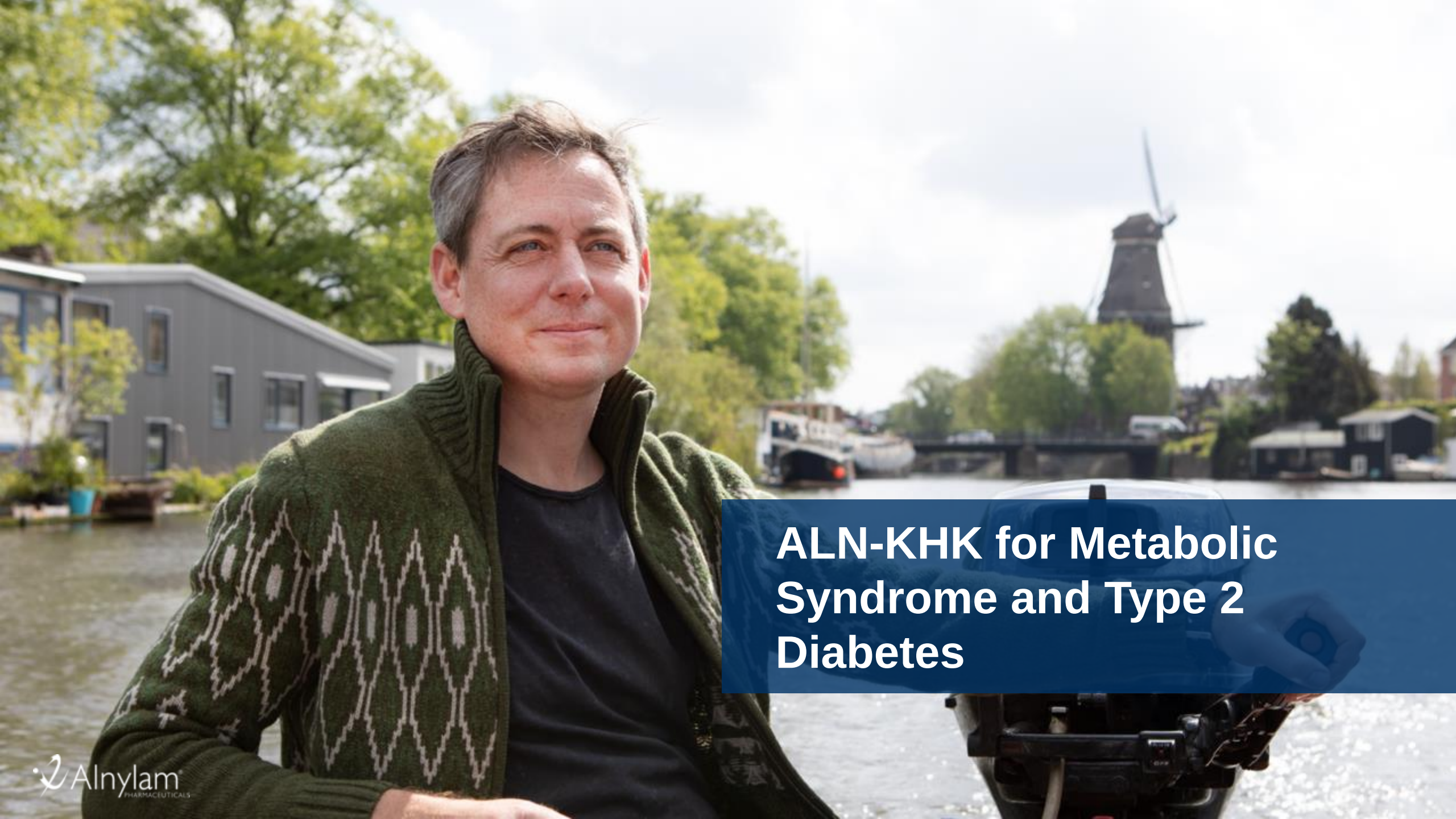
- Current gout therapies have substantial limitations
  - Allopurinol most commonly prescribed; however, side effects limit ability to achieve target uric acid levels in majority of patients
  - Uricosuric agents (e.g., probenecid) dosed multiple times per day and can promote stone formation
  - Newer agents (e.g., febuxostat, pegloticase) associated with other challenges (e.g., potential cardiovascular risk, immunogenicity)

- As a result, majority of patients are untreated, cannot adhere to prescribed therapy, or do not reach target uric acid levels

- ALN-XDH is an investigational RNAi therapeutic that may address key unmet needs for gout patients
  - Potent urate-lowering effects
  - Infrequent dosing with tonic control between doses
  - Reduction in gout flares
  - Acceptable safety and tolerability

CTA filing planned **late 2021**
Phase 1/2 study start expected **early 2022**

Chen-Xu et al. Arthritis & Rheumatology 71(6): 991-999 (2019); Kim et al. *Arthritis Care & Research* 65(4): 578-584 (2013); Reinders et al. *Ann Rhuem Dis* 68: 51-56 (2009); UpToDate
July 2020 US KOL & PCP Market Research



ALN-KHK for Metabolic Syndrome and Type 2 Diabetes

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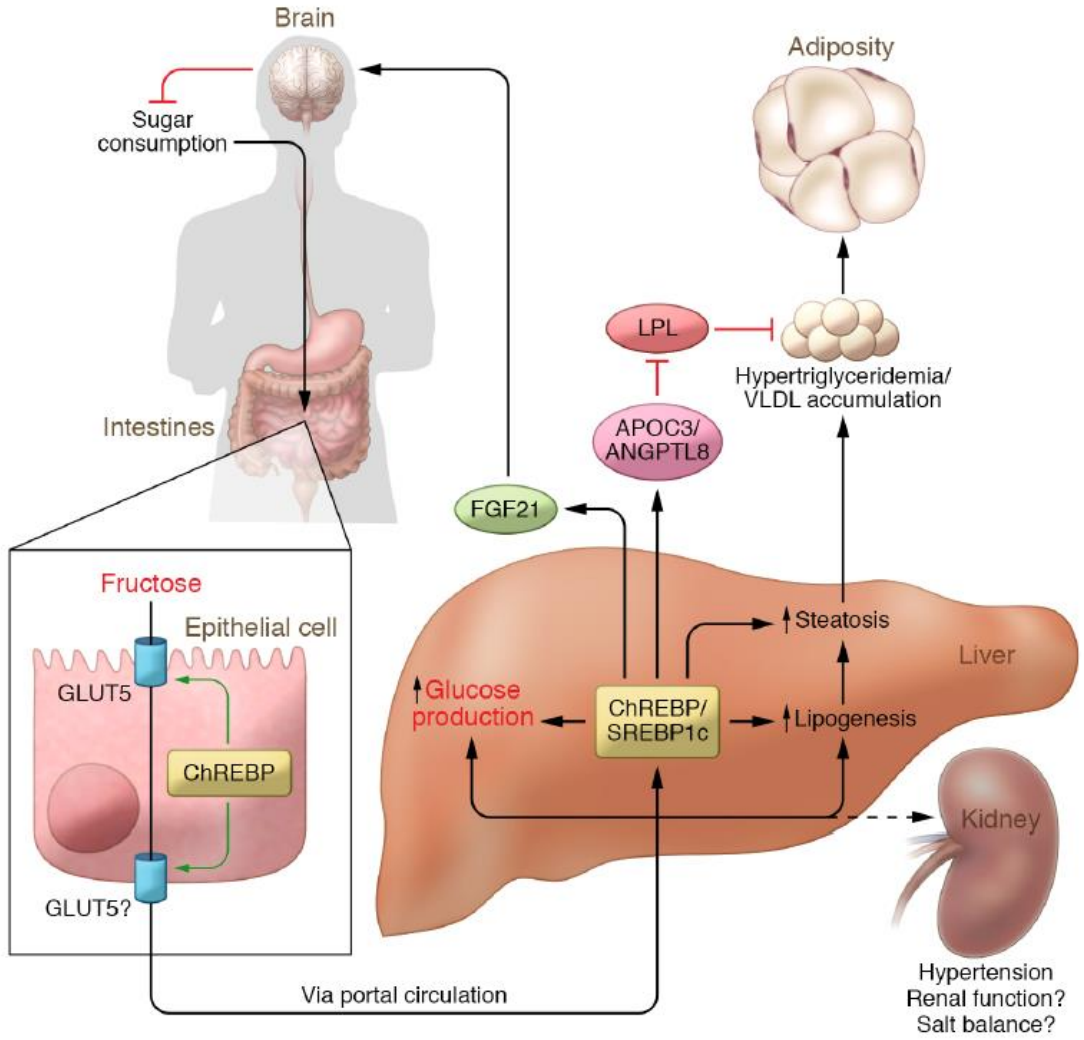
Fructose Metabolism and Metabolic Syndrome

- Sucrose (glucose-fructose disaccharide) and high-fructose corn syrup are added to numerous manufactured foods and beverages
- The average fructose consumption in the US accounts for ~9% of total energy
- Increased fructose consumption is associated with metabolic syndrome – a syndrome consisting of high blood pressure, hyperglycemia, obesity, dyslipidemia, and risk of heart disease, stroke, and diabetes

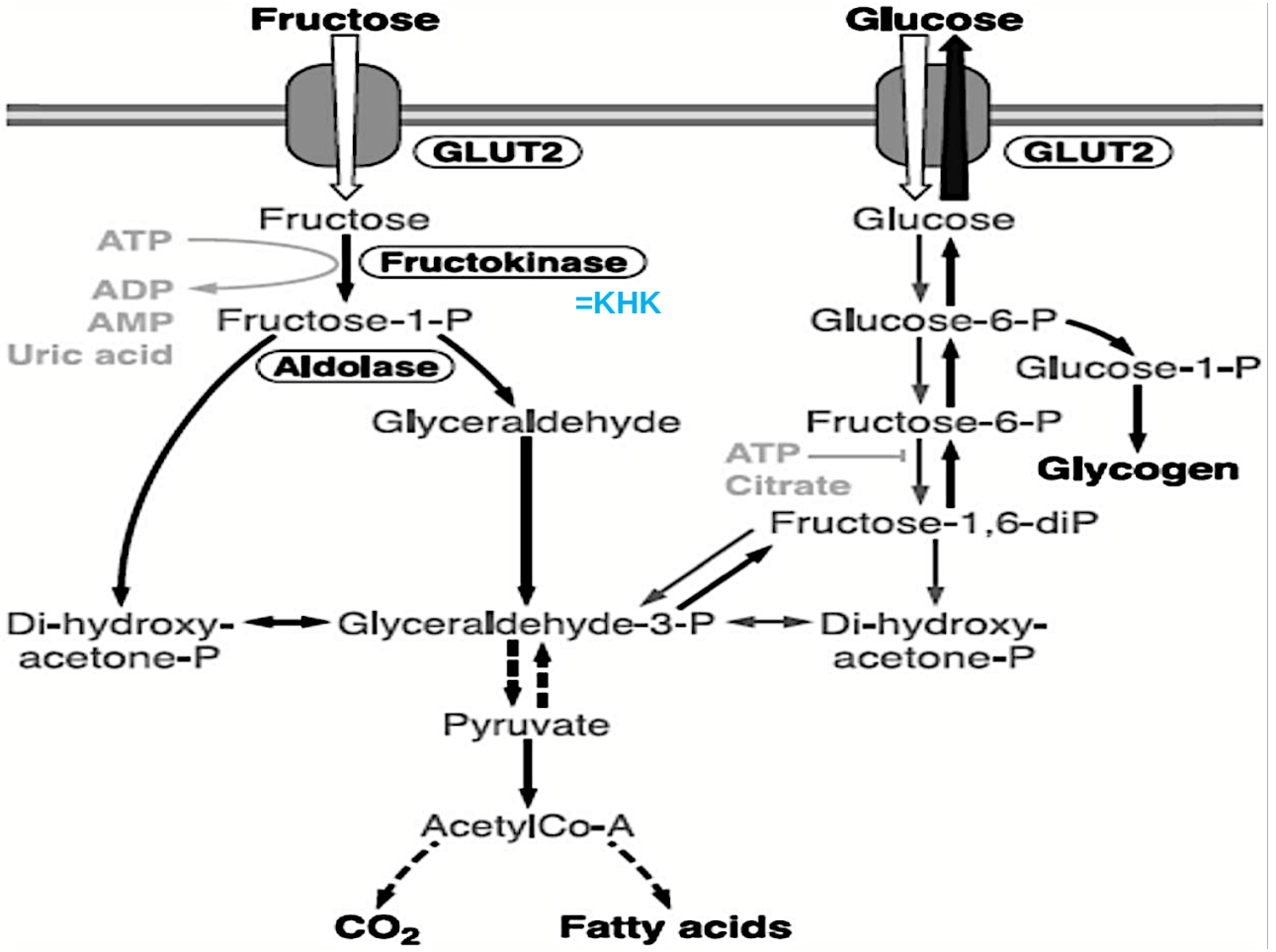


Hannou et al. JCI review, 2018

Ketohexokinase (KHK), a Target for Metabolic Syndrome and Type 2 Diabetes

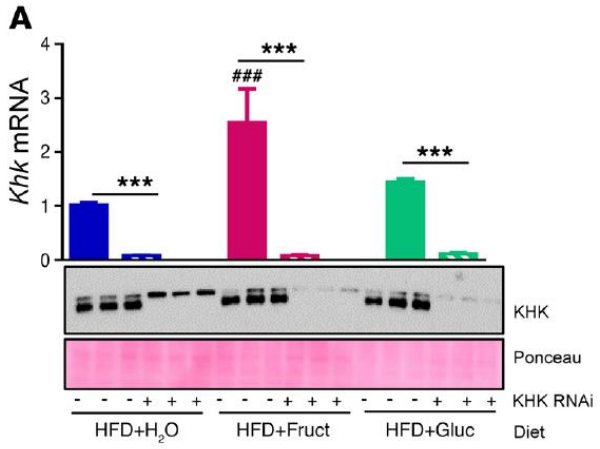
Ketohexokinase (KHK)

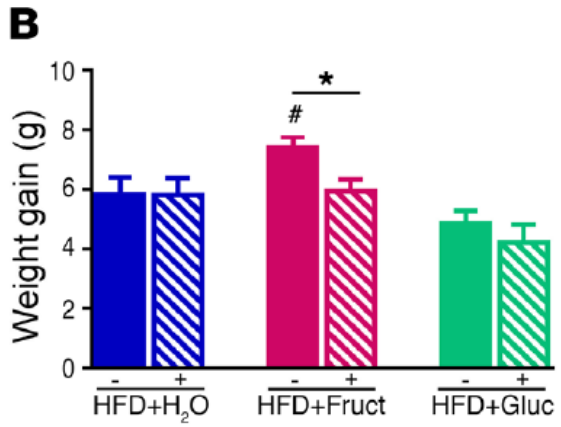
- First enzyme in fructose metabolism pathway
  - Fructose mainly metabolized in liver
  - Implicated in the development of NASH
- KO mice are protected from diet-induced insulin resistance, liver steatosis, and fibrosis
- LOF mutations lead to essential fructosuria associated with increased urinary fructose excretion
  - No clinical manifestations or treatment; suggests chronic KHK knockdown safe

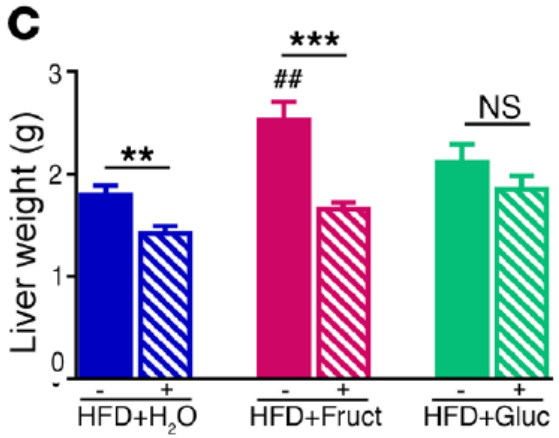


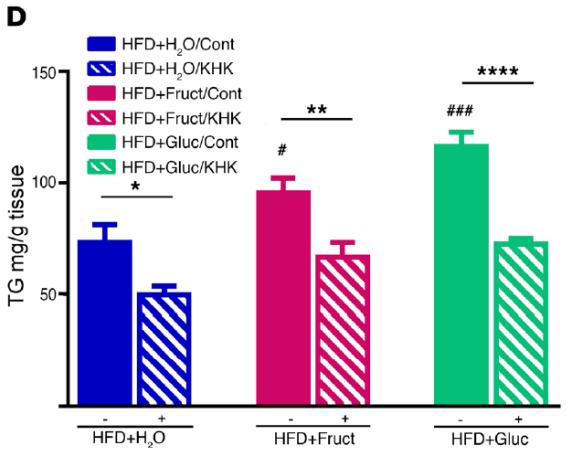
Rippe et al 2013, Adv Nut

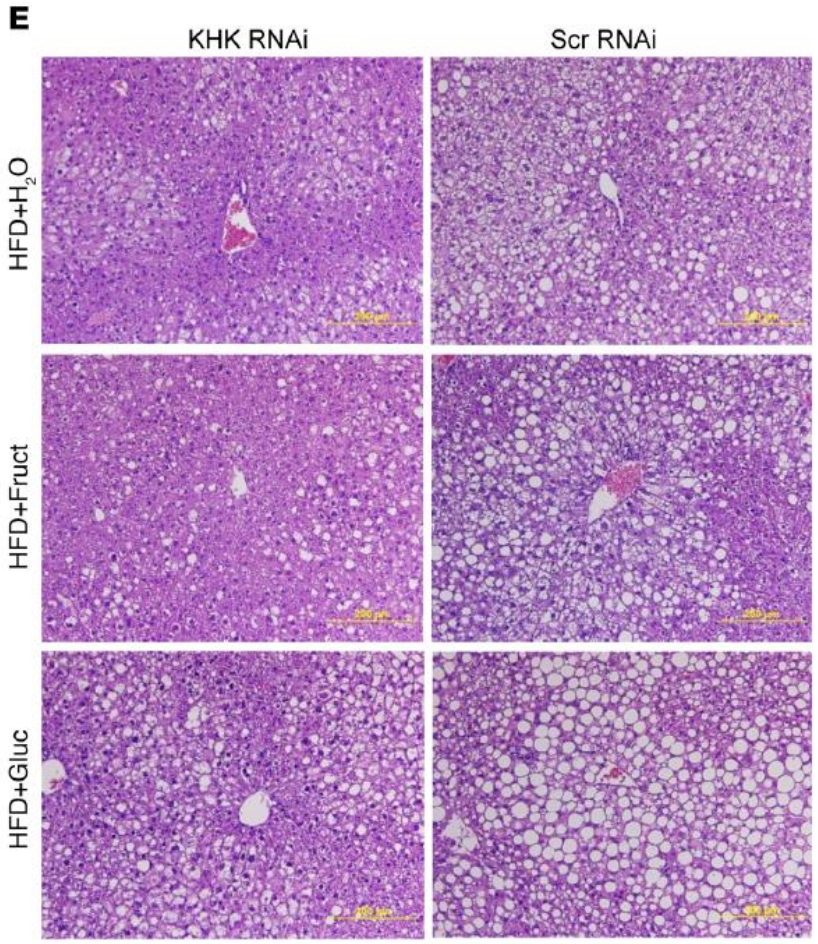
KHK siRNA is Protective in High Fat-High Fructose Diet in Mice











Softic et al. (2017) *J. Clin. Invest.* 127:4059 [Alnylam collaboration]

Potential to Improve Insulin Resistance in T2D with ALN-KHK

- Approximately 25% of T2D patients fail to achieve goal hemoglobin A1C despite lifestyle changes and maximal medical therapy (excluding insulin)
- As a result, there is a medical need for therapies to avoid or delay insulin use and progression of T2D complications
- ALN-KHK is an investigational RNAi therapeutic that may address key unmet needs for T2D patients with inadequate responses to 1st and 2nd-line medical therapy, including:
  - Improvements in insulin resistance, hepatic steatosis
  - Infrequent dosing with tonic control between doses
  - Reduction in progression to insulin use
  - Acceptable safety and tolerability

Development Candidate expected **early 2022**

Additional Opportunities from Liver-Directed Investigational RNAi Therapeutics

Summary

- Multiple attractive programs addressing areas of high unmet need
  - ALN-HBV02 (VIR-2218) for HBV infection
  - Cemdisiran for complement-mediated diseases
  - ALN-HSD and ALN-PNP for NASH
  - ALN-XDH for gout
  - ALN-KHK for metabolic syndrome and type 2 diabetes
- Reliance on genetically validated targets increases probability of success
- Increasing focus on specialty and large market opportunities, enabled by platform safety profile and potential for tonic control of target genes with infrequent dosing

Agenda

Welcome

- Joshua Brodsky – Senior Director, Investor Relations & Corporate Communications

Introduction

- Eric Green – Senior Vice President, Development Programs

Clinical and Pre-clinical Liver-Directed Programs

- Tanya Fischer, M.D., Ph.D. – Vice President, Clinical Development
- Josh Friedman, M.D., Ph.D. – Senior Director, Clinical Research

Q&A Session

Upcoming RNAi Roundtables

CNS & Extrahepatic RNAi Pipeline Programs

- Friday, October 1, 1:30 pm ET

Additional details will be provided on the Capella section of the Company's website,
www.alnylam.com/capella

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