Alnylam R&D Day 2020

Day 2

December 16, 2020

Alnylam PHARMACEUTICALS

Agenda

Timing	Topic	Speaker
9:00 – 9:05 a.m. ET	**Welcome**	Christine Lindenboom *SVP, Investor Relations and Corporate Communications*
9:05 – 9:45	**Succeeding in NASH with Genetically Validated Targets**	Arun Sanyal, MBBS, M.D. *Virginia Commonwealth University* Joshua Friedman, M.D., Ph.D. *Senior Director, Clinical Research*
9:45 – 10:00	**Realizing Additional Opportunities from Liver-Directed RNAi Therapeutics**	Pushkal Garg, M.D. *Chief Medical Officer*
10:00 – 10:20	**Beyond the Liver with RNAi Therapeutics**	Kevin Fitzgerald, Ph.D. *Chief Scientific Officer*
10:20 – 10:30	**Transitioning to a Self-Sustainable Financial Profile**	Jeff Poulton *Chief Financial Officer*
10:30 – 11:00	**Q&A**	All

Reminders

- Event scheduled to end ~11:00 a.m. ET.
- Moderated Q&A session at the conclusion of the presentations.
- To submit a question, type your question in the ‘Ask a Question’ field.
- Replay will be available on Investors page of our website later today.

Forward Looking Statements, Non-GAAP Financial Measures & Other Notices

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. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates, including patisiran, vutrisiran, cemdisiran, ALN-AGT, ALN-HSD, ALN-APP, ALN-AAT02, ALN-HBV02,–ALN-COV, ALN-XDH and ALN-KHK; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates and our marketed products, including ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO™ (lumasiran), inclisiran and vutrisiran; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner's ability to obtain regulatory approval for our product candidates, including inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO, GIVLAARI and OXLUMO; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO, GIVLAARI and OXLUMO, and achieve net product revenues for ONPATTRO within our further revised expected range during 2020; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses within the reduced ranges of guidance provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products such as ALN-APP, and Vir for the development of ALN-HBV02 and ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance 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. Today's discussions and presentations are for the investor community only, and are not intended to promote any Alnylam products or product candidates or to influence any prescription, recommendation or use of Alnylam products. All trademarks in today's presentations are the property of their respective owners.

This presentation references non-GAAP financial measures. These measures are not in accordance with, or an alternative to, GAAP, and may be different from non-GAAP financial measures used by other companies. The items included in GAAP presentations but excluded for purposes of determining non-GAAP financial measures for the periods referenced herein are stock-based compensation expenses, unrealized gain on marketable equity securities, costs associated with our strategic financing collaboration, loss on contractual settlement and change in estimate of contingent liabilities. The Company has excluded the impact of stock-based compensation expense, which may fluctuate from period to period based on factors including the variability associated with performance-based grants for stock options and restricted stock units and changes in the Company's stock price, which impacts the fair value of these awards. The Company has excluded the impact of the unrealized gain on marketable equity securities, costs associated with our strategic financing collaboration, loss on contractual settlement and change in estimate of contingent liabilities because the Company believes these items are non-recurring transactions outside the ordinary course of the Company's business.

Acknowledgments and Disclosures

All speakers are employees of Alnylam Pharmaceuticals except for Dr. Akshay Desai, Professor Philip Hawkins and Dr. Arun Sanyal, who are paid consultants to Alnylam. Alnylam Pharmaceuticals and the speakers at this event wish to thank patients, families, caregivers and dedicated researchers at their affiliated as well as other entities for their contributions to the findings presented.

VOICES OF **PATIENTS & CAREGIVERS**

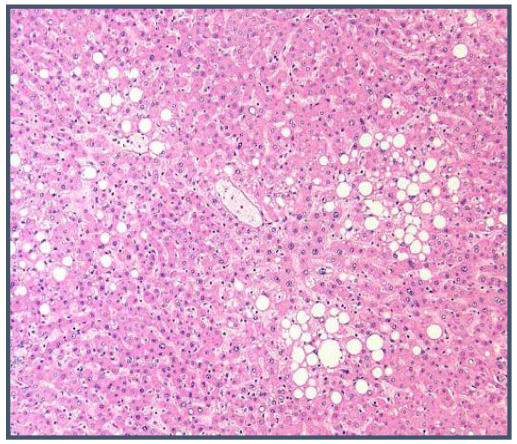
“You’re not able to function. You can’t really work. You can’t do anything. You just want to die. It is that bad.”

Ania, living with AHP

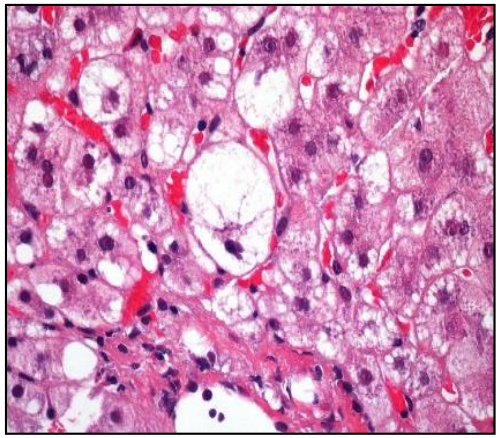
Alnylam® PHARMACEUTICALS

TRANSLATING DISEASE PATHOGENESIS IN TO THERAPEUTICS FOR NASH

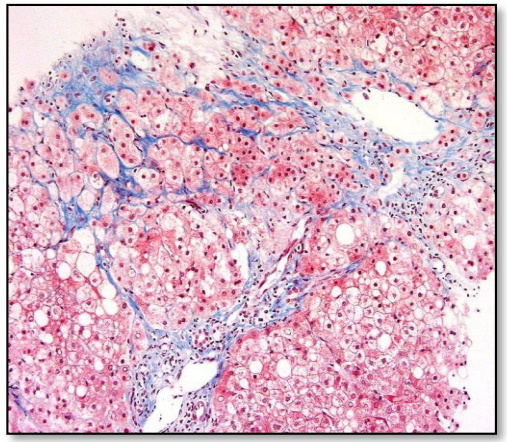
NAFL



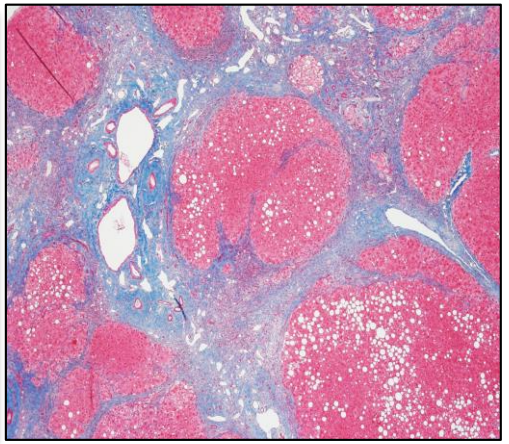
NASH



NASH with fibrosis



NASH Cirrhosis



Arun J. Sanyal MBBS, MD

Z Reno Vlahcevic Professor of Medicine

Virginia Commonwealth University School of Medicine

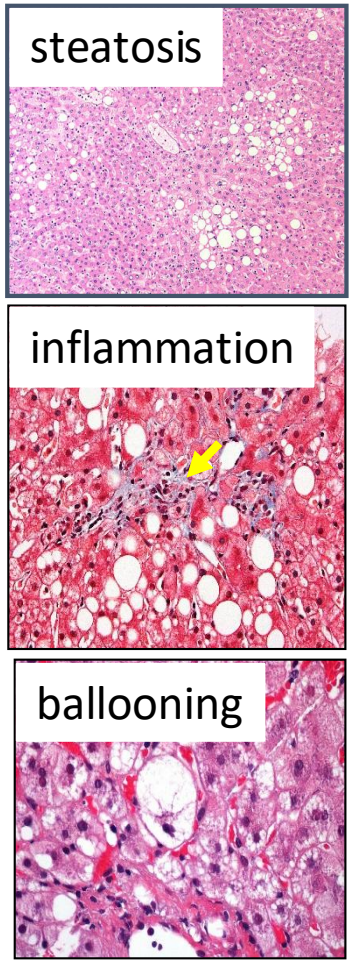
Richmond, VA

Nonalcoholic steatohepatitis (NASH)

nonalcoholic

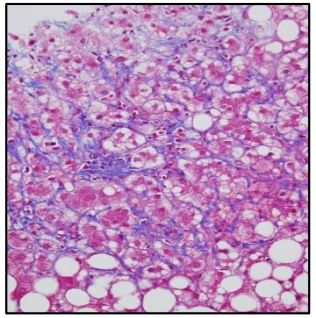
+

Steatohepatitis



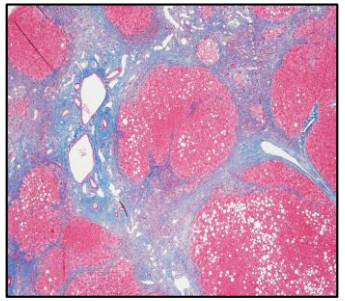
Disease activity

Pericellular fibrosis



stage

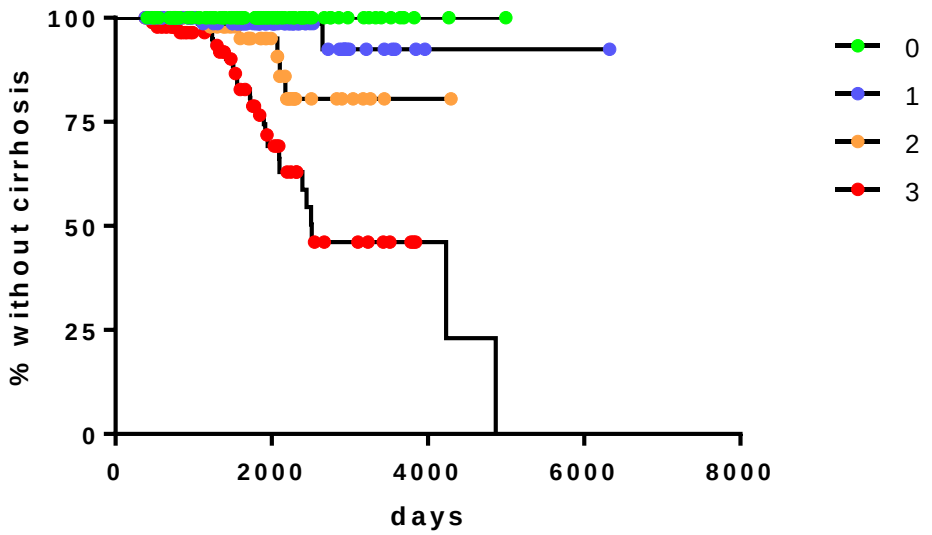
cirrhosis



outcomes

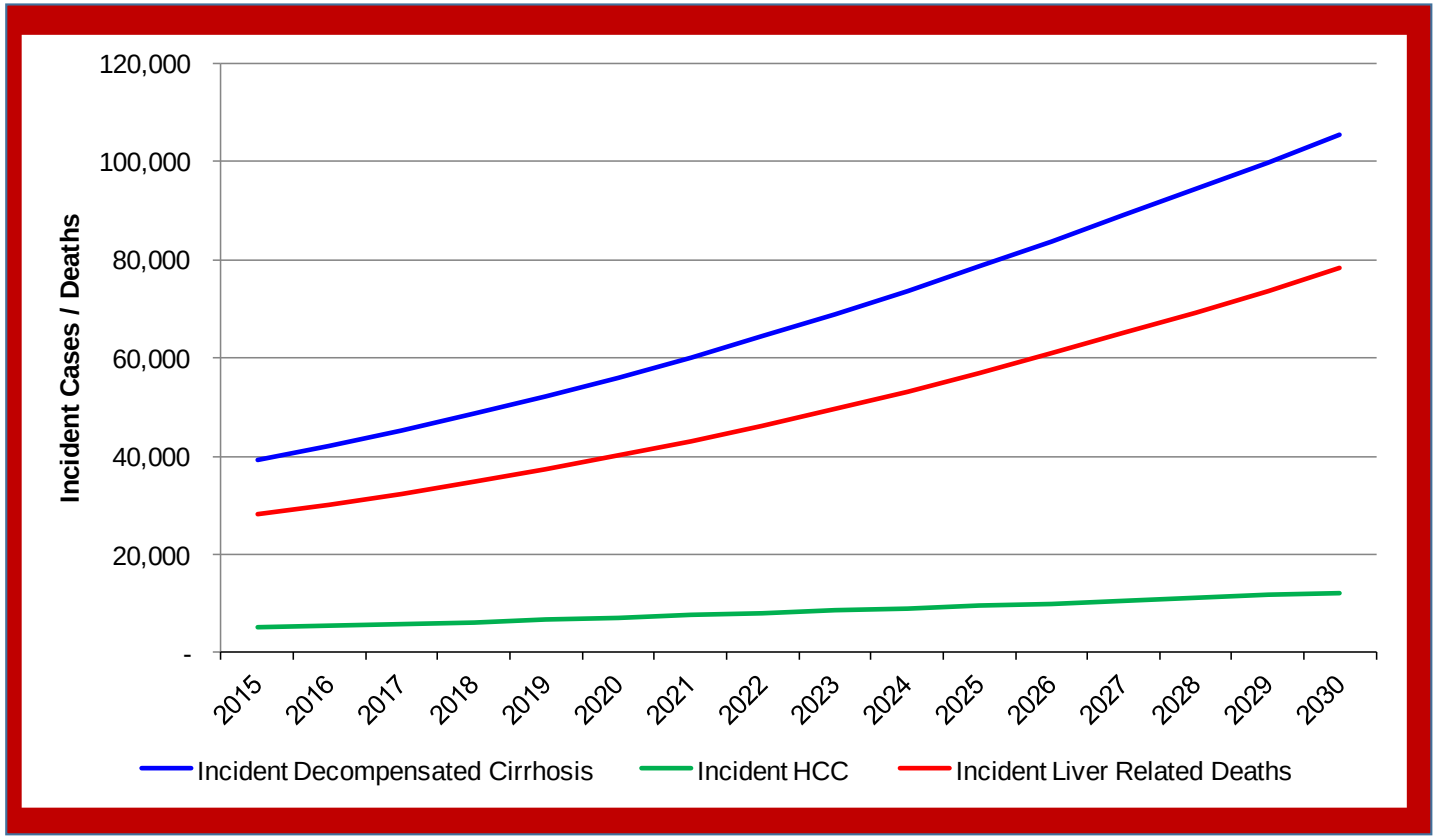
There is an urgent unmet need for effective therapeutics for NASH

Progression to cirrhosis



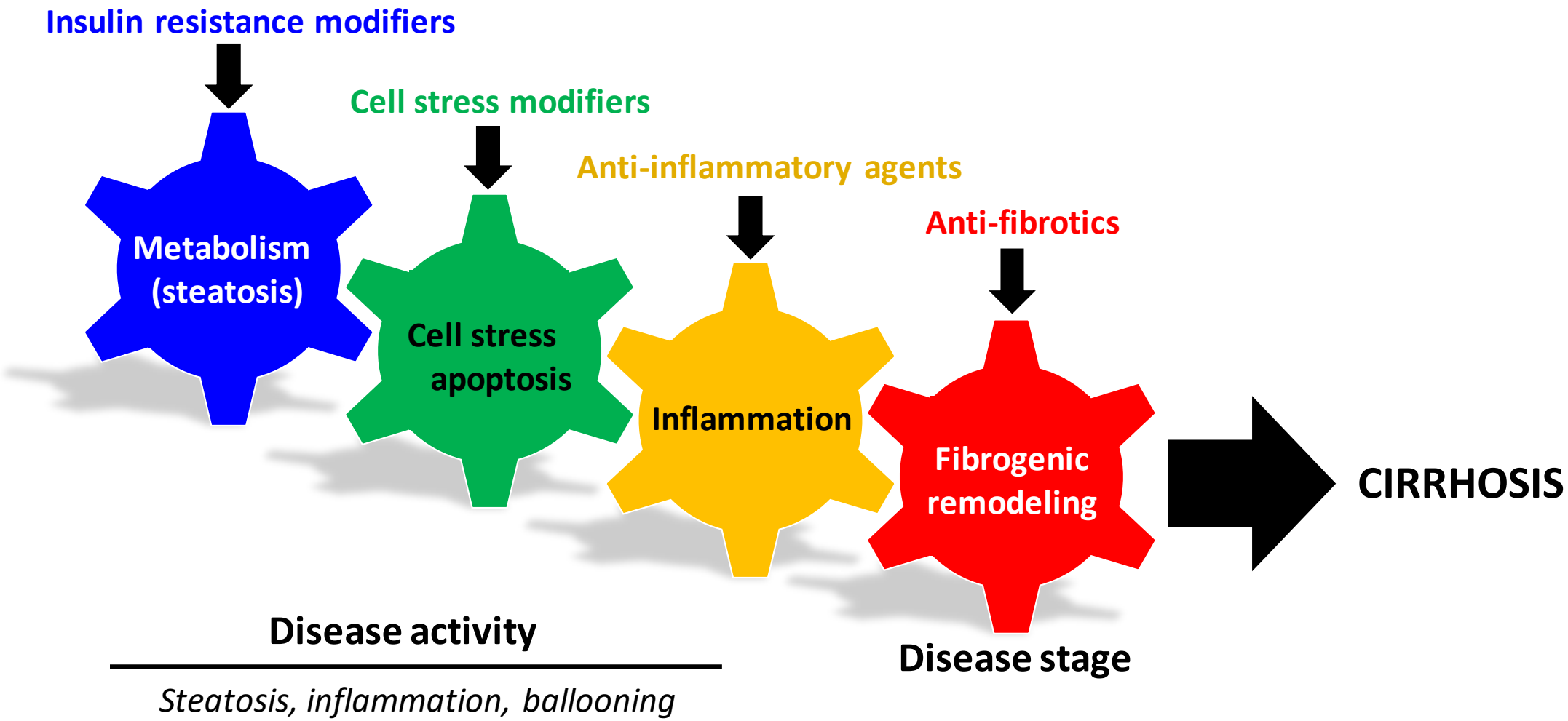
Kleiner et al, JAMA Netw Open. 2019 Oct; 2(10): e1912565.

Burden of outcomes

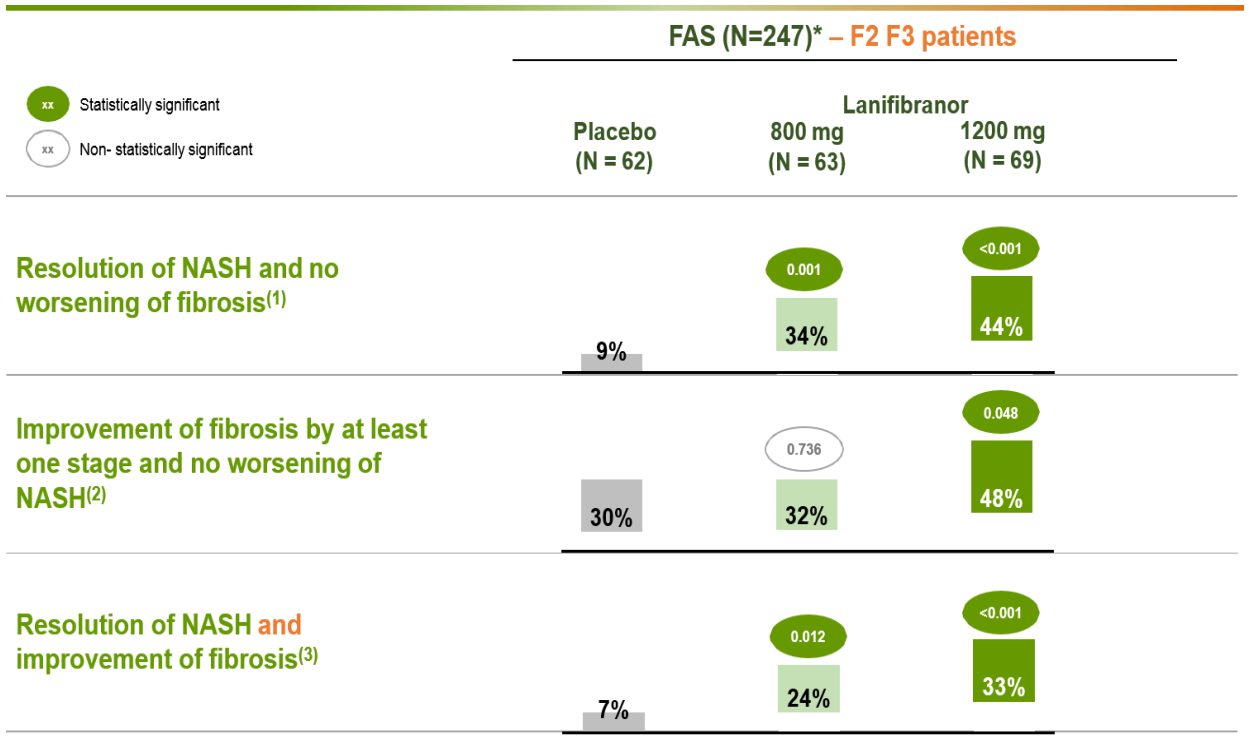


Estes et al, 2018 Jan;67(1):123-133. doi: 10.1002/hep.29466. Epub 2017 Dec 1.

Disease biology provides targets for therapeutics



Lanifibranor- benefit vs risk

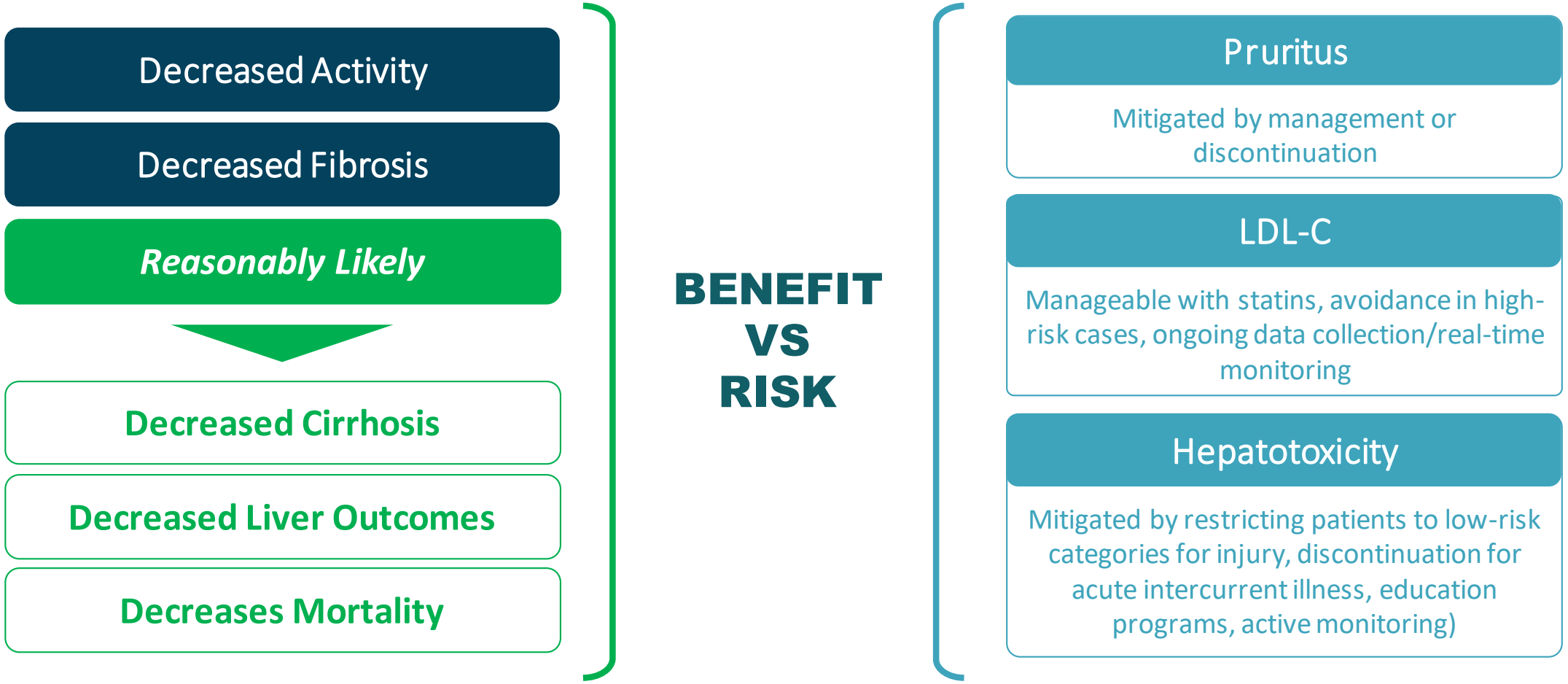


- Increase HDL-C
- No change LDL-C
- Decrease TG
- Decrease HBA1C

- Diarrhea 12%
- Edema 8.4%
- Weight gain 8.4%

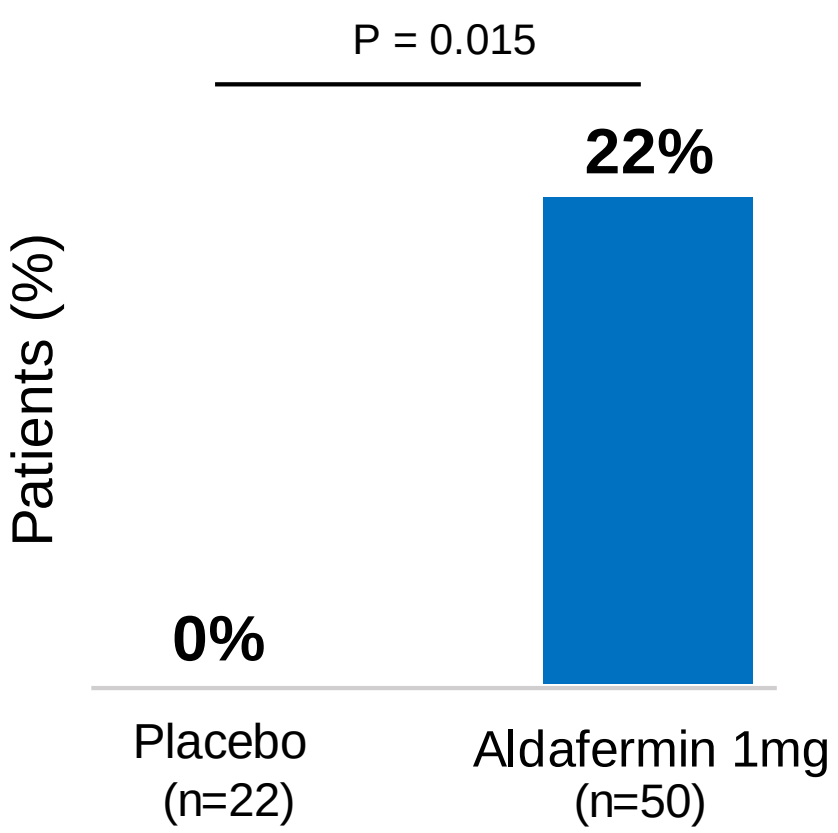
Franque et al, AASLD plenary session 2020

OCA- Benefits vs risk



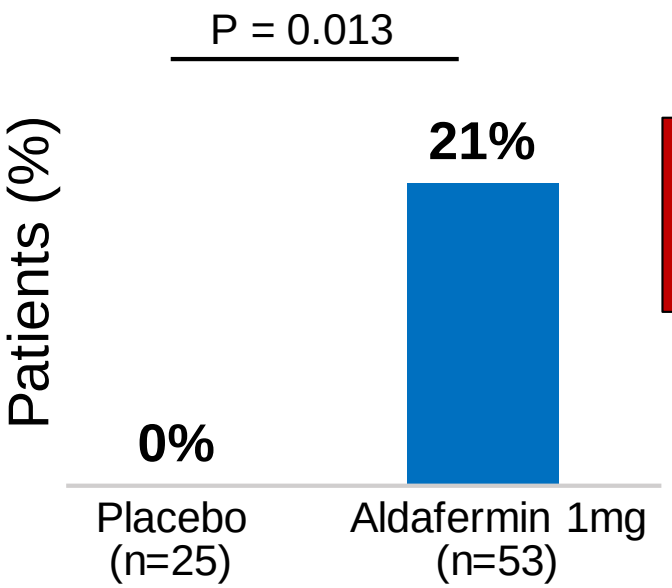
Aldafermin-Cohort 4: Benefits and risks

Both Fibrosis Improvement ≥ 1 stage AND Resolution of NASH[1] at Week 24

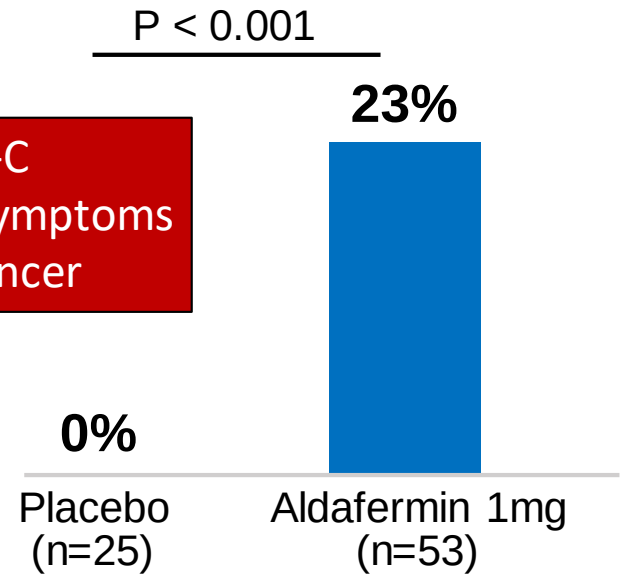


Sensitivity analysis

Patients who did not have end-of-treatment biopsies were imputed as non-responders (intention-to-treat principle)



Multiple imputation with missing-at-random assumption

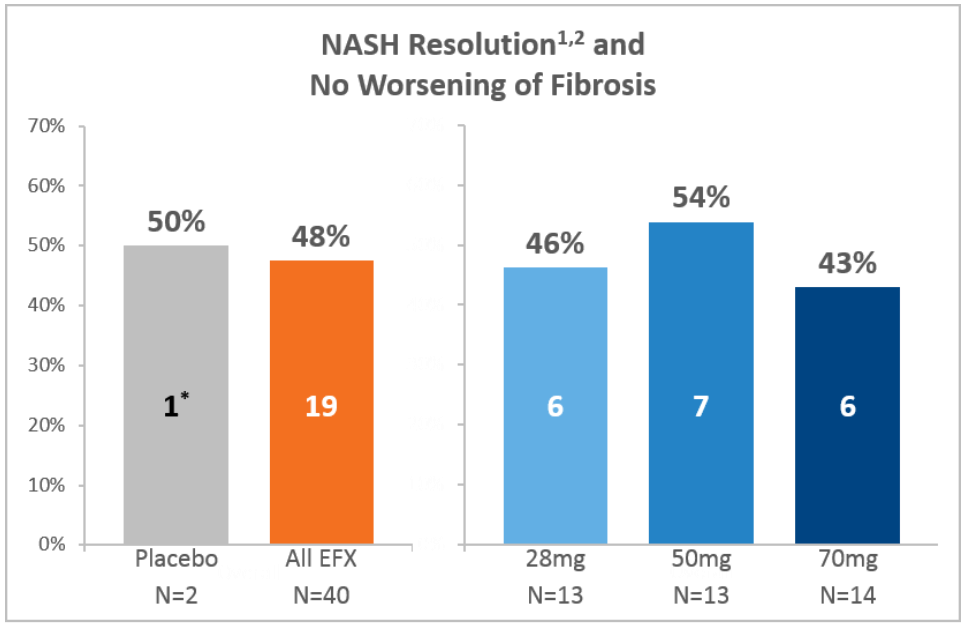


- LDL-C
- GI symptoms
- ? cancer

[1] Defined as patients who have an improvement in liver fibrosis by ≥1 stage AND have a NAS score of 0 or 1 for inflammation and 0 for ballooning at W24 (not powered for statistical significance);

Harrison et al, AASLD 20207

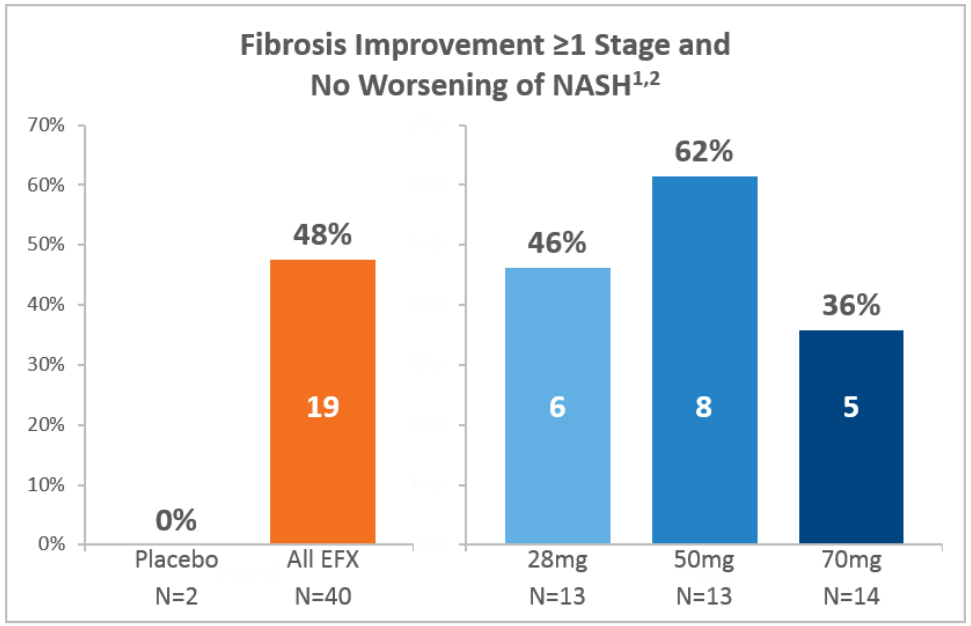
FGF21-Efruxifermin data



[1] NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning
[2] Secondary and exploratory histological endpoints were not powered for statistical significance
* A single placebo responder lost 25 pounds over 16 weeks (11% weight reduction)

Improved:
- HBA1C
- HDL-C
- TG

Worsened:
- Diarrhea (upto 50%)
- Abdominal pain (25%)



[1] Improvement in liver fibrosis greater than or equal to one stage and no worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis)
[2] Secondary and exploratory histological endpoints were not powered for statistical significance

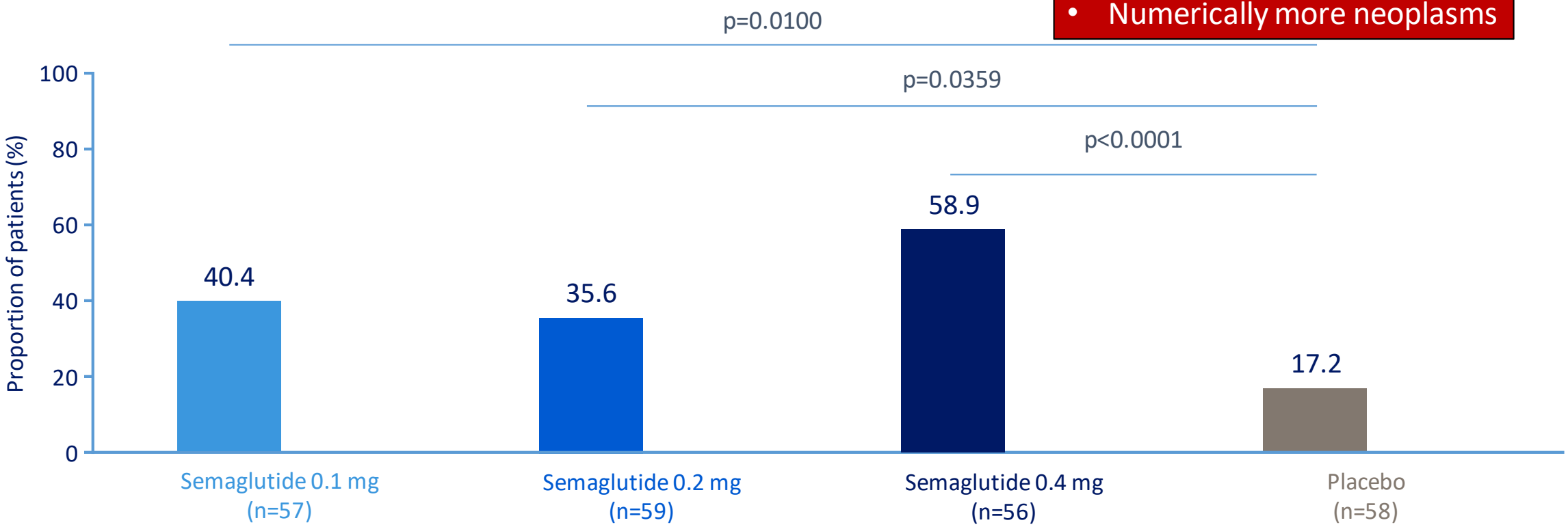
Harrison et al, AASLD 2020

Semaglutide- Resolution of steatohepatitis and no worsening in liver fibrosis

- Improved HDL-C
- Improved TAG
- Weight loss

- Numerically more neoplasms

Patients with fibrosis stage 2 or 3 at baseline

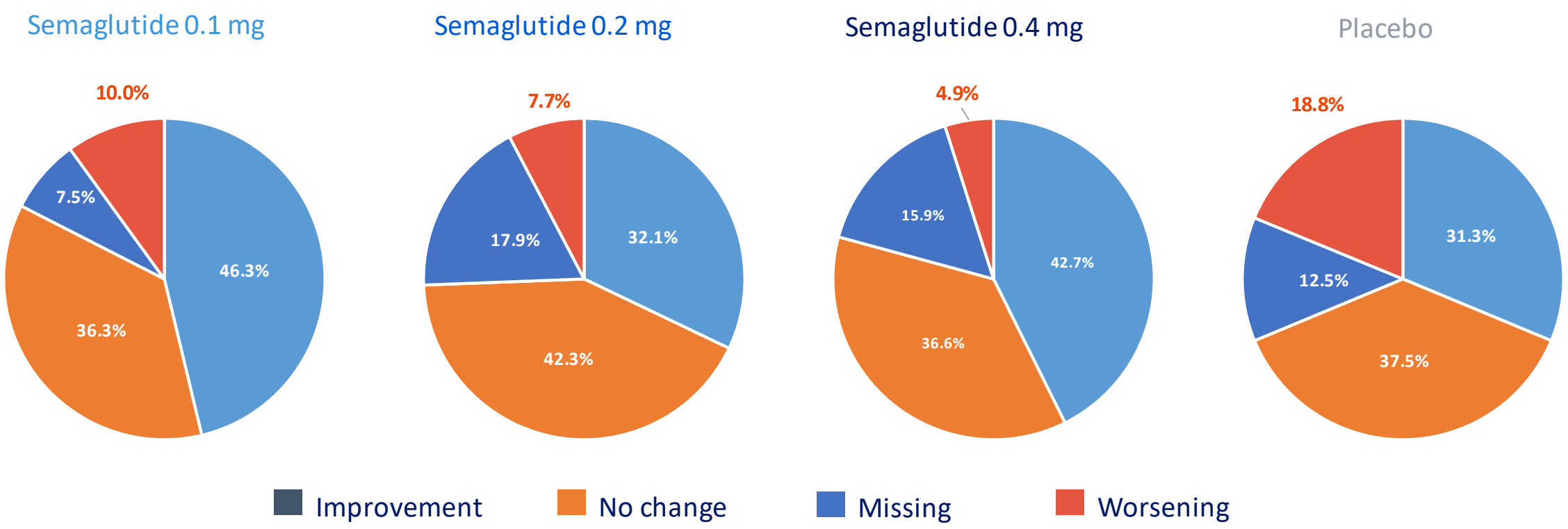


Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

Newsome et al, AASLD 2020

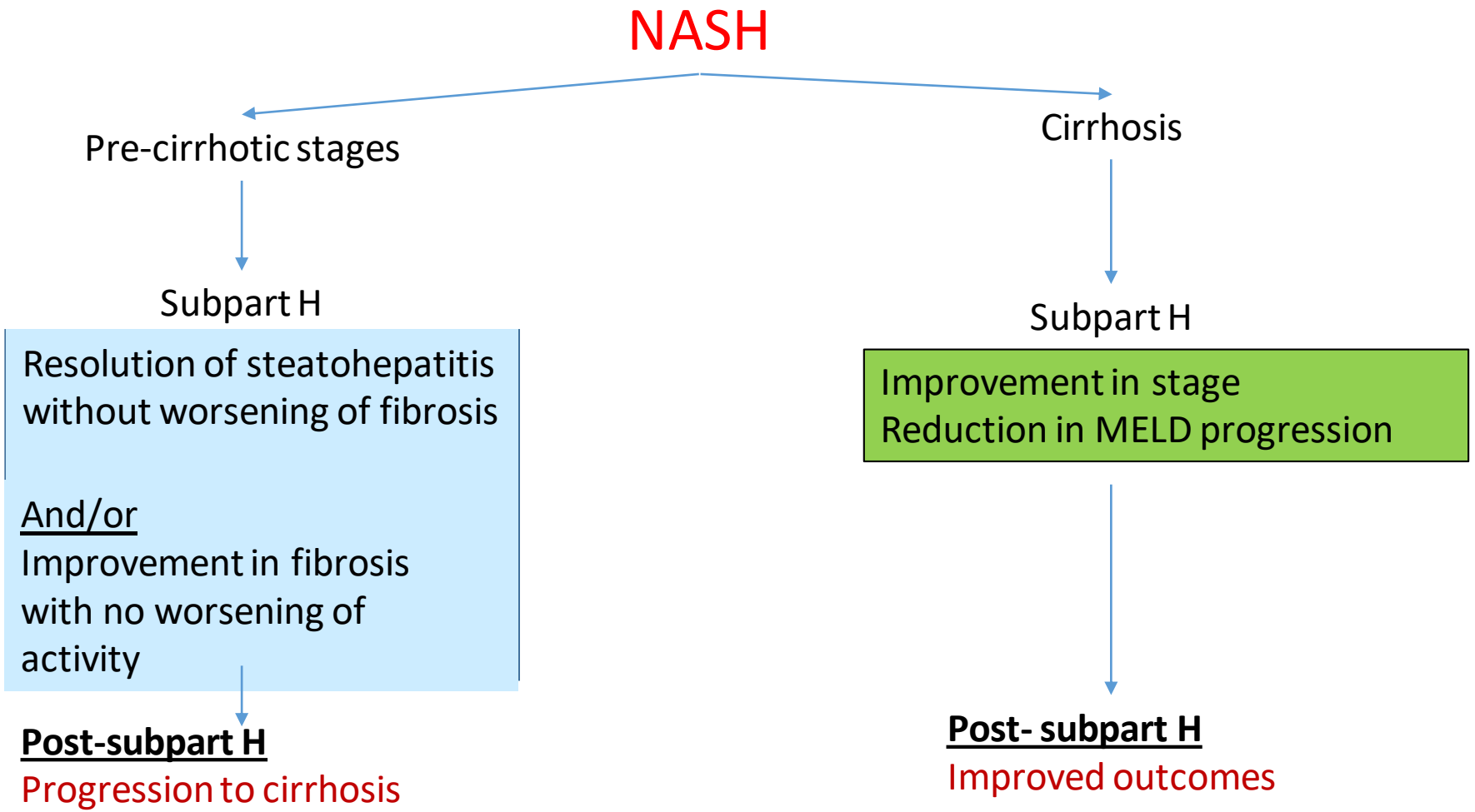
Change in fibrosis stage

All randomized patients



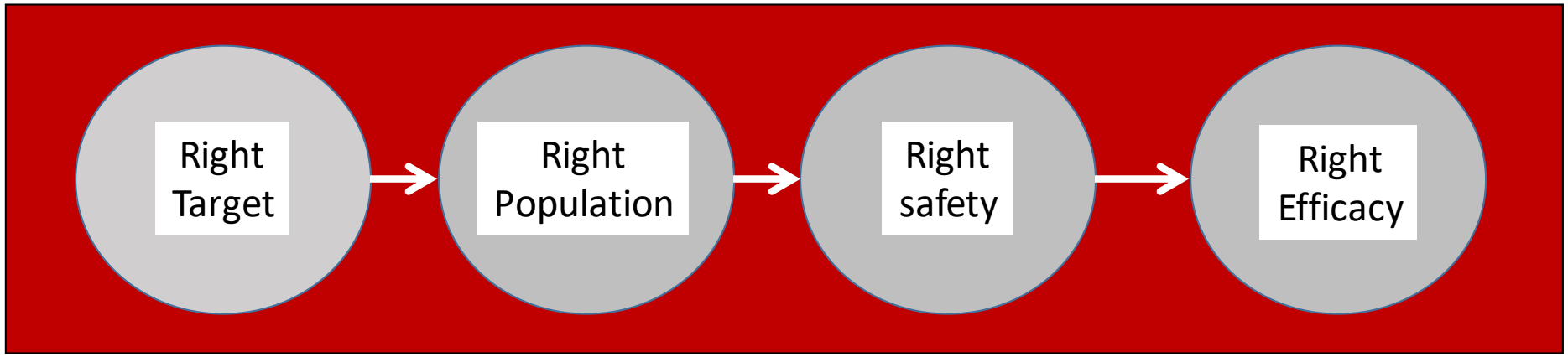
Data based on in-trial period.

The current regulatory path for the approval of therapies for NASH



Sanyal et al, Hepatology 2015; 61(4): 1392–1405
FDA draft guidance 2018

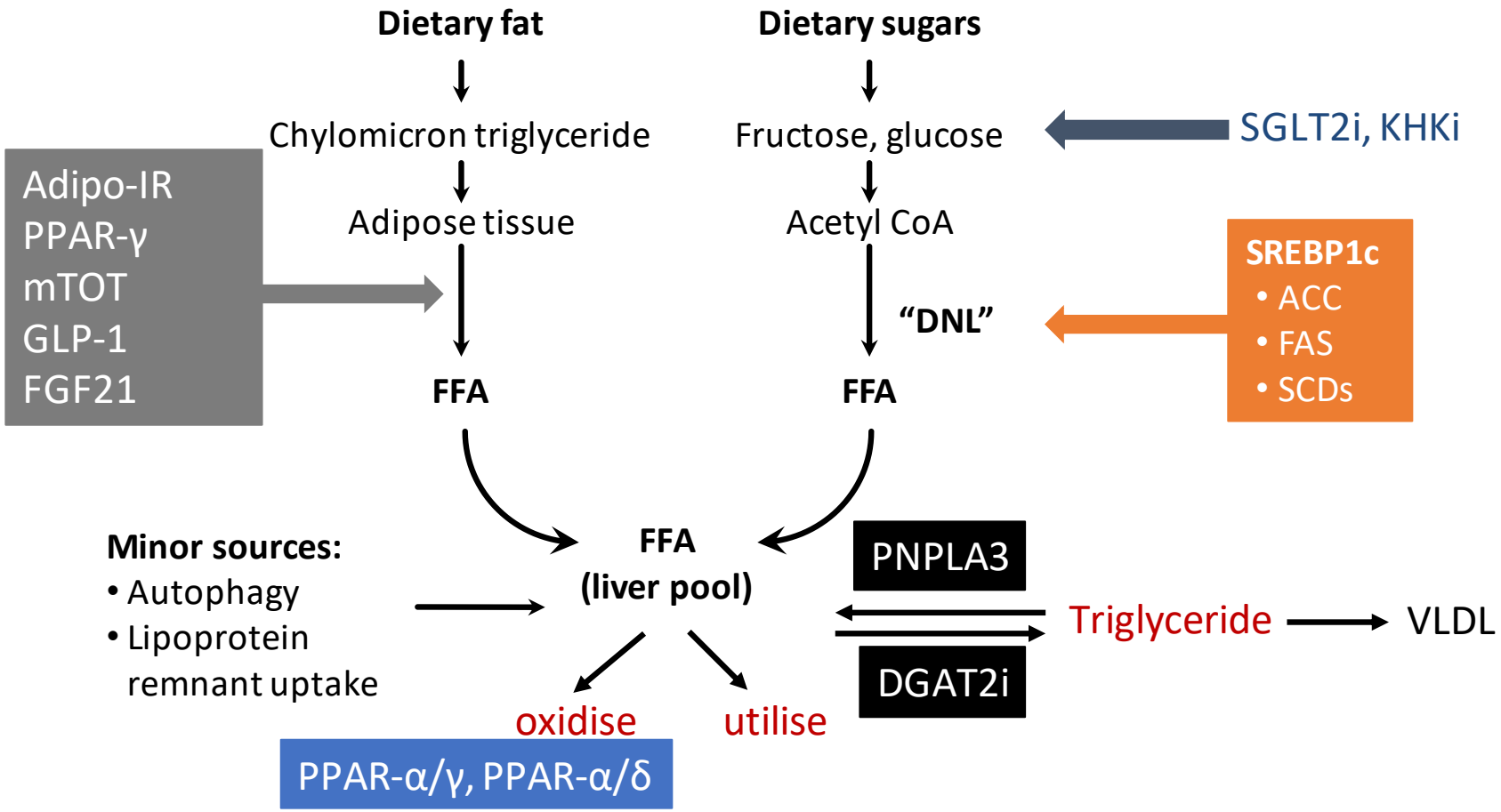
Key takeaways today- successful drug development depends on following core-principles



Common elements of leading programs in NASH:

- Upstream metabolic or pleiotropic targets (FXR-FGF19, TBR, PPAR, FGF21)
- Well designed and properly powered phase 2 programs with robust findings
- Meeting endpoints that are agreed upon by regulatory agencies
- Common weakness: not enough attention to safety (maybe FGF19 is exception)

Metabolic substrate loading promotes energy storage as triglyceride

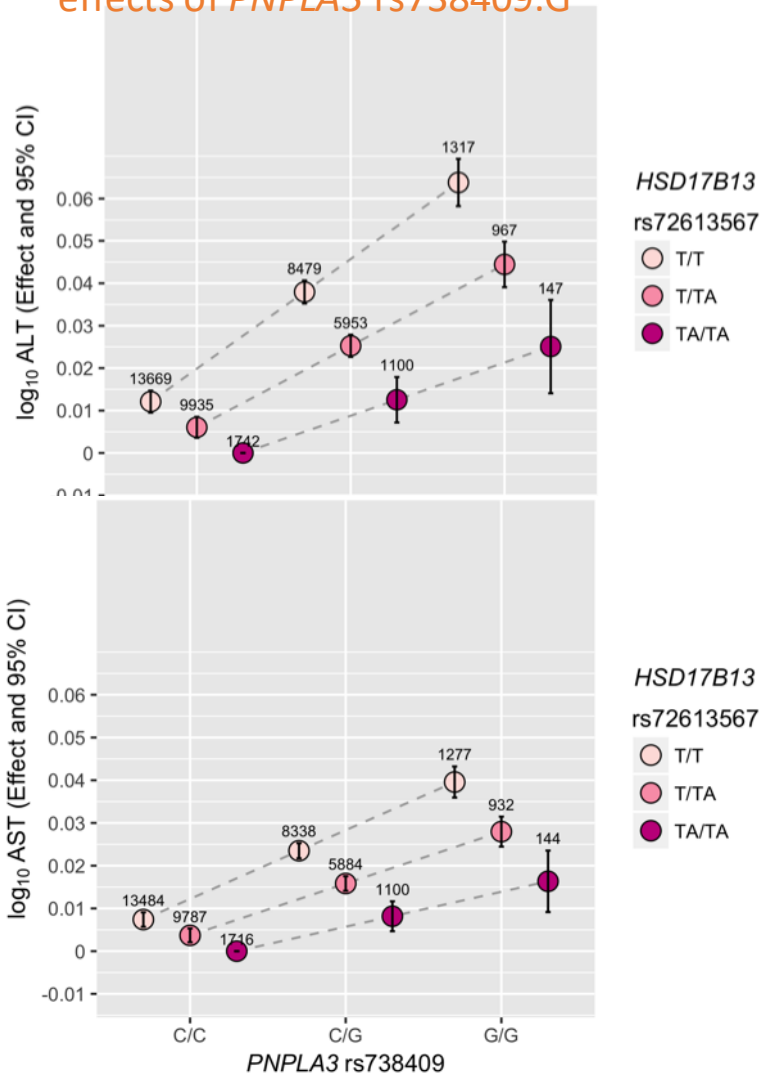


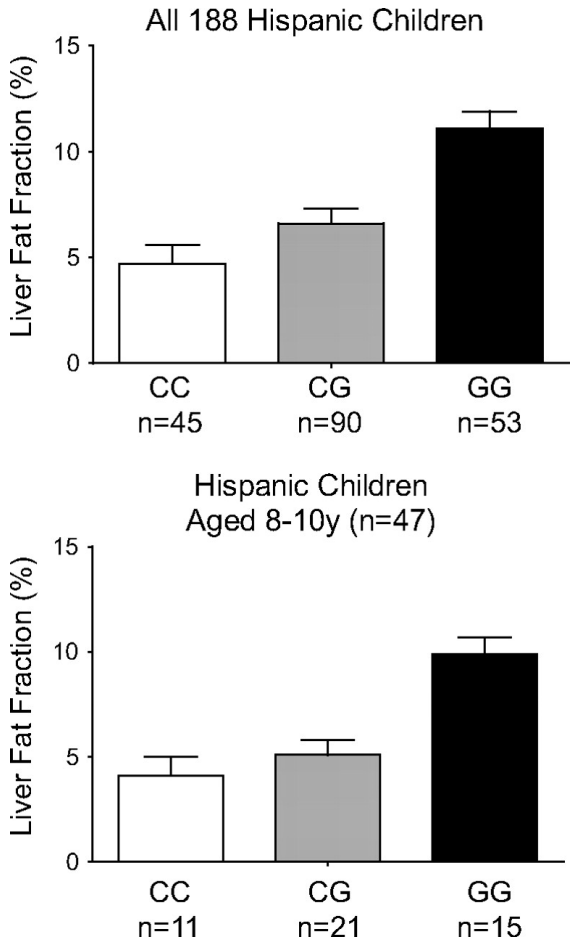
ACC, acetyl-CoA carboxylase alpha; adipo-IR, adipose tissue insulin resistance; DGAT2i, diacylglycerol O-acyltransferase 2 inhibitor; DNL, de novo lipogenesis; FAS, fatty acid synthase; FFA, free fatty acid; FGF21, fibroblast growth factor 21; GLP-1, glucagon-like peptide-1; KHKi, ketohexokinase inhibitors; mTOT, mitochondrial target of thiazolidinediones; PNPLA3, adiponutrin; PPAR, peroxisome proliferator-activated receptor; SCD, stearoyl-coA desaturase; SGLT-2i, sodium-glucose cotransporter-2 Inhibitor; SREBP-1c, sterol regulatory element-binding protein 1c; VLDL, very-low-density lipoprotein

Adapted from Brunt et al. *Nat Rev Dis Primers* 2015;1:15080

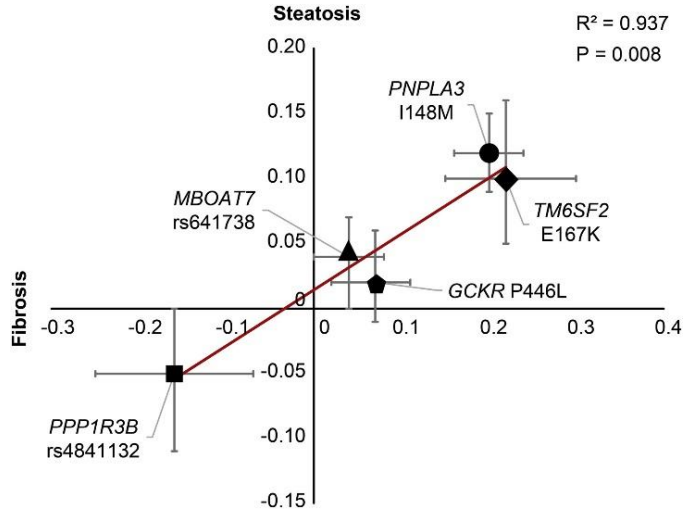
Genetics based targets in NASH

HSD17B13 rs72613567:TA mitigates effects of *PNPLA3* rs738409:G



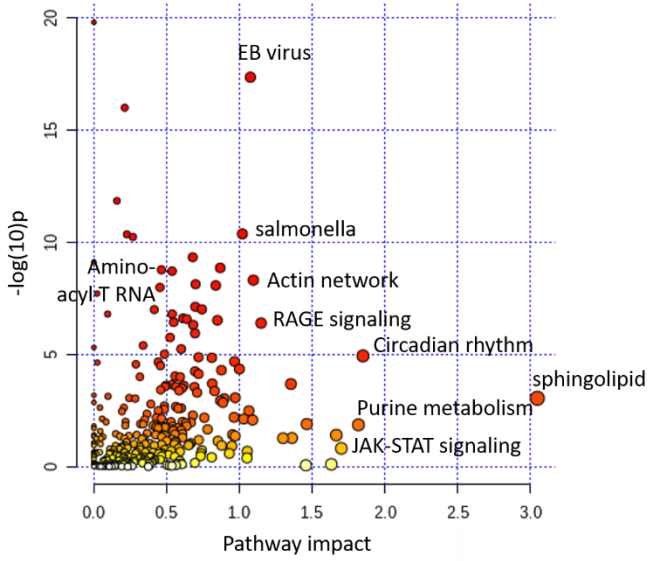


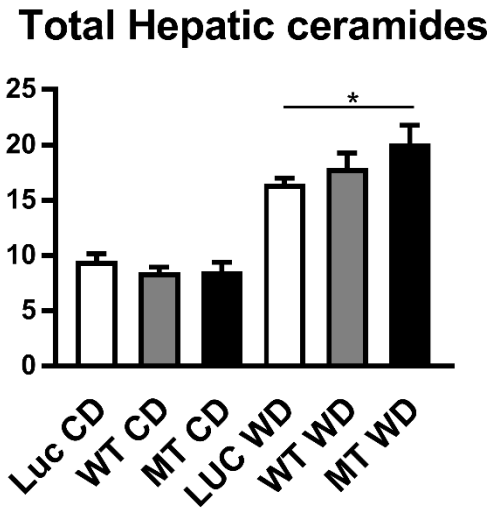
Michael I. Goran et al. Diabetes 2010;59:3127-3130

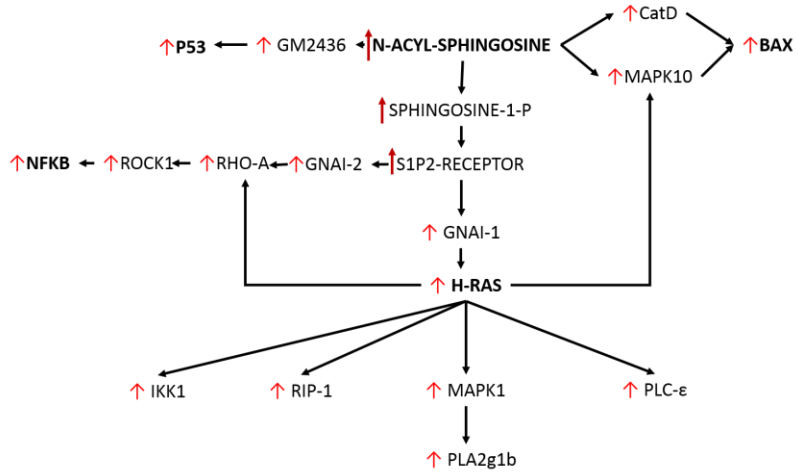


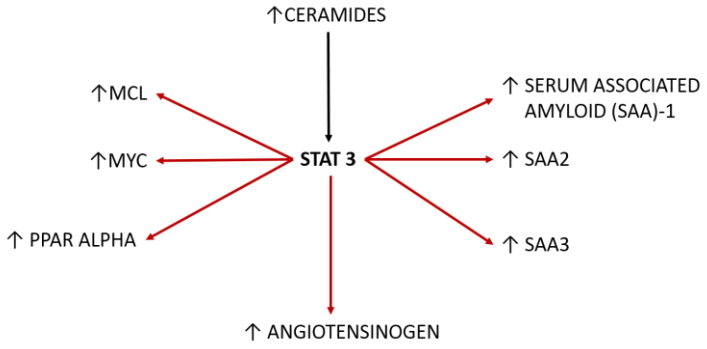
Romeo, Sanyal and Valenti, Cell Metab. 2020 Jan 7;31(1):35-45

Connecting the dots between PNPLA3 and NASH progression and HCC









Banini et al, Hepatology 2020 (epub)

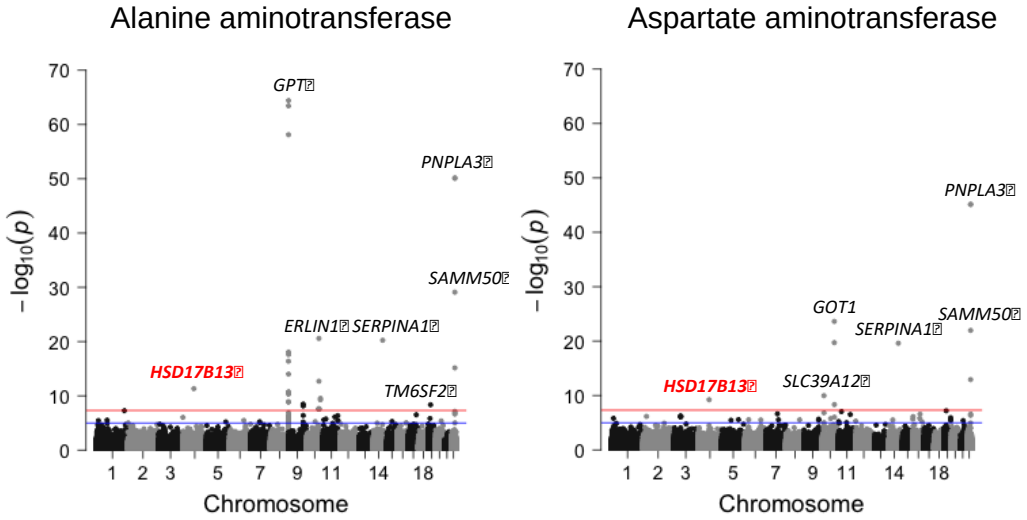
HSD17B13: A Novel Genomics-Driven Drug Target

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

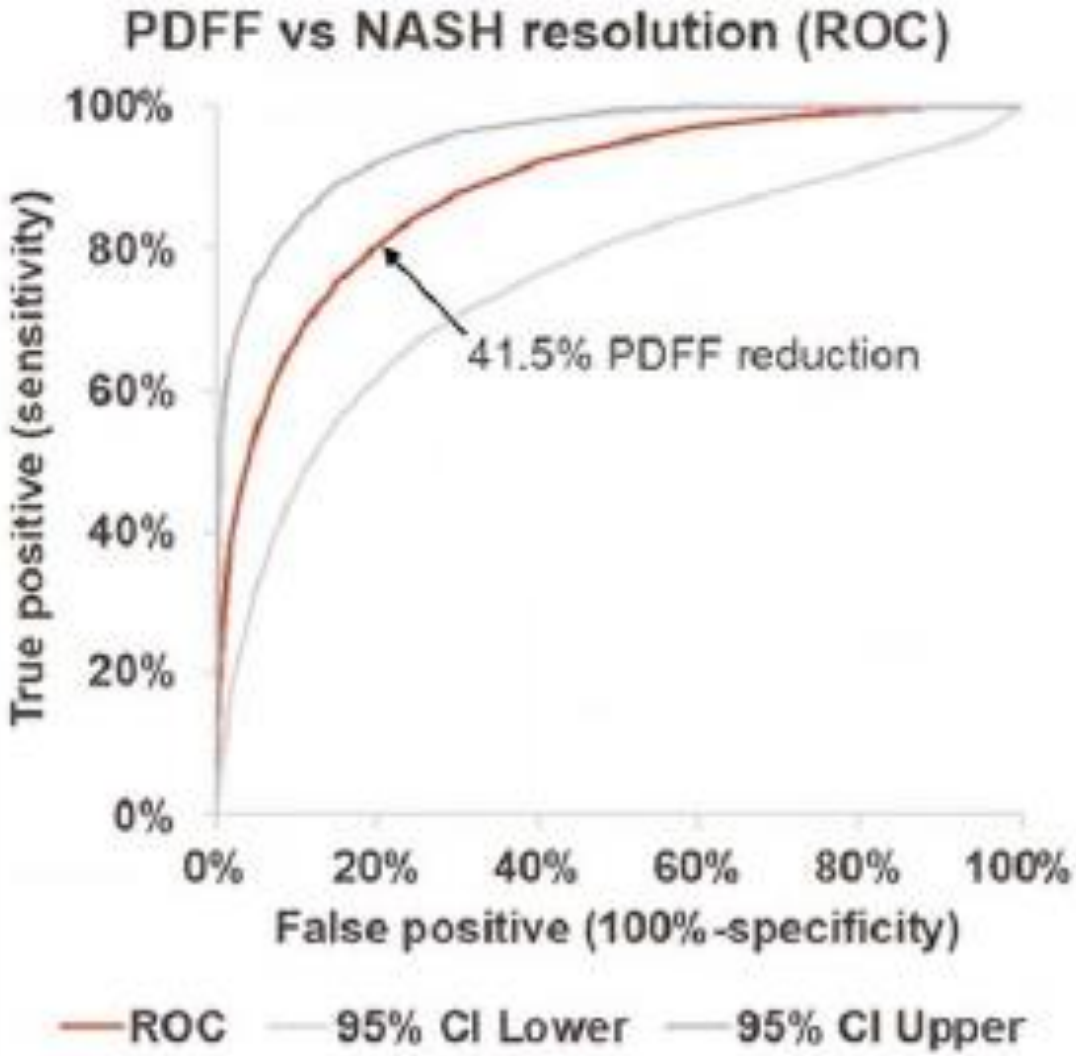
N.S. Abul-Husn, X. Cheng, A.H. Li, Y. Xin, C. Schurmann, P. Stevis, Y. Liu, J. Kozlitina, S. Stender, G.C. Wood, A.N. Stepanchick, M.D. Still, S. McCarthy, C. O'Dushlaine, J.S. Packer, S. Balasubramanian, N. Gosalia, D. Esopi, S.Y. Kim, S. Mukherjee, A.E. Lopez, E.D. Fuller, J. Penn, X. Chu, J.Z. Luo, 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



- *HSD17B13* rs72613567:TA is a common splice variant (AF ~26%).
- The rs72613567:TA variant is associated with:
  - Decreased Liver Transaminases
  - Reduced risk of alcoholic and non-alcoholic liver disease and cirrhosis.
  - Protection from NASH in individuals with fatty liver.

N. S. Abul-Husn *et al. NEJM* 2018; 378(12)

Right efficacy: predicting NASH resolution from MRI-PDFF change



- The **AUROC was 0.89**, the optimal MRI-PDFF reduction with best balance of true positive and false negative rates was 41.5% ($p<0.001$) with a sensitivity of 82% (95% confidence interval (CI) 61%, 93%) and specificity of 83% (95%CI 0.74%, 90%)

- In patients with NASH resolution, the mean week 12 fat reduction (MRI-PDFF) was 56%

Loomba et al, EASL/ILC 2020

Right efficacy: Histological assessment of NASH is not precise

Table 2. Inter-reader reliability regarding endpoints derived from NASH CRN Scores for 339 patients with Paired Biopsies

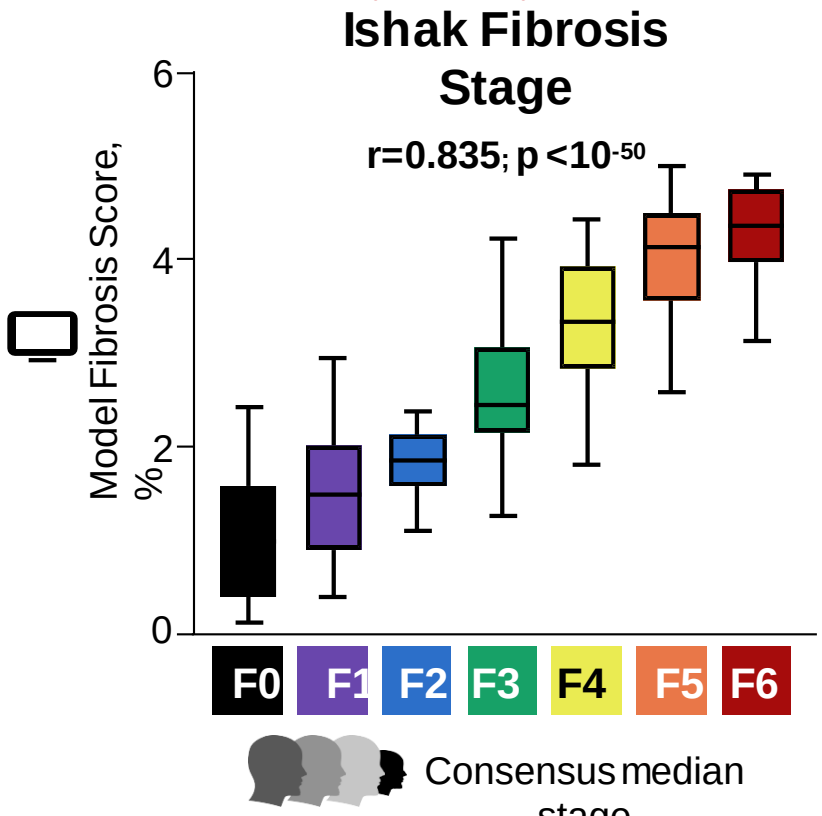
Endpoint	Inter-reader Comparison	% Agreement*	% Agreement Expected by Chance*	Unweighted Kappa (95% CI)
Hepatic histological improvement in NAS	Original v. H1	71.68	54.62	0.376 (0.276, 0.476)
	Original v. H2	74.04	58.93	0.368 (0.264, 0.472)
	H1 v. H2	74.93	57.36	0.412 (0.310, 0.514)
	Average	73.55	57.17	0.382 (0.308, 0.456)
Resolution of NASH with no worsening of fibrosis	Original v. H1	79.65	60.09	0.490 (0.389, 0.590)
	Original v. H2	81.12	69.45	0.382 (0.268, 0.497)
	H1 v. H2	76.99	65.91	0.325 (0.219, 0.432)
	Average	79.25	65.65	0.396 (0.315, 0.477)
Improvement of fibrosis with no worsening of NASH	Original v. H1	76.11	60.70	0.392 (0.286, 0.497)
	Original v. H2	75.81	65.49	0.299 (0.184, 0.413)
	H1 v. H2	78.76	63.94	0.411 (0.301, 0.521)
	Average	76.89	63.53	0.366 (0.289, 0.444)
Resolution of NASH with at least a 2-point improvement in NAS	Original v. H1	80.53	67.11	0.408 (0.293, 0.523)
	Original v. H2	84.66	75.10	0.384 (0.256, 0.513)
	H1 v. H2	79.35	72.65	0.245 (0.125, 0.365)
	Average	81.51	71.87	0.343 (0.256, 0.430)

* Unevaluable score considered as a response category.

Davison et al, J Hepatology, 2020 in press

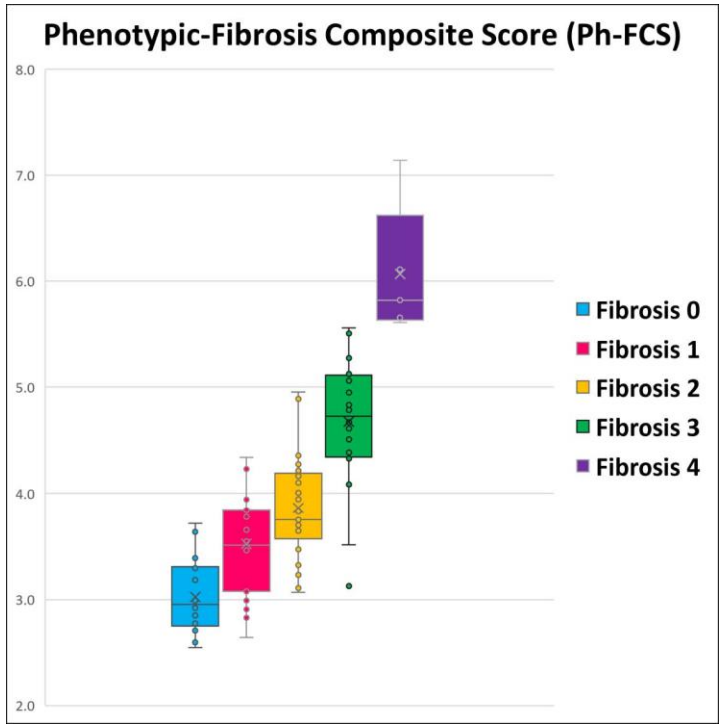
Machine learned systems of reading histology are in evolution

PATH-AI
Improved precision



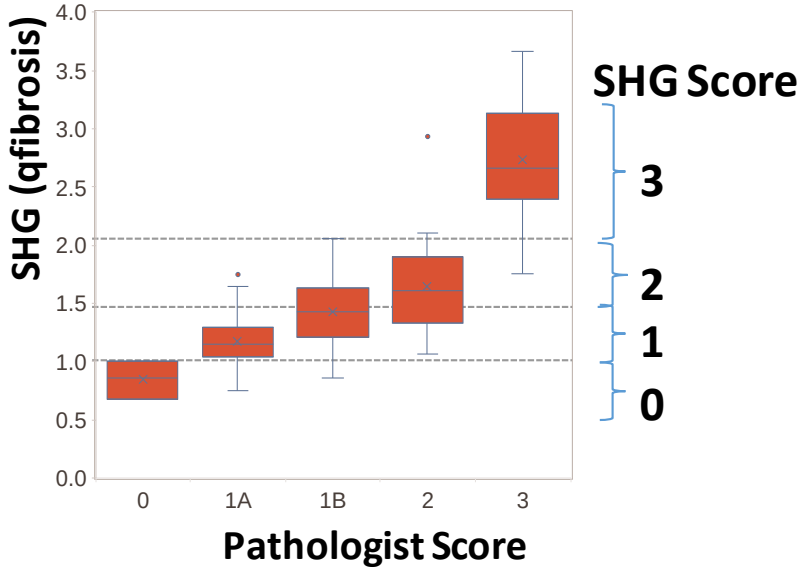
Younossi et al, AASLD 2019

PHARMANEST
Continuous scaling
Dynamic changes



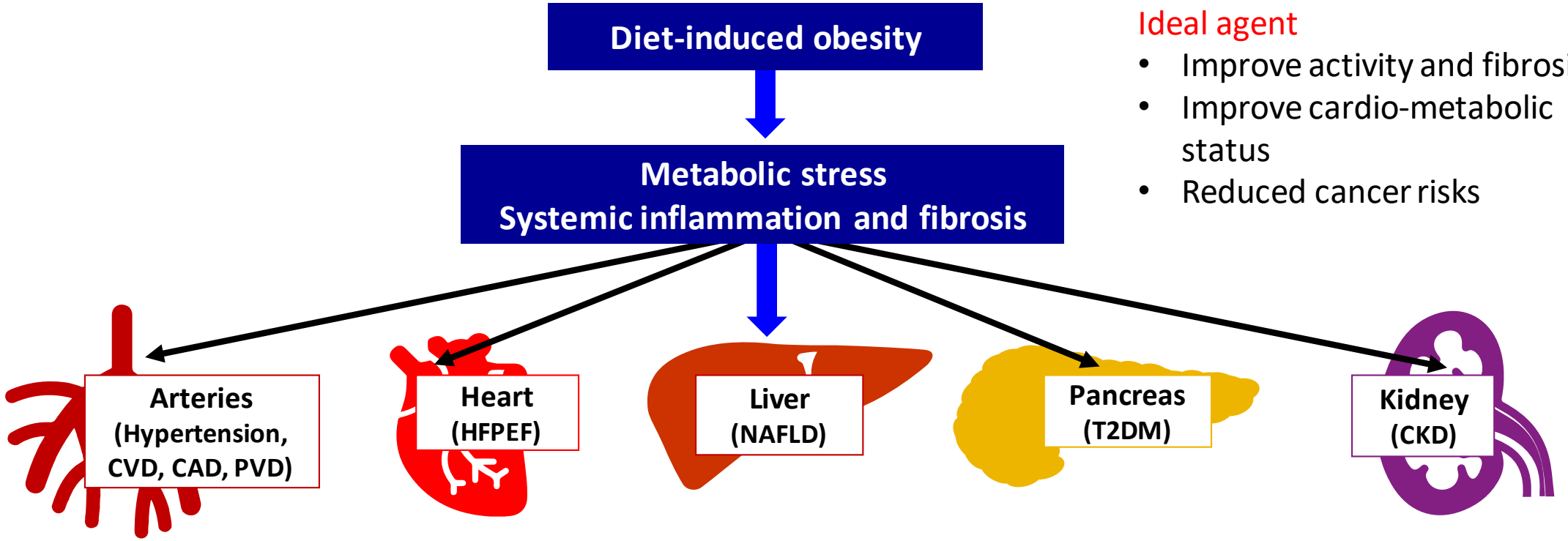
Chen et al, AASLD 2019

HISTOINDEX
Dynamic changes in fibrosis
Continuous scaling



Harrison et al, AASLD 2018

What are we looking for in a NASH therapeutic?



Ideal agent

- Improve activity and fibrosis
- Improve cardio-metabolic status
- Reduced cancer risks

In the end, approval of agents requires a high benefit to risk ratio

CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CVS, cardiovascular system; HFPEF, heart failure with preserved ejection fraction; PVD, peripheral vascular disease; T2DM, type 2 diabetes mellitus.

VOICES OF **PATIENTS & CAREGIVERS**

“I worry about my children surviving and making it to adulthood. I am scared of the unknown and will my children be able to take care of all their needs when they are on their own? Will they have productive, fulfilling lives or will they merely be existing because of the limitations they have because of this disease?”

Caregiver of two pediatric patients diagnosed with PH1

Alnylam® PHARMACEUTICALS

Succeeding in NASH with Genetically Validated Targets

Joshua Friedman, M.D., Ph.D.
Senior Director, Clinical Research

Alnylam PHARMACEUTICALS

Nonalcoholic Fatty Liver Disease (NAFLD)

A Disorder of Over-Nutrition Leading to Accumulation of Hepatic Fat

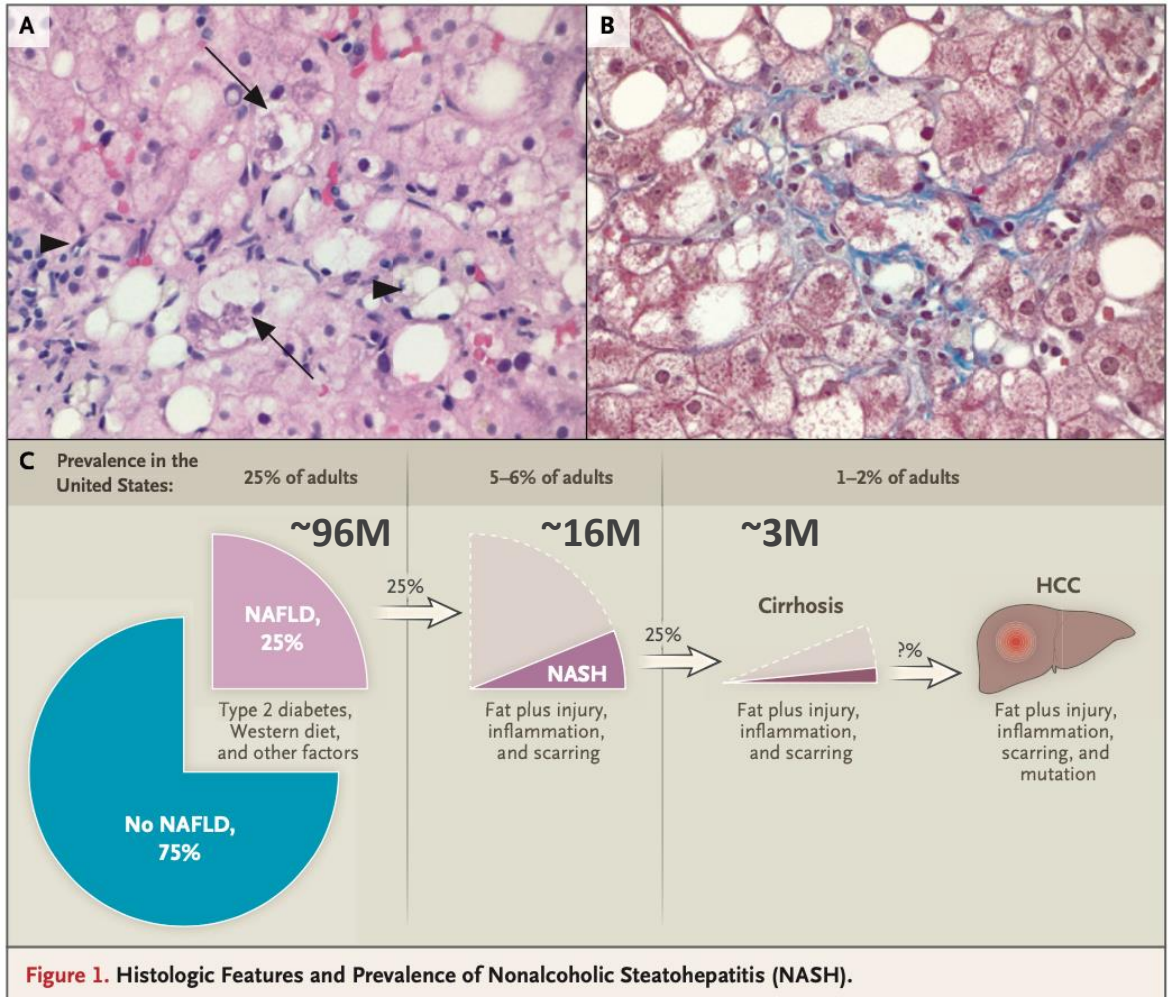


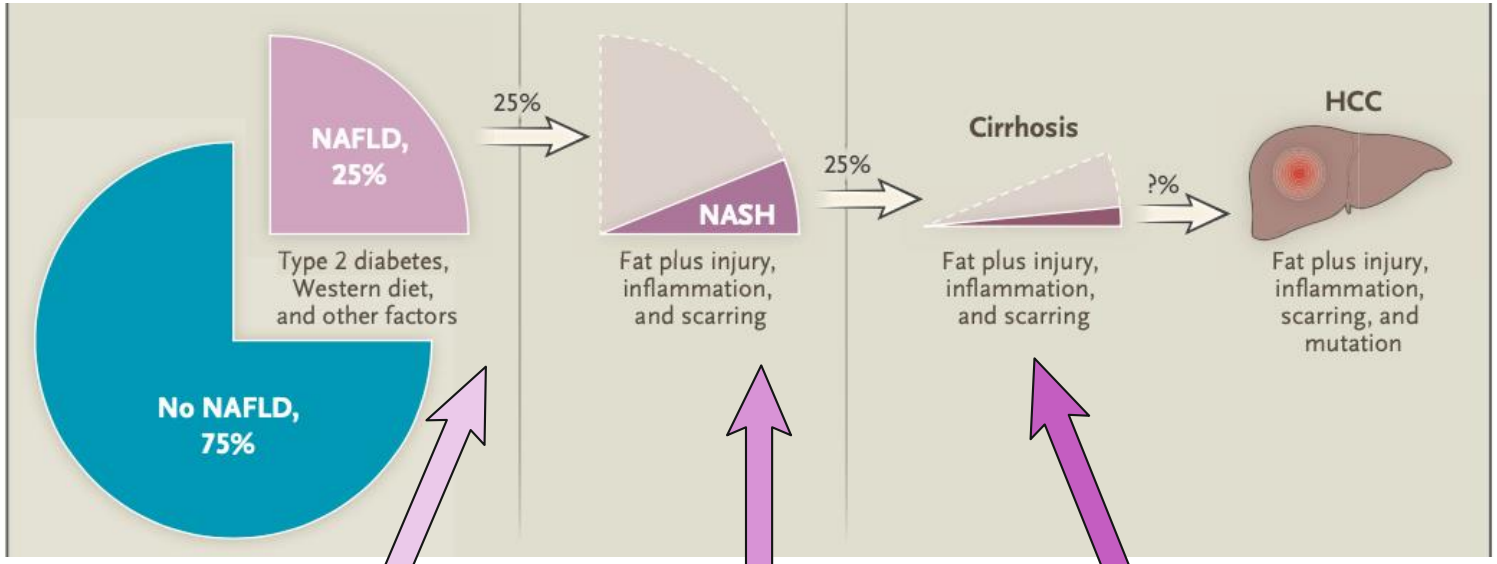
Figure 1. Histologic Features and Prevalence of Nonalcoholic Steatohepatitis (NASH).

- **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 NAFLD

Each Stage of NASH Pathogenesis is a Candidate for Intervention



Steatosis

Inflammation Injury

Fibrosis

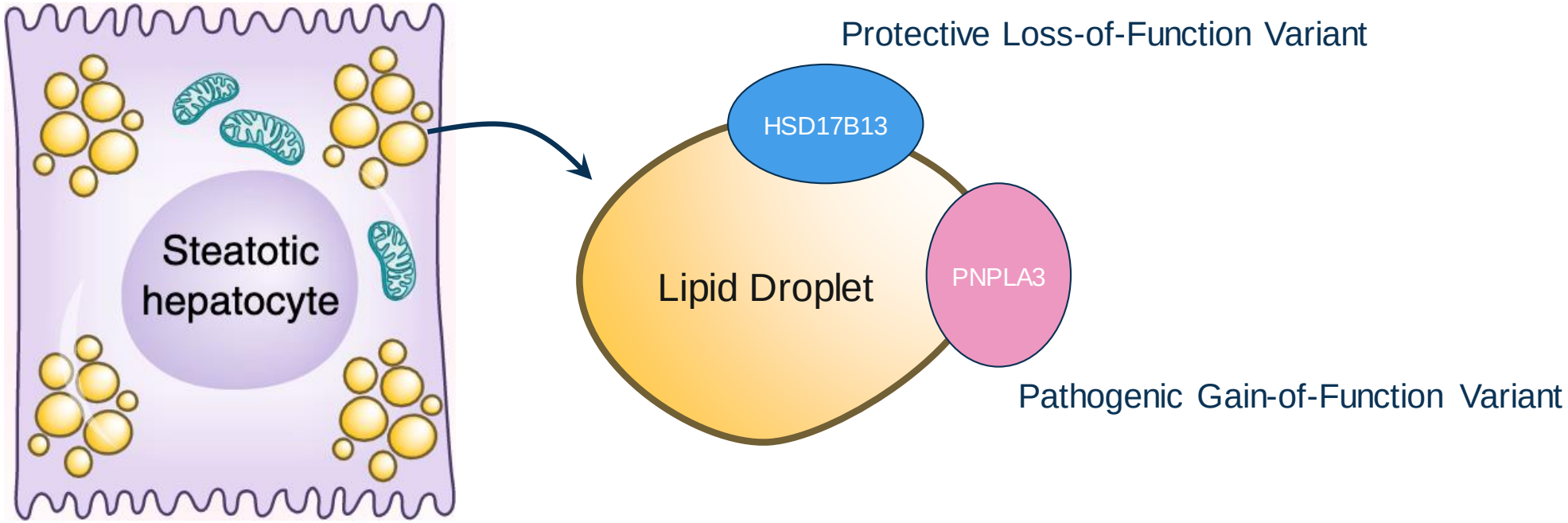
PNPLA3

HSD17B13

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

Genetic Variation: a Natural Experiment to Identify Liver Disease Targets

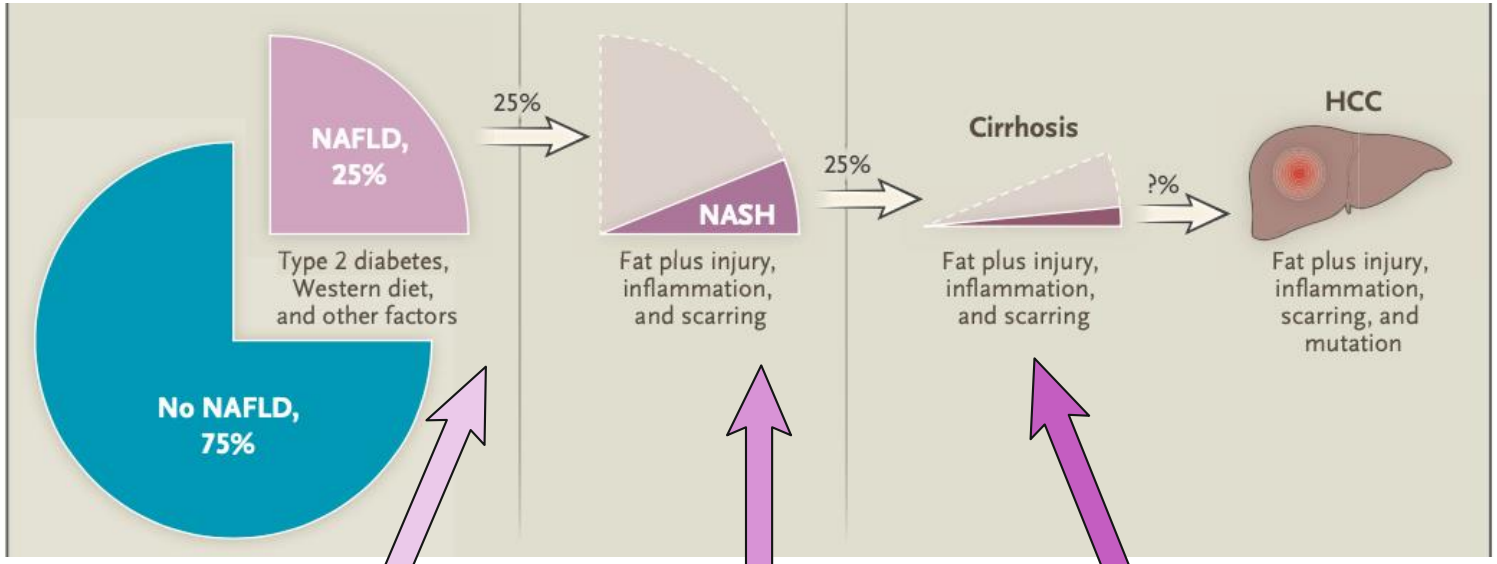
Several Candidates are Lipid Droplet Proteins



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 Strategies for NAFLD

Each Stage of NASH Pathogenesis is a Candidate for Intervention



Steatosis

Inflammation Injury

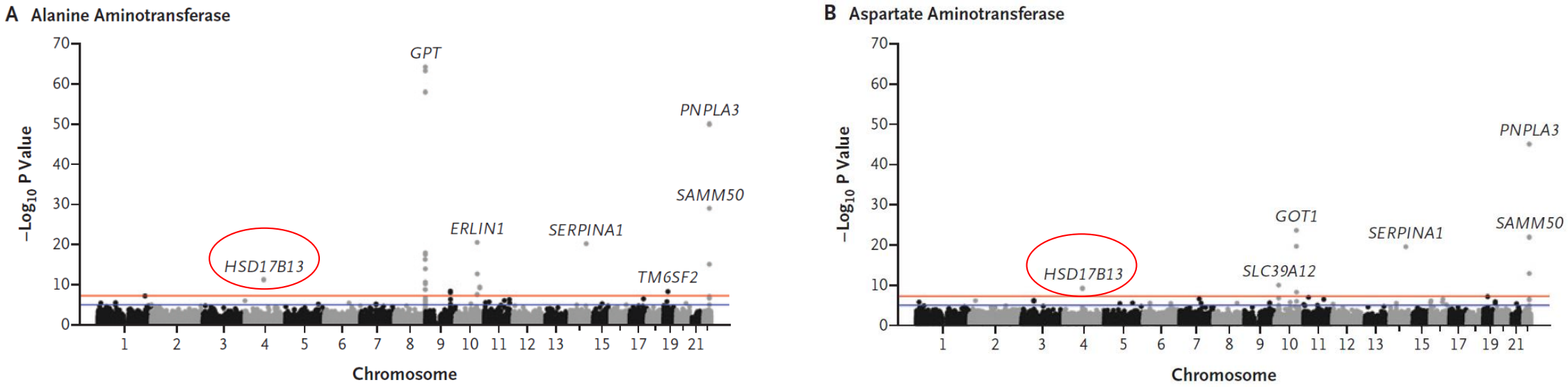
Fibrosis

PNPLA3

HSD17B13

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

A Single Nucleotide Variant in HSD17B13 Associates with Serum LFTs



DiscovEHR study: 46K participants (Geisinger Health System)

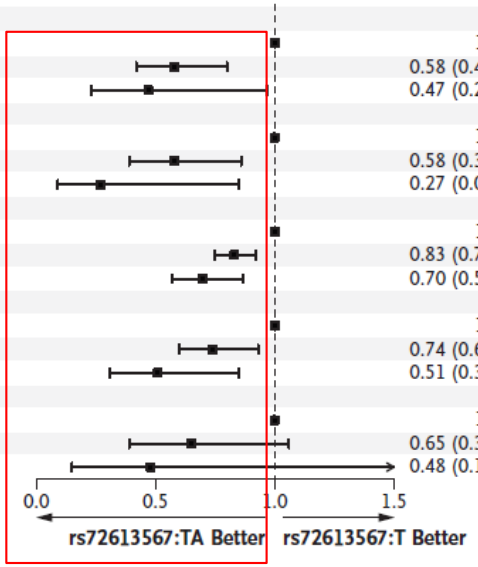
Abul-Husn et al. (2018) *N Engl J Med* 378:1096

HSD17B13 TA allele Associates with Lower Incidence of Chronic Liver Diseases and Hepatocellular Carcinoma

Chronic liver diseases with high unmet need

A GHS Discovery Cohort

Description	Genotype	Case Patients	Controls	Genotypic Odds Ratio (95% CI)	Allelic Odds Ratio (95% CI)	P Value
Alcoholic liver disease (N=190) vs. normal (N=29,928)					0.62 (0.48–0.81)	1.8×10^{-4}
	T/T	128	16,084	1		
	T/TA	54	11,754	0.58 (0.42–0.80)		
	TA/TA	8	2,090	0.47 (0.23–0.97)		
Alcoholic cirrhosis (N=124) vs. normal (N=29,928)					0.56 (0.41–0.78)	3.4×10^{-4}
	T/T	85	16,084	1		
	T/TA	36	11,754	0.58 (0.39–0.86)		
	TA/TA	3	2,090	0.27 (0.09–0.85)		
Nonalcoholic liver disease (N=1857) vs. normal (N=29,928)					0.84 (0.78–0.91)	1.3×10^{-5}
	T/T	1090	16,084	1		
	T/TA	665	11,754	0.83 (0.75–0.92)		
	TA/TA	102	2,090	0.70 (0.57–0.87)		
Nonalcoholic cirrhosis (N=374) vs. normal (N=29,928)					0.74 (0.62–0.88)	4.8×10^{-4}
	T/T	231	16,084	1		
	T/TA	127	11,754	0.74 (0.60–0.93)		
	TA/TA	16	2,090	0.51 (0.31–0.85)		
Hepatocellular carcinoma (N=75) vs. normal (N=29,928)					0.67 (0.45–1.00)	0.047
	T/T	49	16,084	1		
	T/TA	23	11,754	0.65 (0.39–1.06)		
	TA/TA	3	2,090	0.48 (0.15–1.56)		



HSD17B13 is thus an attractive target for the treatment of NASH and other chronic liver diseases

Protective loss-of-function variant (TA) rs72613567 significantly reduces prevalence of NASH, ASH, cirrhosis and HCC

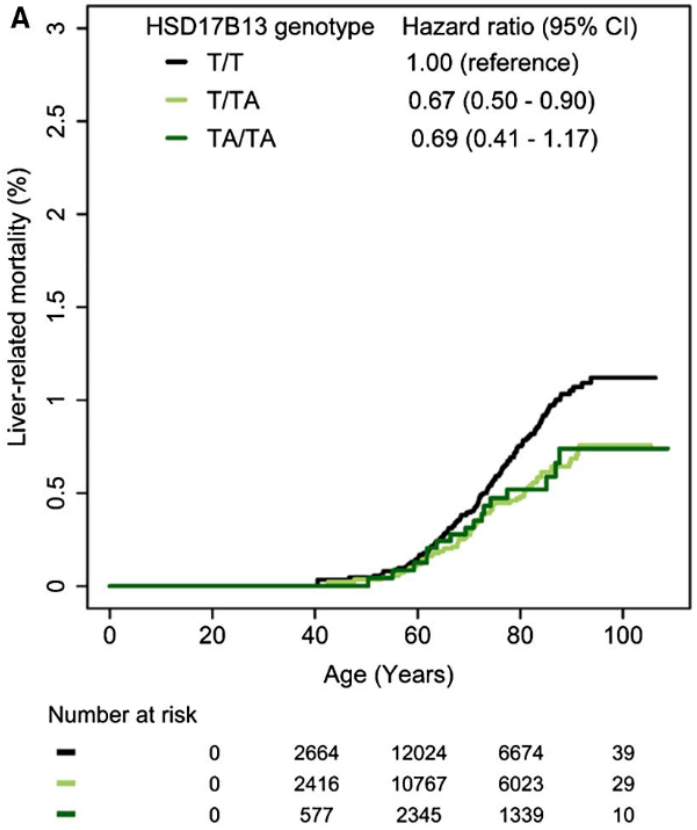
Abul-Husn et al. NEJM 2018 378;12, 1096

Estes et al. Hepatology. 2018;67(1):123

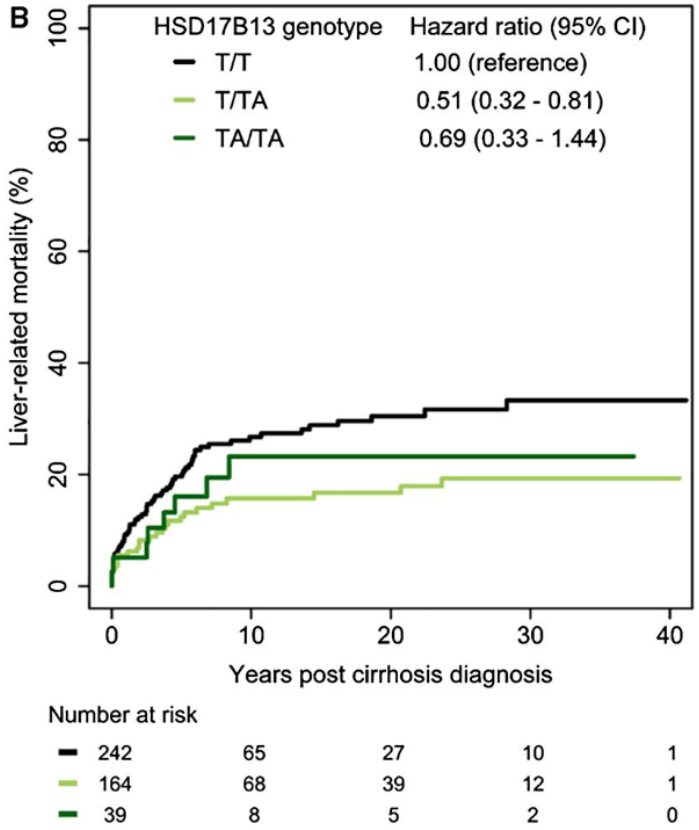
Pirola et al, J Lipid Rs, 2018

Reduced Liver-related Mortality in Carriers of the HSD17B13 TA allele

General population



Cirrhosis patients

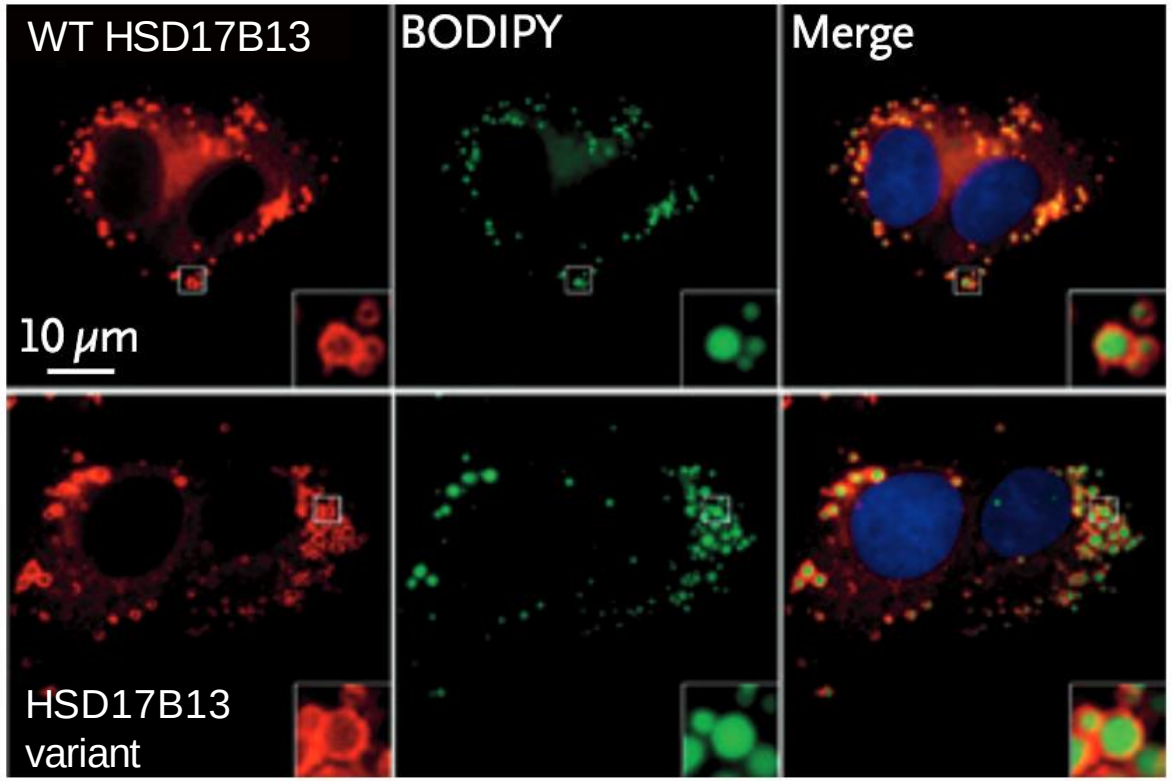


Copenhagen General Population Study (CGPS) and the Copenhagen City Heart Study (CCHS): n=~111K

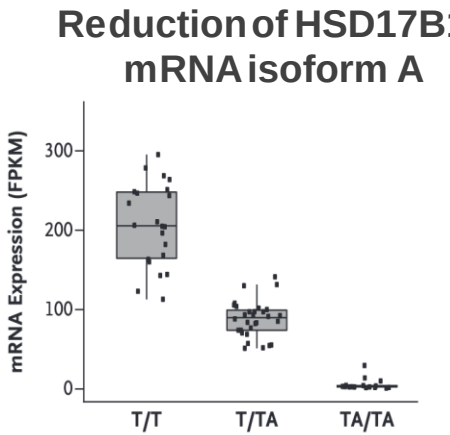
Gellert-Kristensen et al, (2020) Hepatology

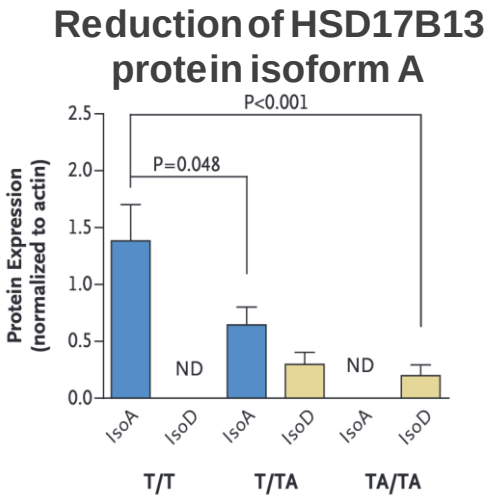
HSD17B13 is a Hydroxysteroid Dehydrogenase Localized to Hepatocyte Lipid Droplets

- The protective *HSD17B13* variant (rs72613567) disrupts splice site at exon 6
- As a result, wild-type mRNA isoform A is replaced with isoform D
- Isoform D protein is expressed at low levels in vivo and has minimal enzymatic activity in vitro



HepG2 cells transfected with wild-type HSD17B13 or the isoform produced by the protective variant

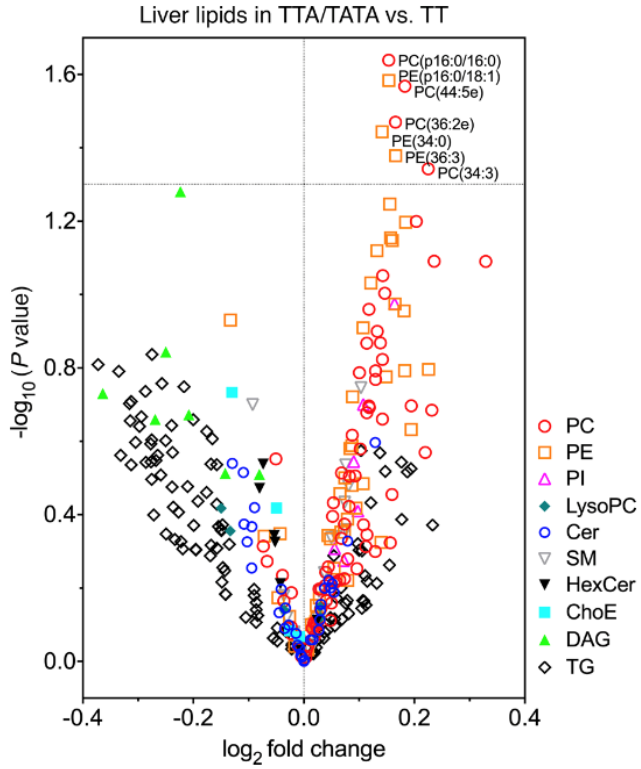




Abul-Husn et al. NEJM 2018 378;12,1096

Additional Findings Relevant to ALN-HSD Mechanism of Action

HSD17B13 Variant is Associated with Elevated Phosphatidylcholine (PC) and Phosphatidylethanolamine (PE)



Comparison of hepatic lipids in carriers of the protective HSD variant versus non carriers. Significant elevations of several PC and PE species were detected (top right).

Other findings for the protective variant

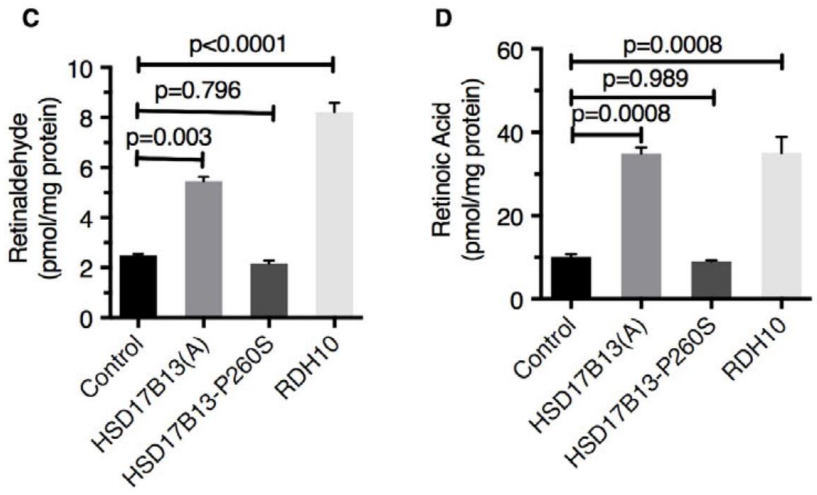
- RNA-seq: decreased inflammatory pathways, increased mitochondrial protein targeting pathways
- Plasma cytokines: slightly decreased IL-6, IL-1β, IL-10
- No differences in hepatic free fatty acids, de novo lipogenesis, adipose tissue lipolysis, or insulin sensitivity

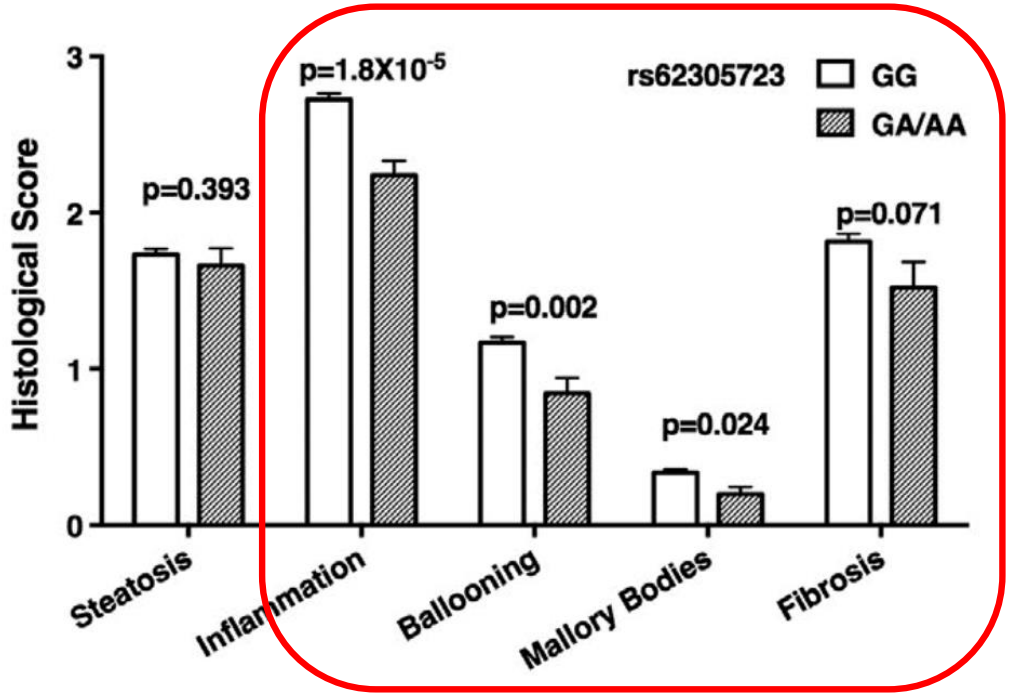
Luukkonen, P.,et al. (2020). JCI Insight 5(5), e132158.

Independent HSD17B13 Variant (rs62305723) Associated with Decreased Liver Inflammation and Injury in NASH

rs62305723 (P260S) results in loss of enzymatic activity in vitro

Human	240-	DEVVRSLIDGILTNKKMIFVPSYINIFLRL
Chimpanzee	240-	DEVVRSLIDGILTNKKMIFVPSYTNIFLRL
Monkey	240-	DEVVRSLIDGILTNKKMIFVPSYINIFLIL
Horse	240-	DEVARSLIDGILTNKKMIFVPSYLNISLTL
Pig	240-	DEVARSLIDGILTNKKMIFVPSYLNISLTL
Dog	240-	DTVARSLIDGILTNKKMIFVPSYYNIYLIL
Mouse	240-	EEVARSLINGILTNKKMIFVPSYINISLIL
Rat	240-	DEVARSLIDGILTNKKMIFVPSYINISLIV
Frog	240-	EDVVKCLMEGILTNKKMIIVPSSVKYSLIL
HSD17B13	240-	DEVVRSLIDGILTNKKMIFVPSYINIFLRL
HSD17B11	240-	EEVVNRLMHGILTEQKMIFIPSSIAFLTTL
RDH10	270-	DYCVKQAMKAILTDQPMICTPRLMYIVTFM
RDHE2	248-	KYAVEKIVEAILQEKMYLYMPKLLYFMMFL
DHRS3	244-	ETVARRTVEAVQLNQALLLLPWTMHALVIL

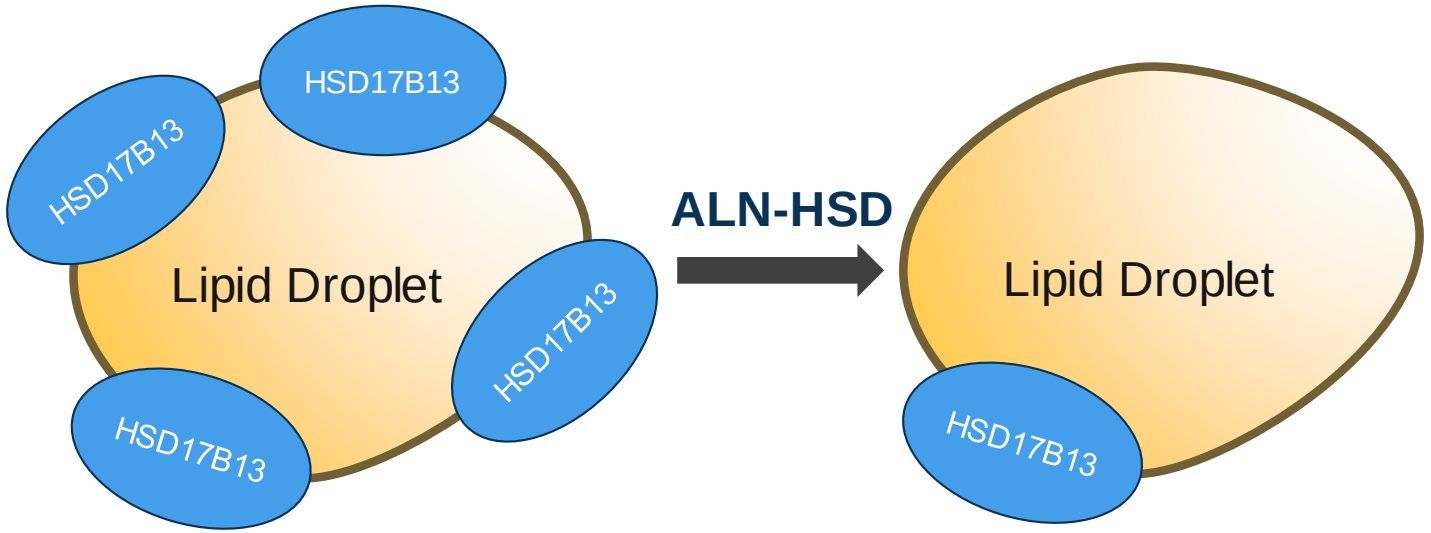




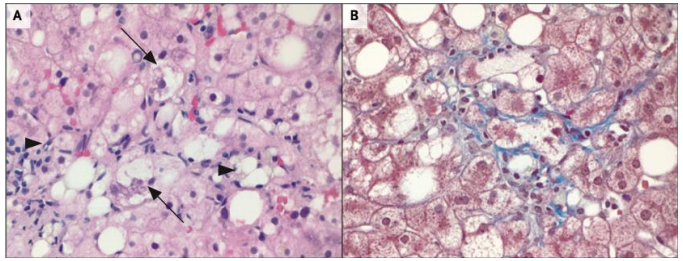
N=768 adult Caucasians with biopsy-proven NAFLD

Ma et al, (2019) Hepatology

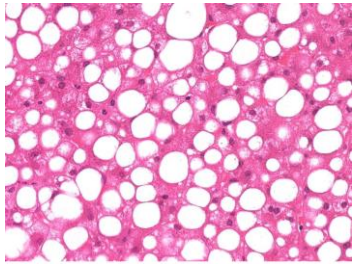
Therapeutic Hypothesis: siRNA-mediated knockdown of HSD17B13 will mimic genetic loss of function, reducing hepatic inflammation, injury, and fibrosis in NASH patients



Hepatocyte injury
Inflammation
Fibrosis



Resolution of inflammation
Reduction of fibrosis
Increased phospholipids



ALN-HSD Results in Potent Knockdown of HSD17B13

>750 siRNA screened in vitro

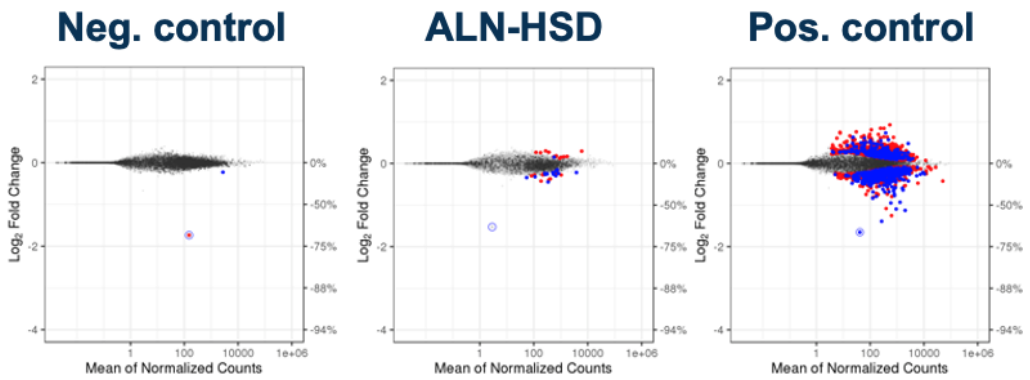
>55 siRNA screened in vivo (mice)

5 siRNA screened in vivo (NHP)

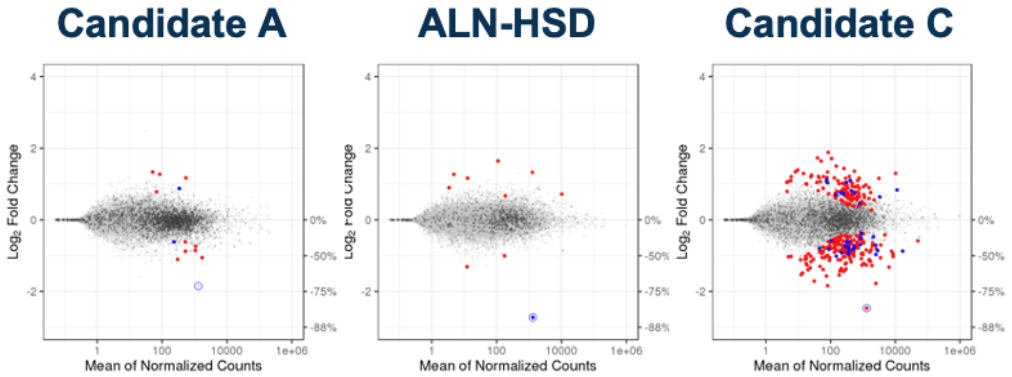
ALN-HSD Development Candidate selected

Assessment of knockdown and off-target effects

RNAseq in primary human hepatocytes

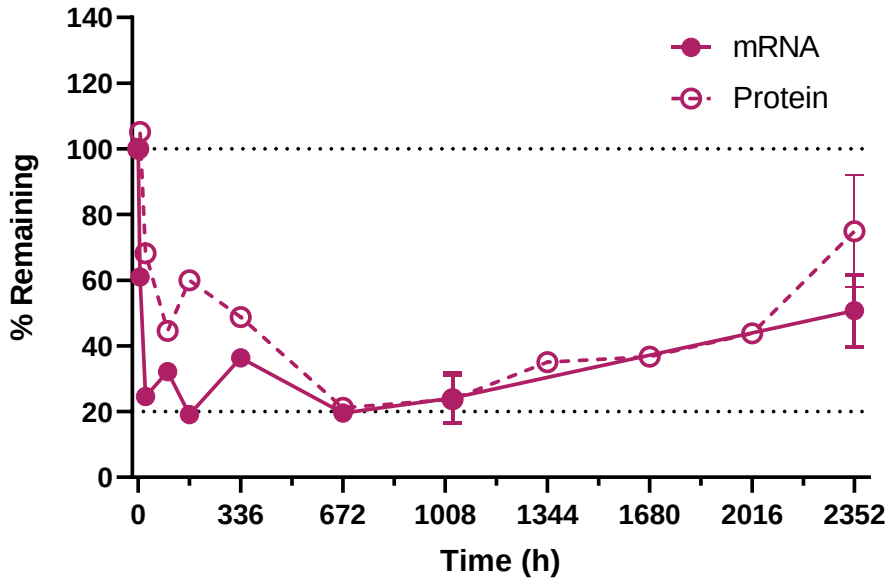


RNAseq in NHP liver in vivo (Day 21, 10 mg/kg)

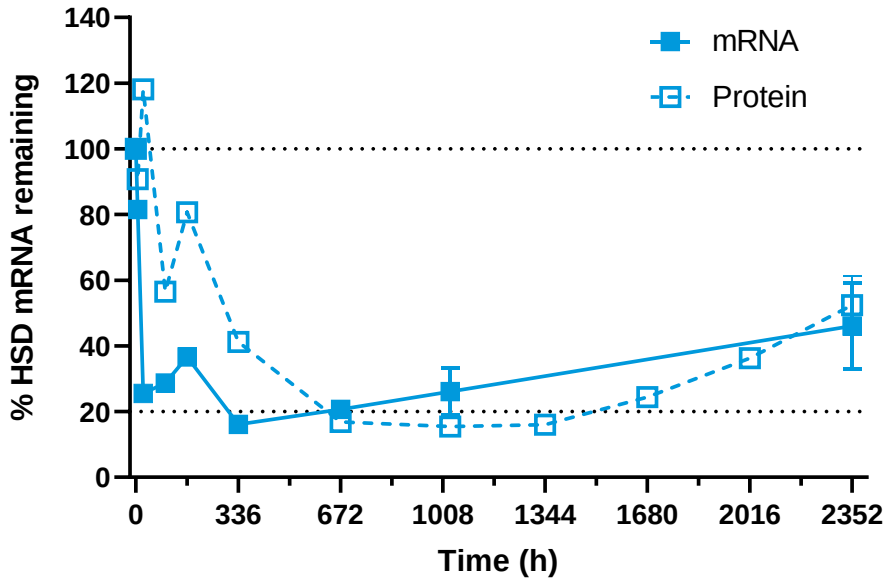


ALN-HSD Results in Potent mRNA and Protein HSD17B13 Knockdown in NHP Liver

3 mg/kg single dose



10 mg/kg single dose



- 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

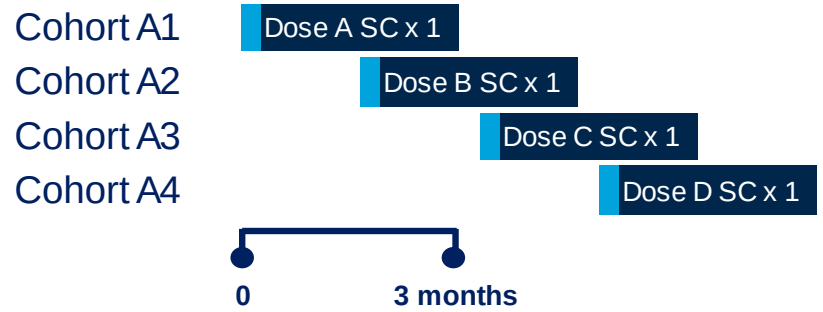
Part A: Healthy Volunteers

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

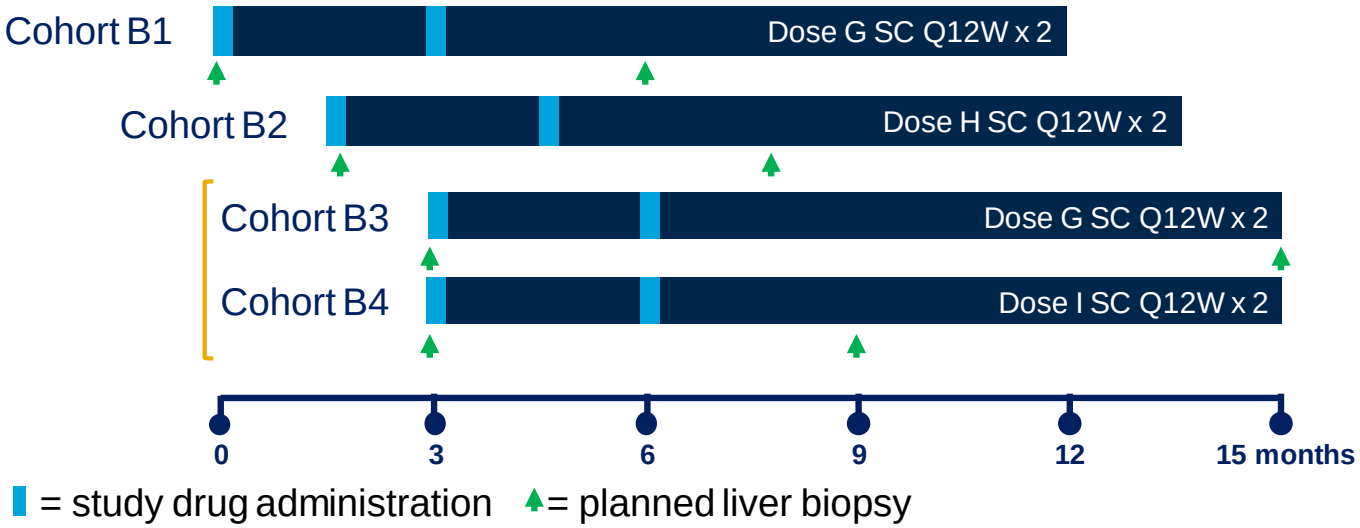
SAD Cohorts



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

MD Cohorts



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 ESC+ GalNAc-siRNA conjugate targeting HSD17B13

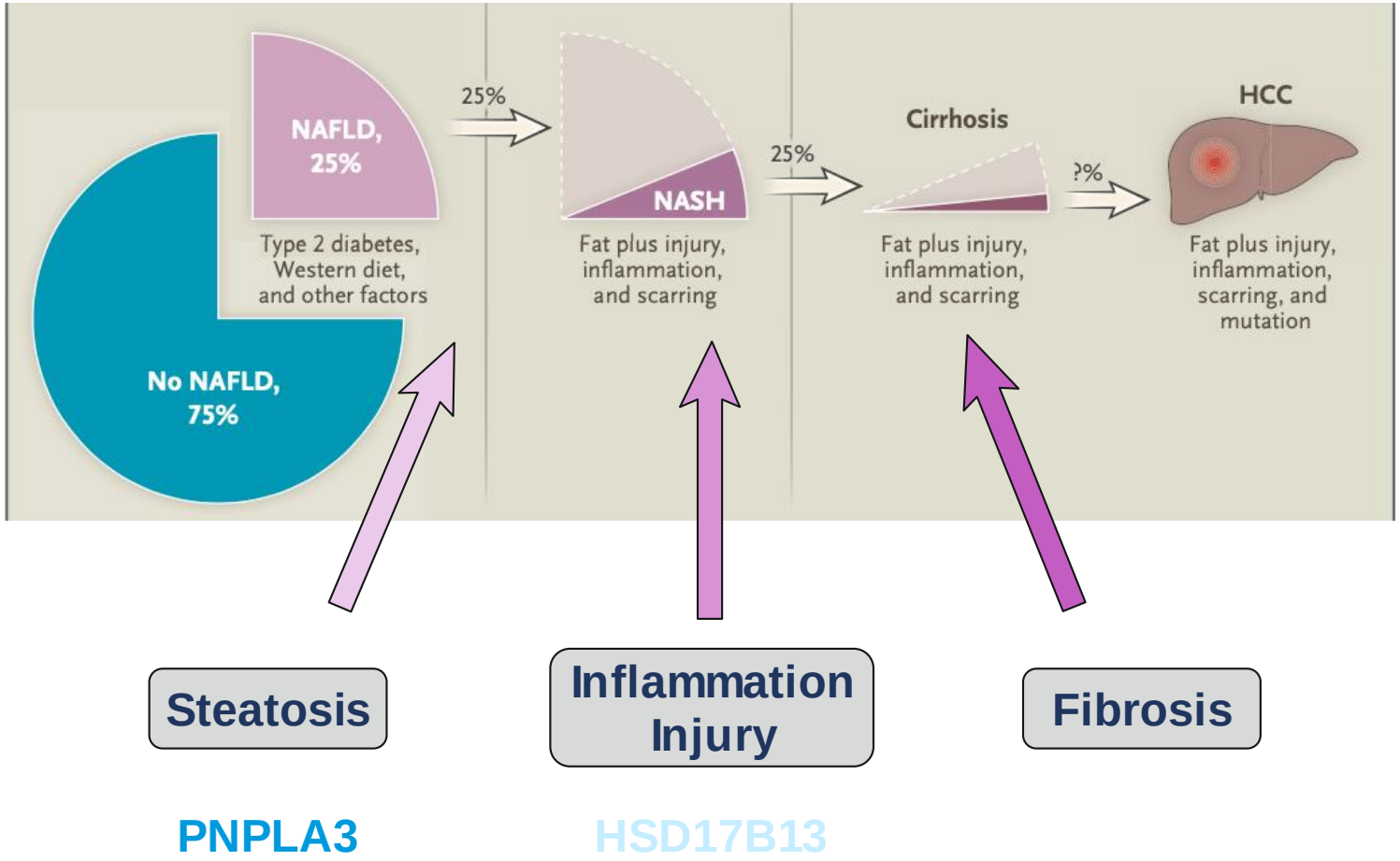
No pre-clinical toxicity of concern observed, with high safety margins demonstrated

Phase 1 trial initiated; POC expected in 2022

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

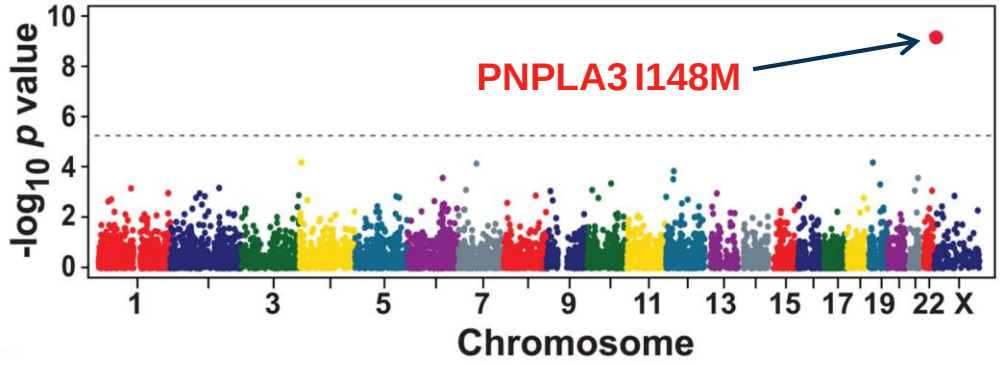
Therapeutic Strategies for Nonalcoholic Fatty Liver Disease (NAFLD)

Each Stage of NASH Pathogenesis is a Candidate for Intervention

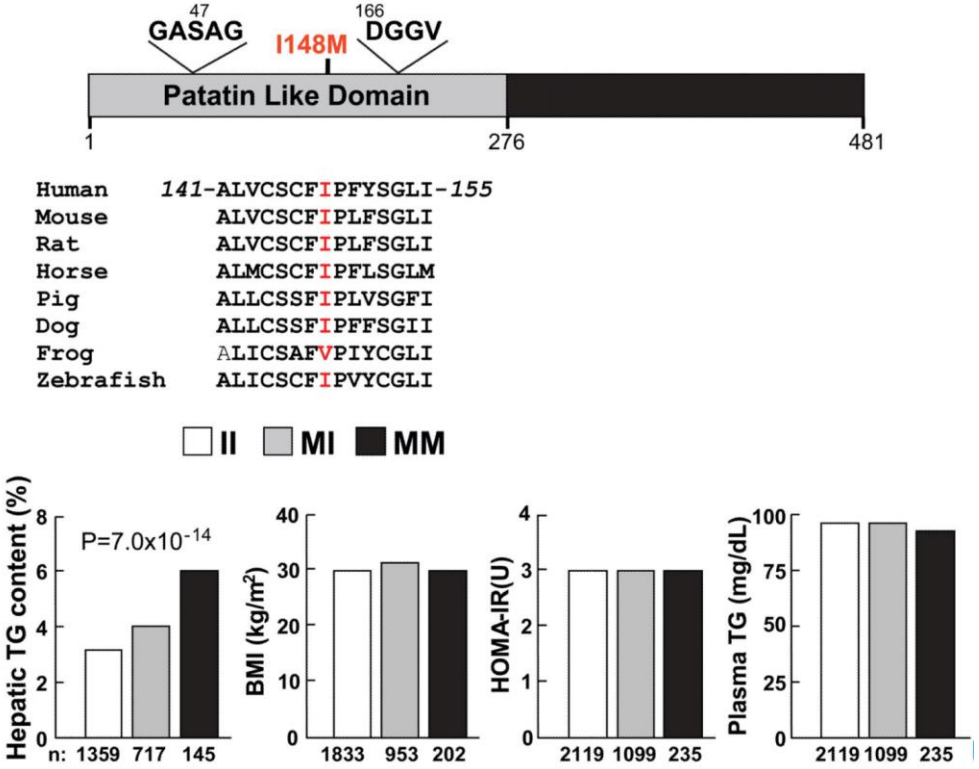


Adapted from *Diehl, A., Day, C.* (2017). NEJM 377(21), 2063-2072.

A PNPLA3 Variant (I148M) is 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 is Associated with a 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

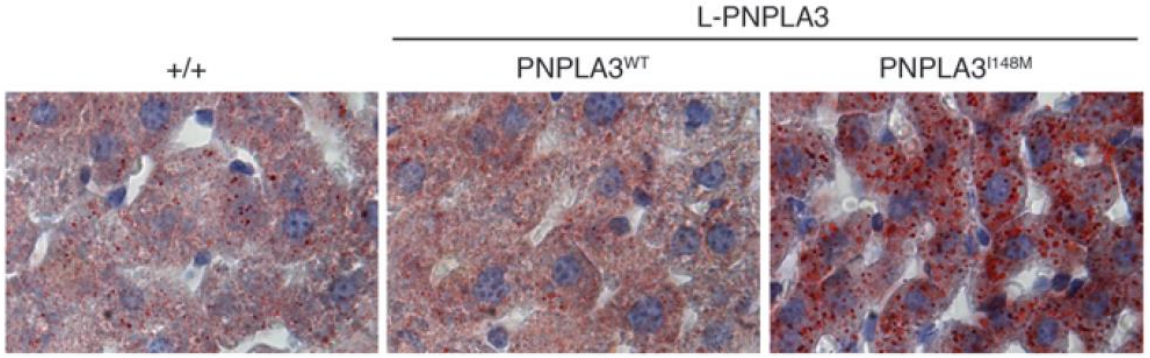
Luca Valenti[a,*], Paola Dongiovanni[a], Stefano Ginanni Corradini[b], Maria Antonella Burza[c], Stefano Romeo[c,d,**]

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) 619–624

PNPLA3 I148M Variant Leads to Hepatic TG Accumulation

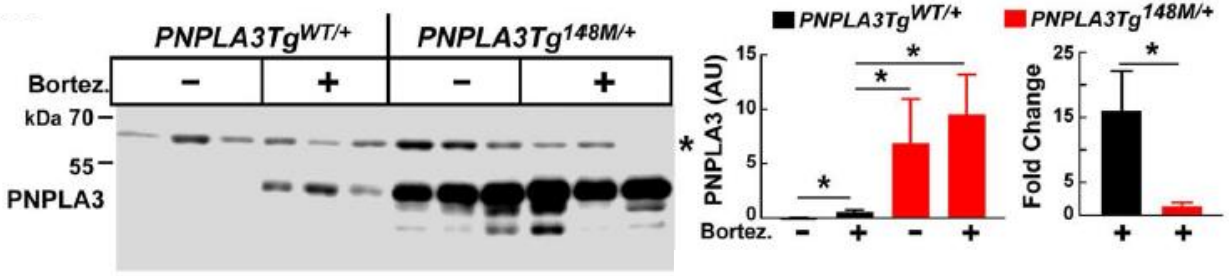
PNPLA3 I148M resists degradation and competes with triglyceride lipase for co-factor CGI-58

- Liver-specific hPNPLA3 WT and I148M transgenic mice



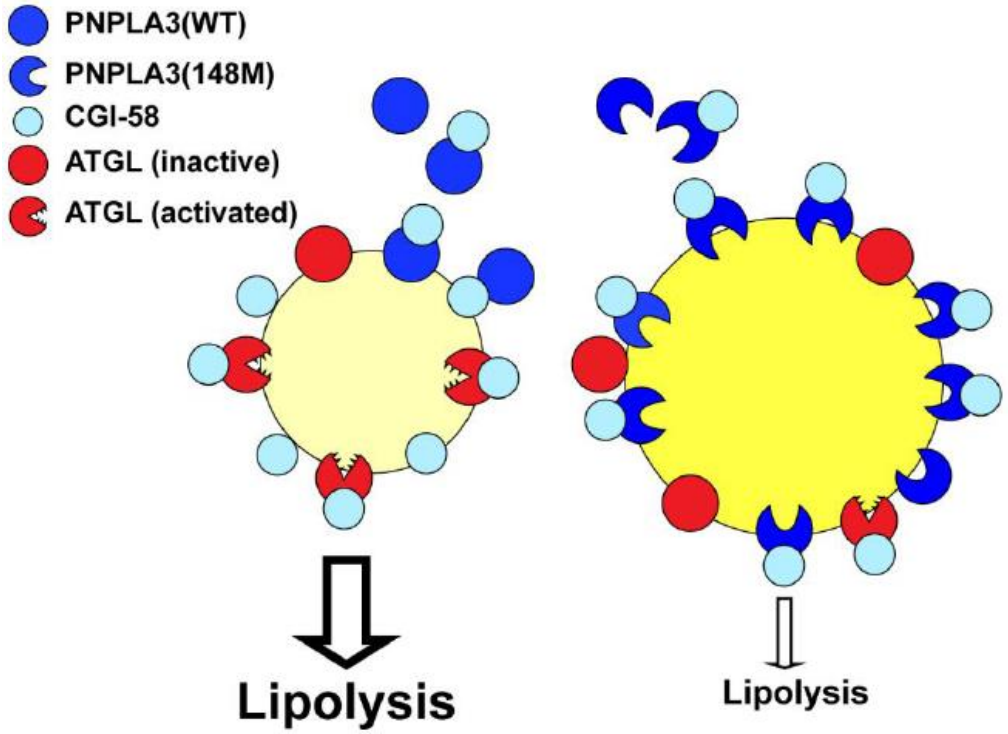
Oil Red O

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



Bortez: proteasome inhibitor

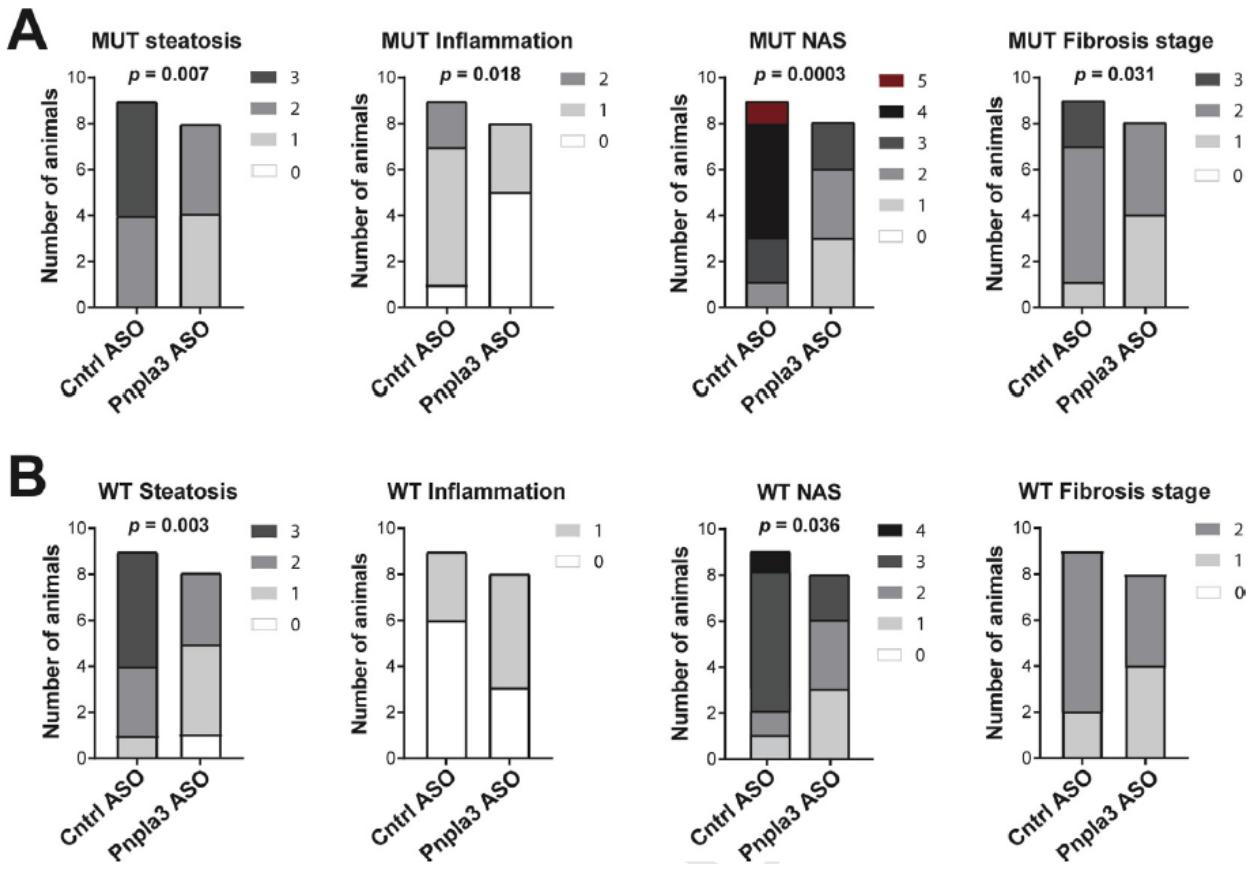
Excess PNPLA3 competes with ATGL for CGI-58



Li et al, (2012) JCI, BasuRay et al, (2016) Hepatology; Wang et al, (2019) Hepatology

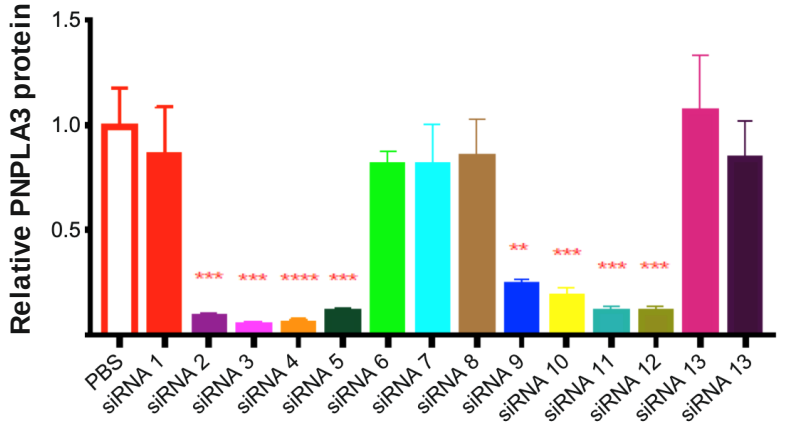
Silencing Hepatic PNPLA3 to Treat NASH

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



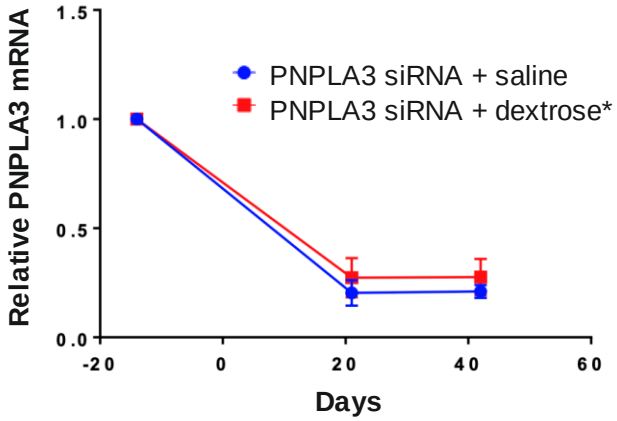
Efficient KD of PNPLA3 protein by candidate siRNAs

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

Development candidate selection expected early 2021

IP for broadly targeting PNPLA3 with RNAi filed Dec 2015

VOICES OF **PATIENTS & CAREGIVERS**

“I began to notice some changes in my body. My hands and feet were getting numb and I had some digestive issues. When the numbness started to creep up my legs and arms, I knew it was time to get tested.”

Rick, living with hATTR amyloidosis

Alnylam® PHARMACEUTICALS

Realizing Additional Opportunities from Liver-Directed RNAi Therapeutics

Pushkal Garg, M.D.
Chief Medical Officer

Alnylam PHARMACEUTICALS

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 4)*	REGISTRATION/ COMMERCIAL[1]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis*[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]
Patisiran	*ATTR Amyloidosis*		●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●		15-30% Royalties
Vutrisiran	*ATTR Amyloidosis*		●		Global
Lumasiran	*Recurrent Renal Stones*	●			Global
Cemdisiran	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]	*Complement-Mediated Diseases*	●			Milestone/Royalty
ALN-AAT02 (DCR-A1AT)[7]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
ALN-AGT	*Hypertension*	●			Global
ALN-HSD	*NASH*	●			Milestone/Royalty

[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 for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S. and EU 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 ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development

As of December 2020

Development of Lumasiran for Recurrent Renal Stones

Alnylam PHARMACEUTICALS

The third RNAi therapeutic is

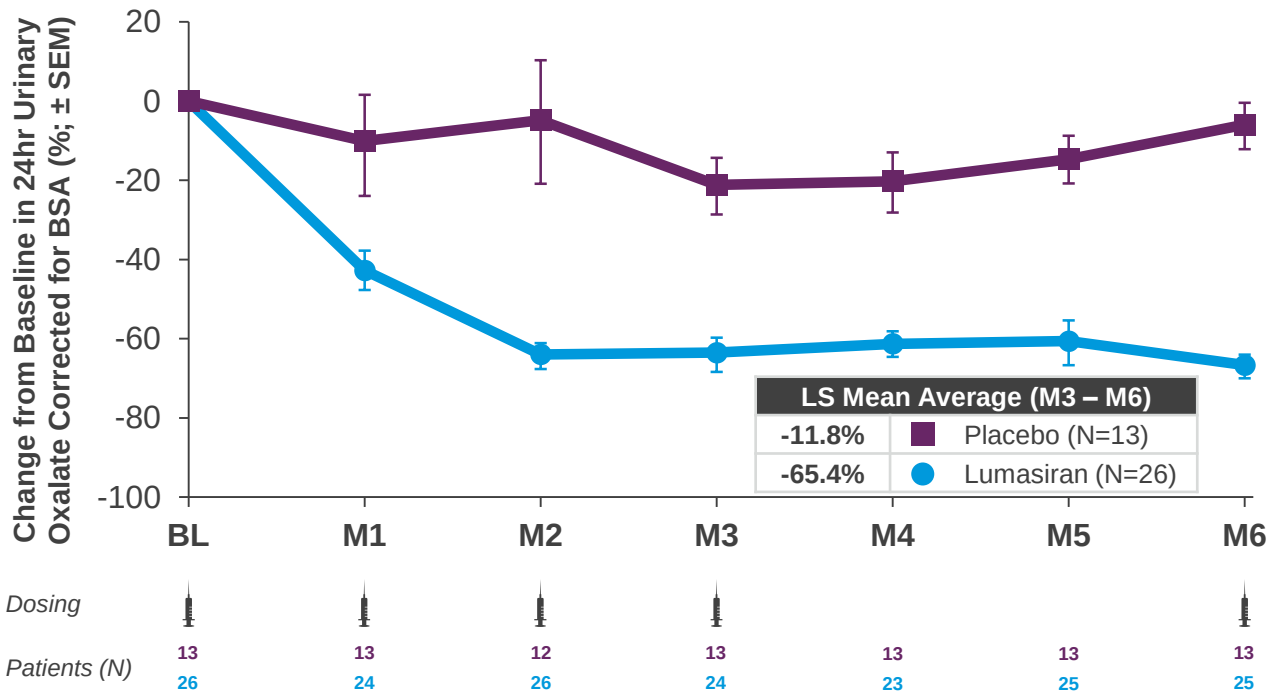
NOW APPROVED IN THE EU and U.S.

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

Lumasiran ILLUMINATE•A Phase 3 Study

Met Primary and All Tested Secondary Endpoints with Encouraging Safety and Tolerability Profile

Rapid and sustained reduction in 24hr urinary oxalate levels from baseline to Month 6



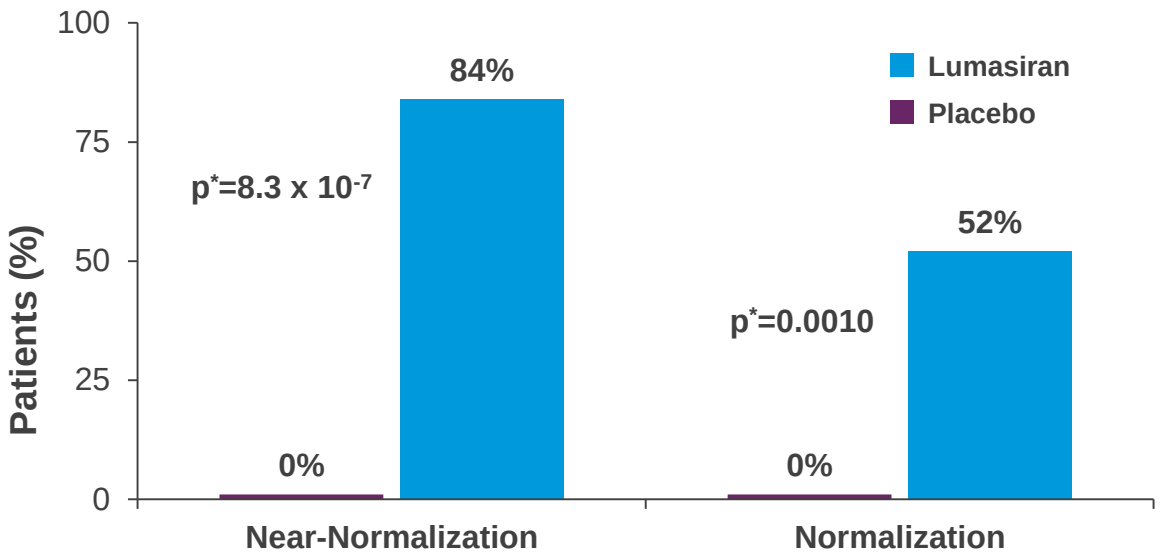
-53%

Difference in LS mean average M3-M6 (Lumasiran-Placebo) ($p=1.7 \times 10^{-14}$)

-76%

Mean maximal reduction

Majority of patients achieved near-normalization (≤1.5 x ULN) or normalization (≤ULN) in 24hr urinary oxalate levels at Month 6



Safety

- No deaths, severe, or serious AEs. All AEs mild or moderate
- Most common drug-related AEs were injection-site reactions
  - All generally mild; no discontinuation of treatment
  - Most common symptoms: erythema, pain, pruritus, and swelling
- No hepatic AEs reported in either group
- No clinically relevant changes in laboratory measures, vital signs, and electrocardiograms related to lumasiran observed

BL, baseline; BSA, body surface area; hr, hour; LS, least squares; M, month; ULN, upper limit of normal; AE, adverse event

* p-value is based on Cochran–Mantel–Haenszel test stratified by baseline 24 hr urinary oxalate corrected for BSA (≤1.70 vs >1.70 mmol/24 hr/1.73 m2)

Oxalate Nephrolithiasis

Potential Life Cycle Expansion Opportunity for Lumasiran

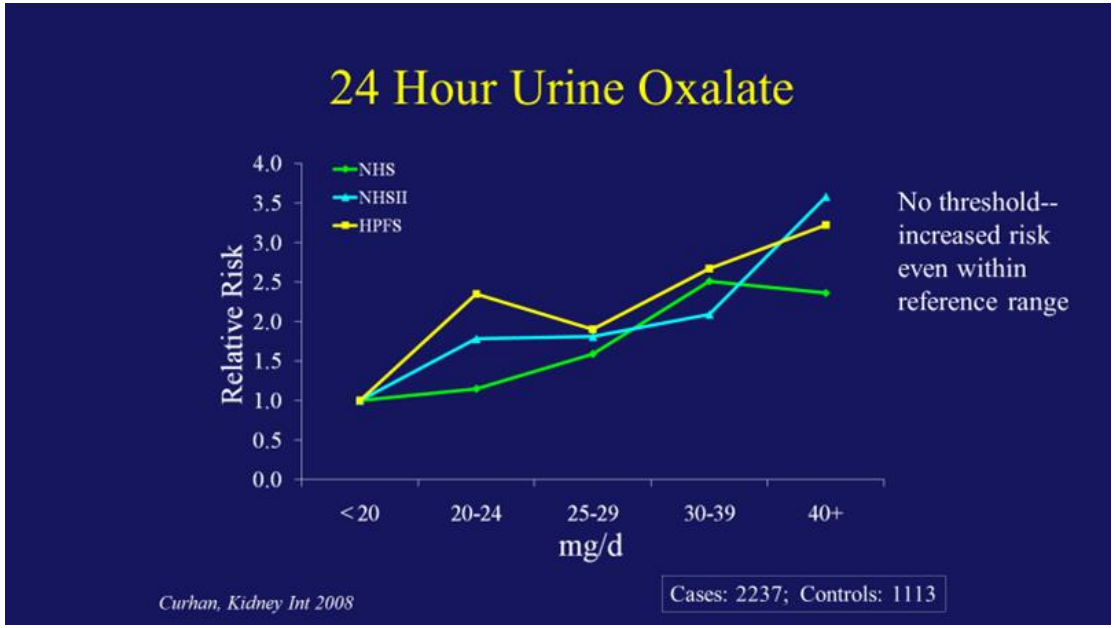
High Unmet Need

- 10.6% men & 7.1% women experience renal stones
- 35% of stone formers have recurrent events
- Significant clinical and cost burden for patients
- Stones lead to ~2x increase in risk of chronic kidney disease
- Limited treatment options: hydration, dietary changes, thiazide diuretics, potassium citrate, allopurinol

Oxalate-lowering may reduce renal stone events and progression to ESRD

- 85% of renal stones consist of calcium oxalate
- Graded relationship between urinary oxalate and renal stone events

Plan to initiate Phase 2 Study in late 2021



Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. Kidney Int. 2008 Feb;73(4):489-96; Scales CD, Jr, Smith AC, Hanley JM, Saigal CS Urologic diseases in America project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62:160–165; Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. Nat Rev Nephrol. 2016 Sep;12(9):519-33; Alexander RT, Hemmelgarn BR, Wiebe N, Bello A, Morgan C, Samuel S, Klarenbach SW, Curhan GC, Tonelli M; Alberta Kidney Disease Network. Kidney stones and kidney function loss: a cohort study. BMJ. 2012 Aug 29;345:e5287; Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR; American Urological Association. Medical management of kidney stones: AUA guideline. J Urol. 2014 Aug;192(2):316-24; Rule AD, Bergstralh EJ, Melton LJ 3rd, Li X, Weaver AL, Lieske JC. Kidney stones and the risk for chronic kidney disease. Clin J Am Soc Nephrol. 2009 Apr;4(4):804-11.

Cemdisiran for Complement-mediated Diseases

Alnylam PHARMACEUTICALS

Complement-Mediated Disorders

Numerous Debilitating Diseases

REGENERON

IgAN
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 1 study underway
- Opportunity to expand to other complement-driven diseases (e.g., aHUS, NMO)

Cemdisiran Phase 1/2 Study*

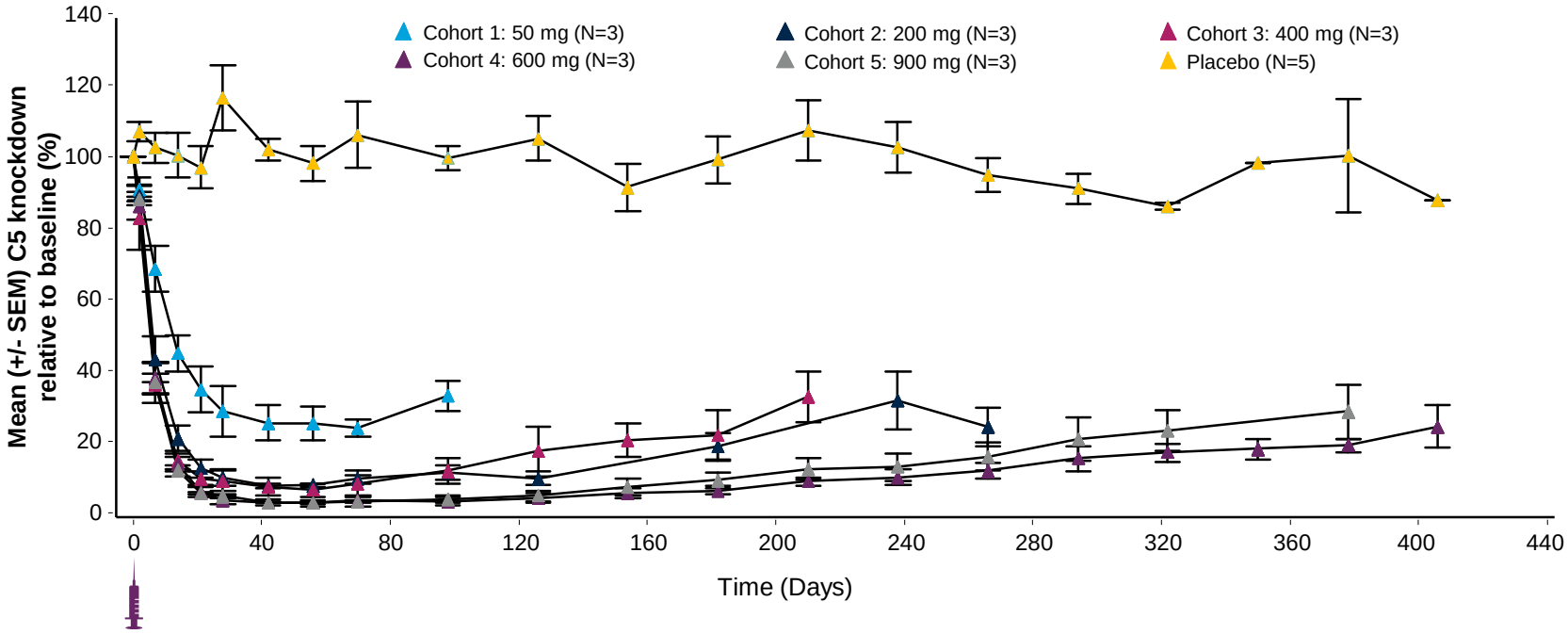
Deep and Durable C5 Inhibition with Single Doses in Healthy Volunteers

Maximum C5 knockdown relative to baseline up to 99%

Mean maximum (± SEM) C5 knockdown: 98 ± 0.9% (600mg)

Mean (± SEM) C5 knockdown:

- Day 98 (600 mg): 97 ± 1.1%; Day 406 (600 mg): 76 ± 6.0%



* Data as of 13 October 2016

IgA Nephropathy

Background

Epidemiology

- Most common cause of glomerulonephritis worldwide

Pathophysiology

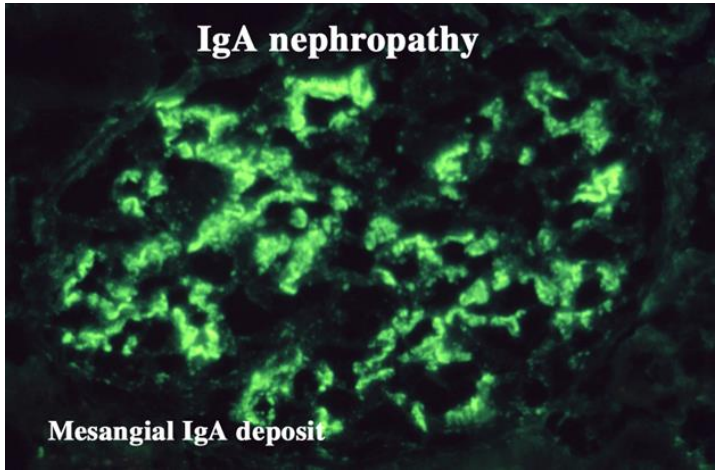
- ~6% have family history of disease
- Abnormally galactosylated IgA1 is antigenic leading to autoantibody formation, glomerular immune complex deposition and complement activation (C3, C5, MAC) causing inflammation

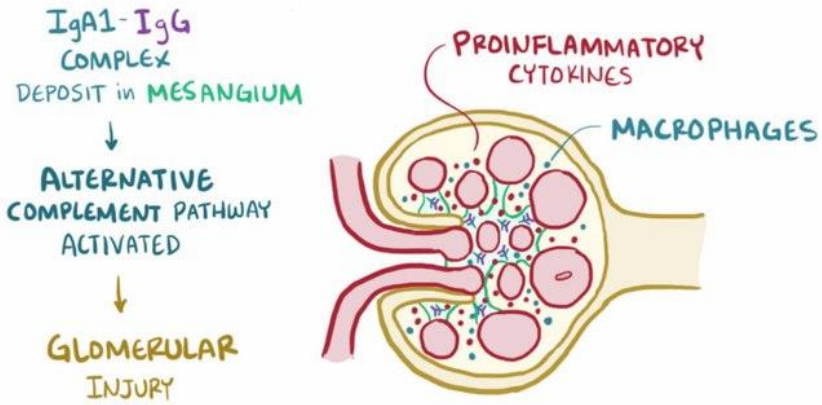
Clinical Features

- 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

Unmet Need

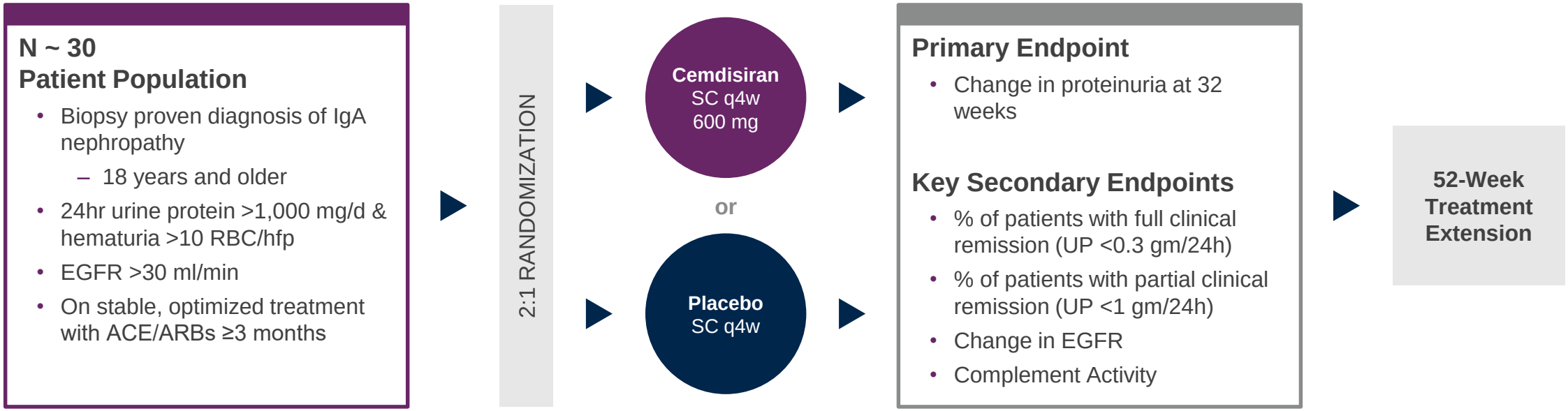
- Only definitive therapy is renal transplantation, but disease can recur in graft





Cemdisiran Phase 2 Study

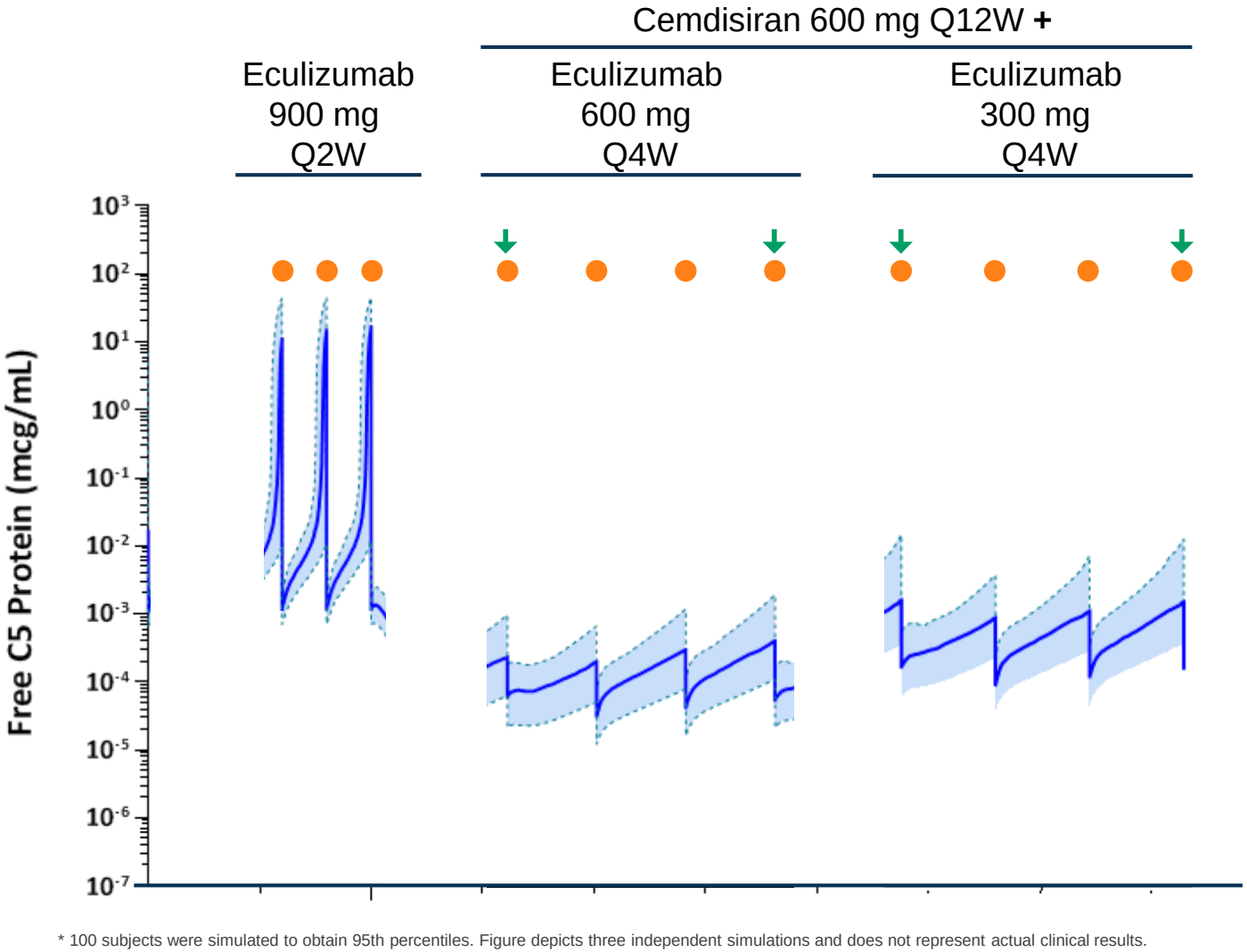
Randomized, Double-Blind Study in Patients with IgA Nephropathy



Initial data expected **2021**

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



* 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.

Prior Experience in PNH

- Co-treatment with cemdisiran + eculizumab studied in PNH patients
- 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

Phase 1 Study Underway

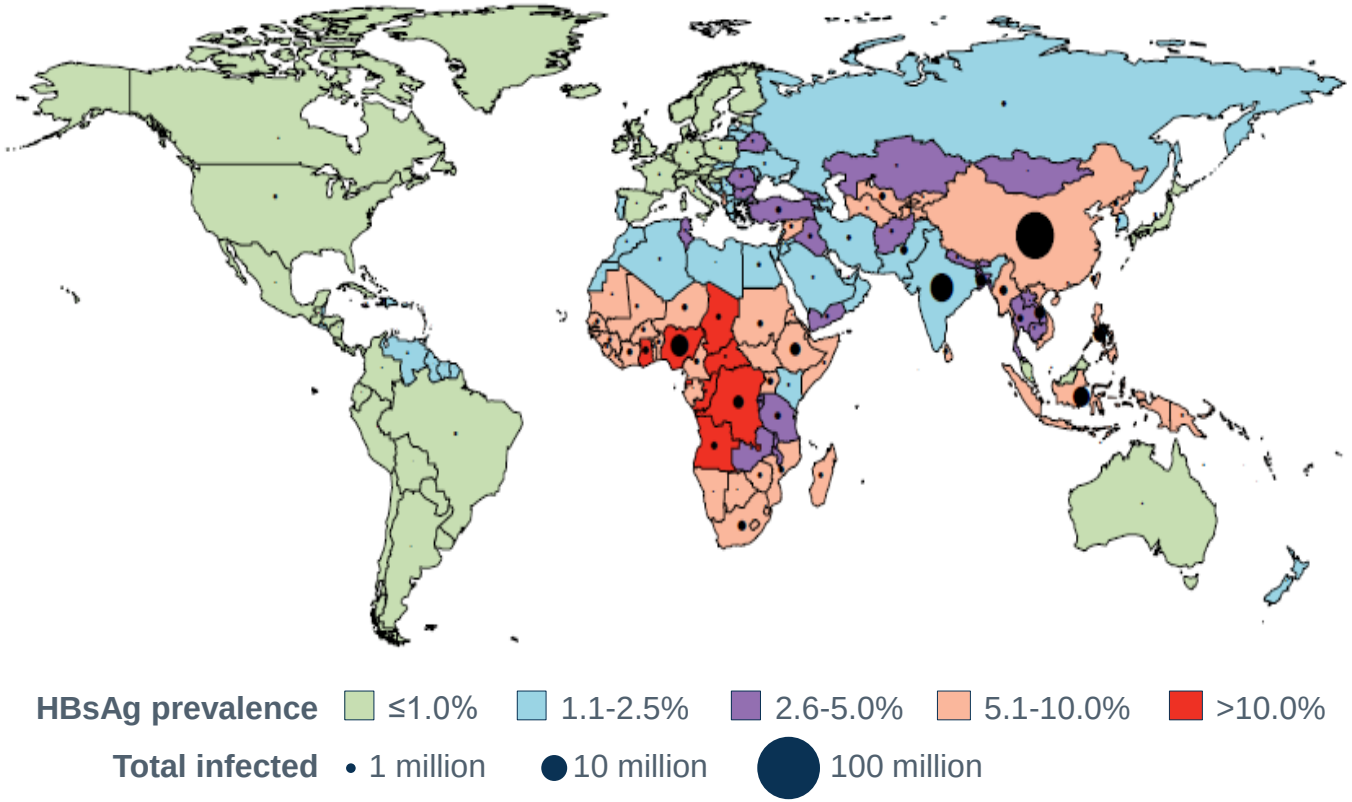
- Evaluating cemdisiran in combination with anti-C5 Mab, pozelimab
- Led by Regeneron

ALN-HBV02 (VIR-2218) for HBV Infection

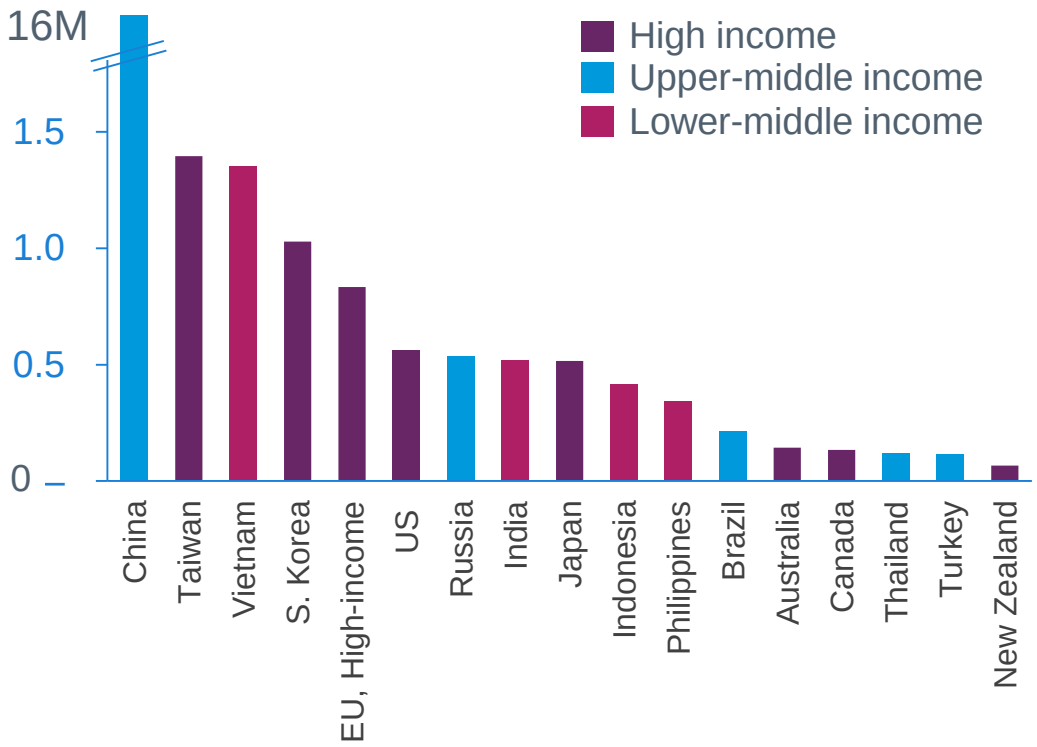
Alnylam PHARMACEUTICALS

HBV: Global Health Problem Impacting Developed and Developing Countries

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



Diagnosed Patients: ~27 M
(top high-/middle-income countries: 24 M)*



*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

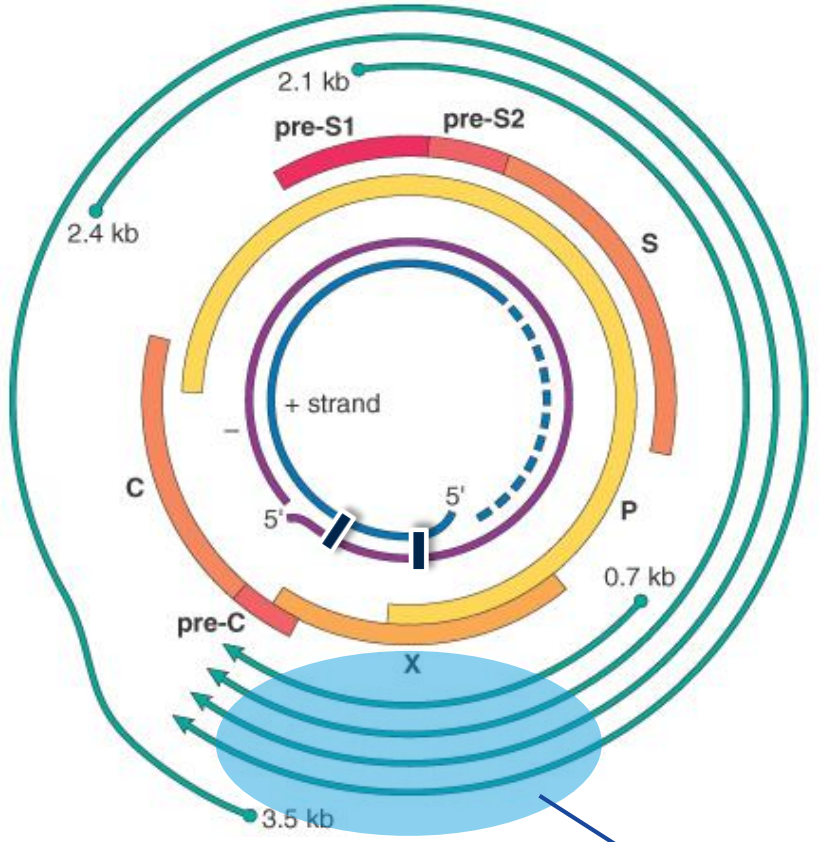
VIR-2218: X-targeting Investigational RNAi Therapeutic for Treatment of Chronic HBV Infection

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[1,2]
- ESC+ technology: improved specificity of RNAi activity[3,4]



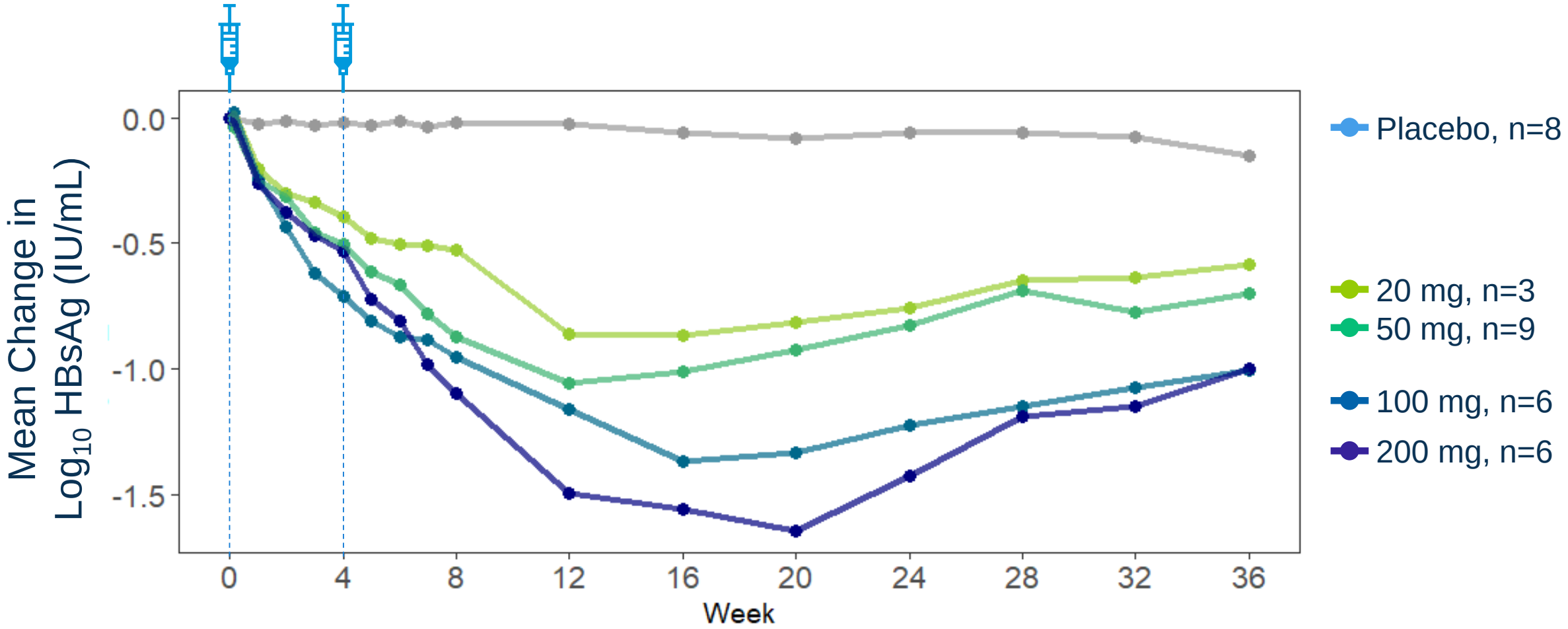
siRNA targeting an overlapping region can silence all transcripts

cccDNA, covalently-closed circular DNA; ESC+, enhanced stabilization chemistry plus; GalNAc, Trivalent *N*-acetylgalactosamine; intDNA, integrated DNA; HBsAg, hepatitis B surface antigen; RNAi, RNA interference; siRNA, small interfering RNA.

1. Nair J, et al. J Am Chem Soc 2014;136:16958-61; 2. Foster D, et al, Nucleic Acids Res 2018; 3. Janas M, et al. Nature Comm 2018;9:723; 4. Schlegel MK, et al. J Am Chem Soc 2017;139:8537-46.

VIR-2218-1001 Phase 2 Study Results

HBsAg Change from Baseline



Accepted Safety and Tolerability Profile

- No clear dose related trend in frequency of AEs; Most common AE: headache (6/24, 25%); Single Grade 3 AE of hypophosphatemia in a patient on tenofovir DF; Single SAE of Grade 2 headache

ALN-HBV02 (VIR-2218) Next Steps

ALN-HBV02

- Phase 2 one-year response durability expected in 1H:2021

ALN-HBV02 + PEG-IFNα combo trial

- Phase 2 initial data expected in 2021

ALN-HBV02 + VIR-3434 (HBV mAb) combo trial

- Phase 2 start expected in 2021

ALN-HBV02 China trial

- Phase 2 trial in mainland China on-going

Alnylam Opt-in Right Prior to Phase 3

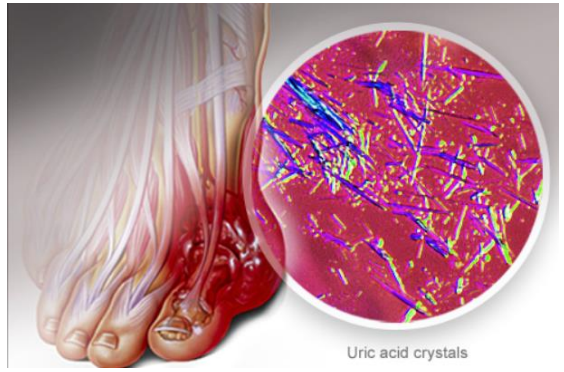
ALN-XDH for Gout

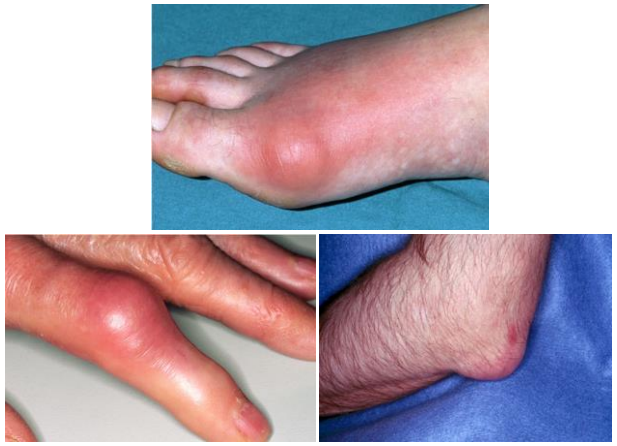
Alnylam PHARMACEUTICALS

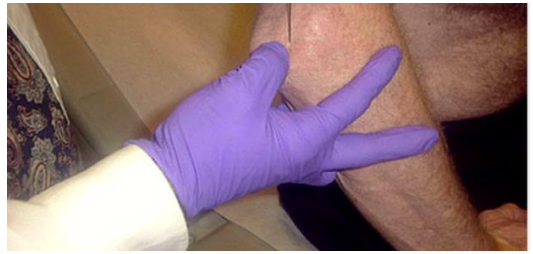
Gout

Arthritis Caused by Uric Acid Crystal Accumulation in the 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



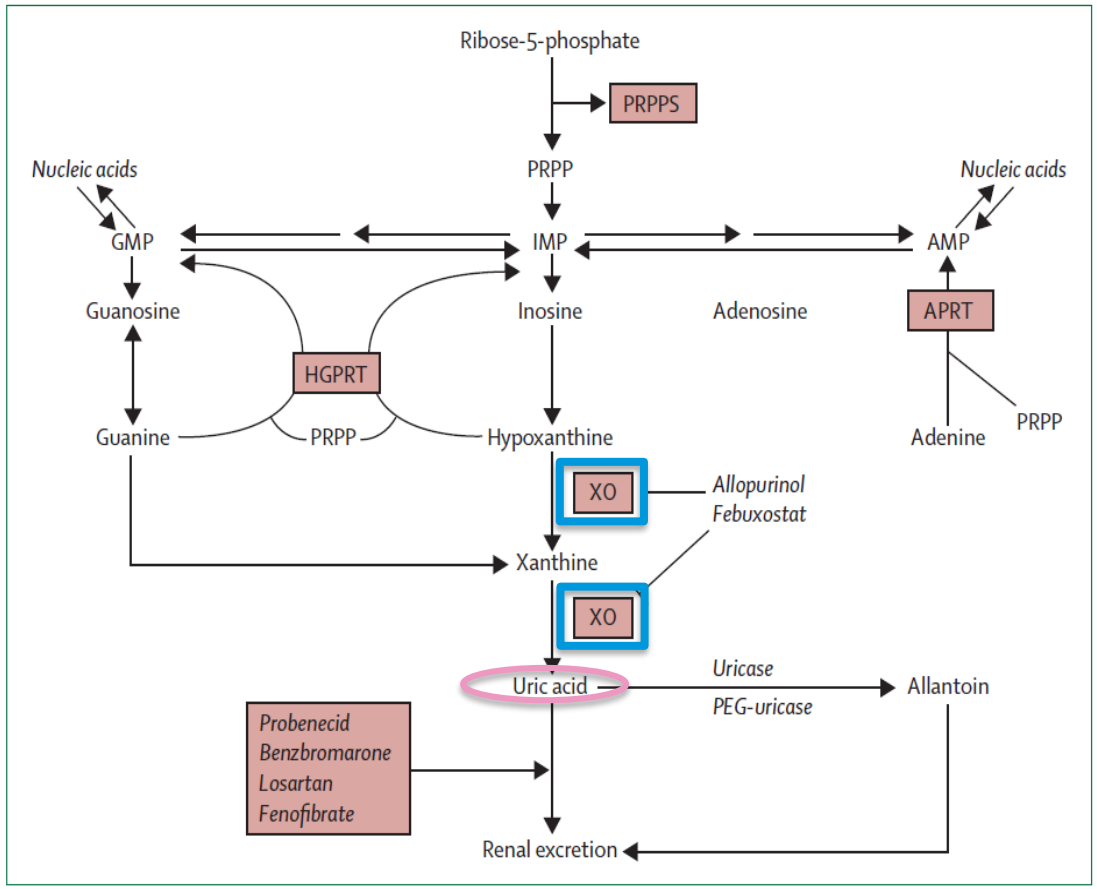




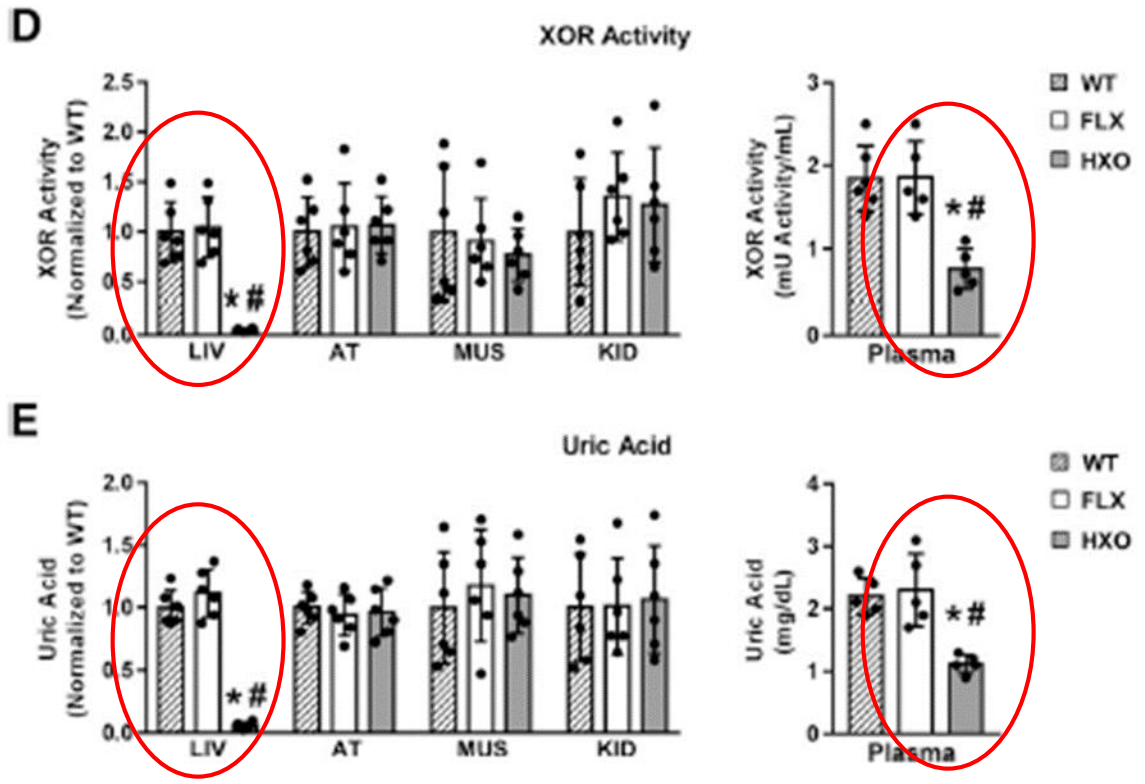
Dehlin et al. *Nature Reviews Rheumatology* 16(7):380-390 (2020); Chen-Xu et al. *Arthritis & Rheumatology* 71(6): 991-999 (2019); Koto et al. *Modern Rheumatology* 20:1-9 (2020); Kuo et al. *Nature Reviews Rheumatology 11*(11):649-662 (2015); GlobalData Disease Analysis

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)

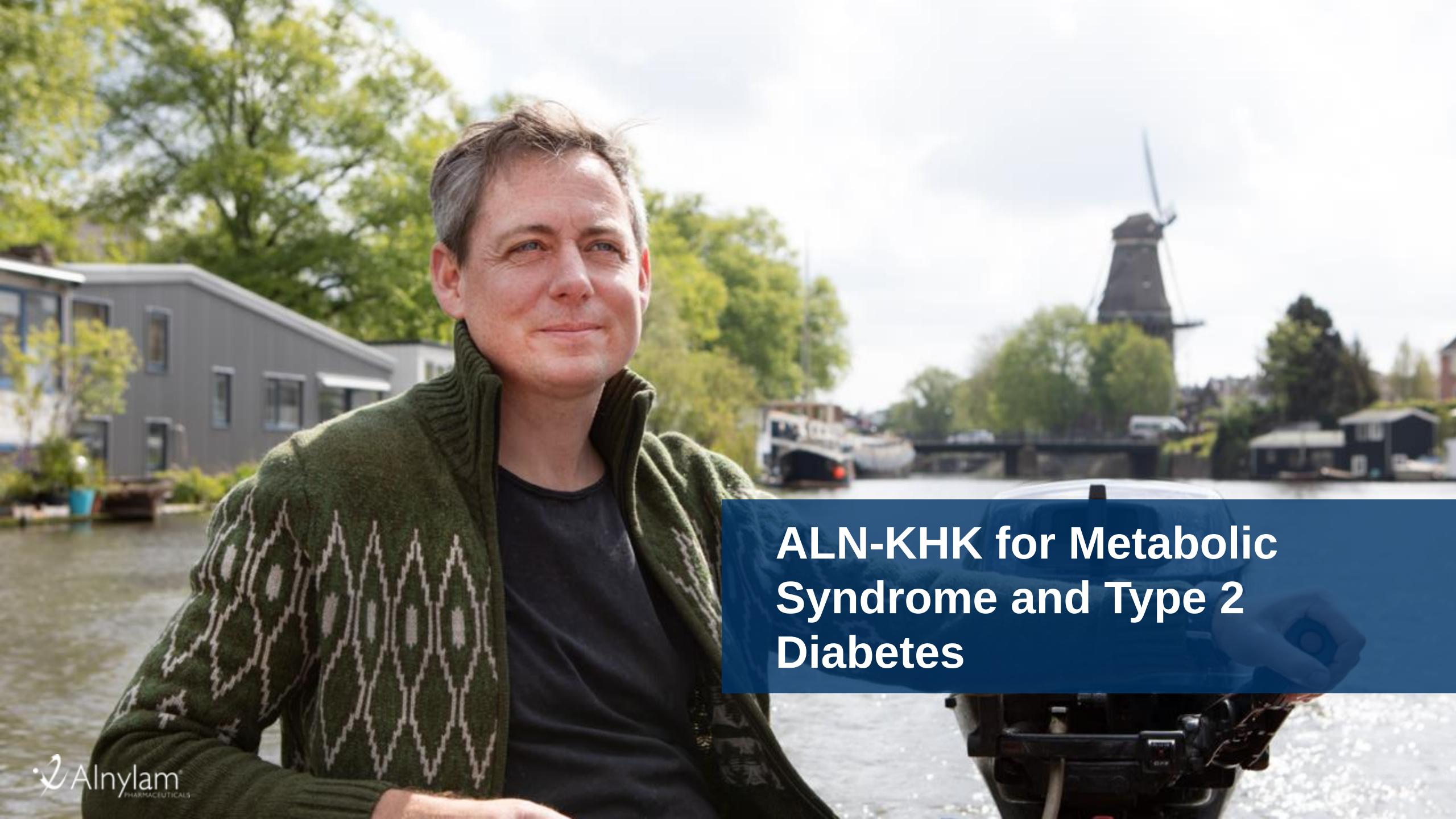
Potential to Improve Gout Control with ALN-XDH

- 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 safety concerns

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

- ALN-XDH 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

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

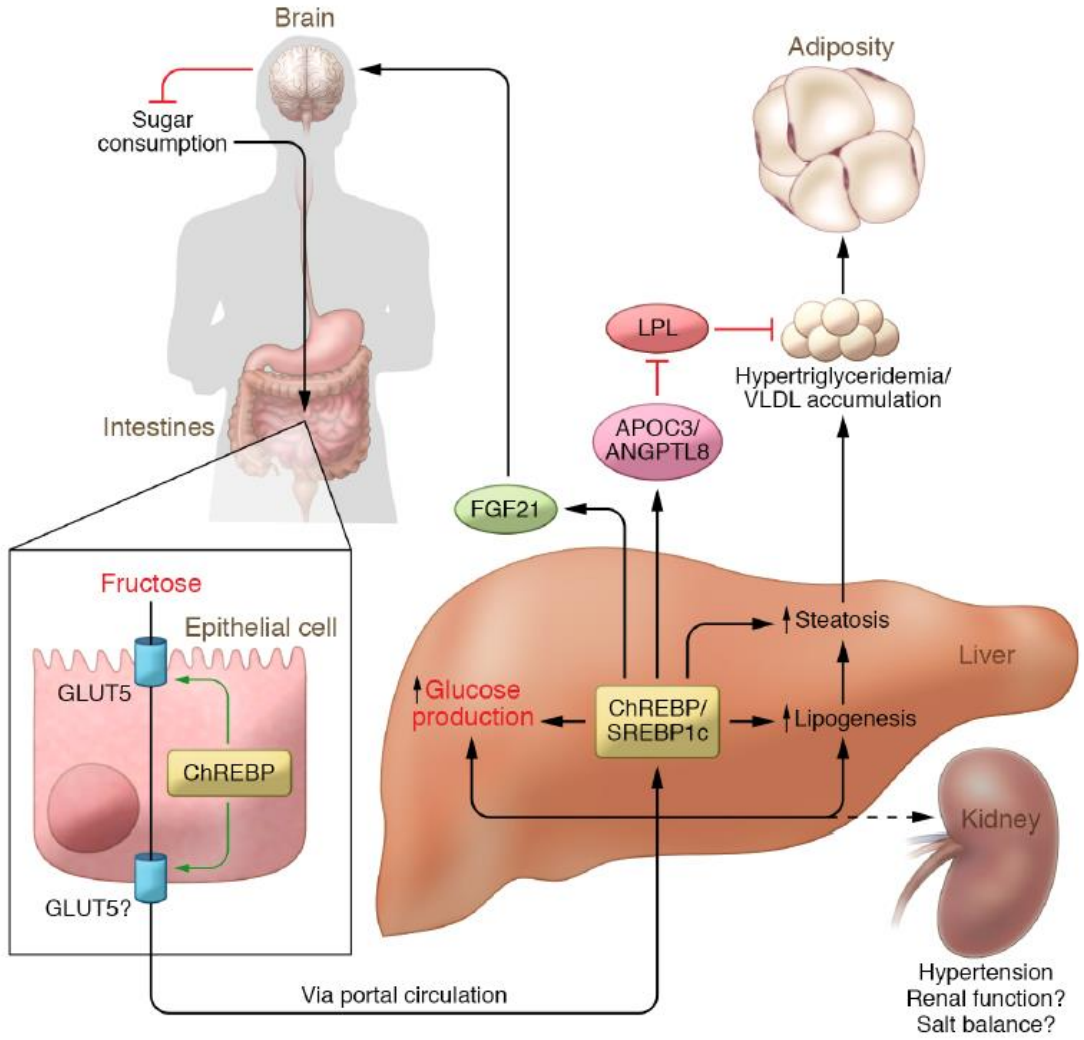


ALN-KHK for Metabolic Syndrome and Type 2 Diabetes

Alnylam PHARMACEUTICALS

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

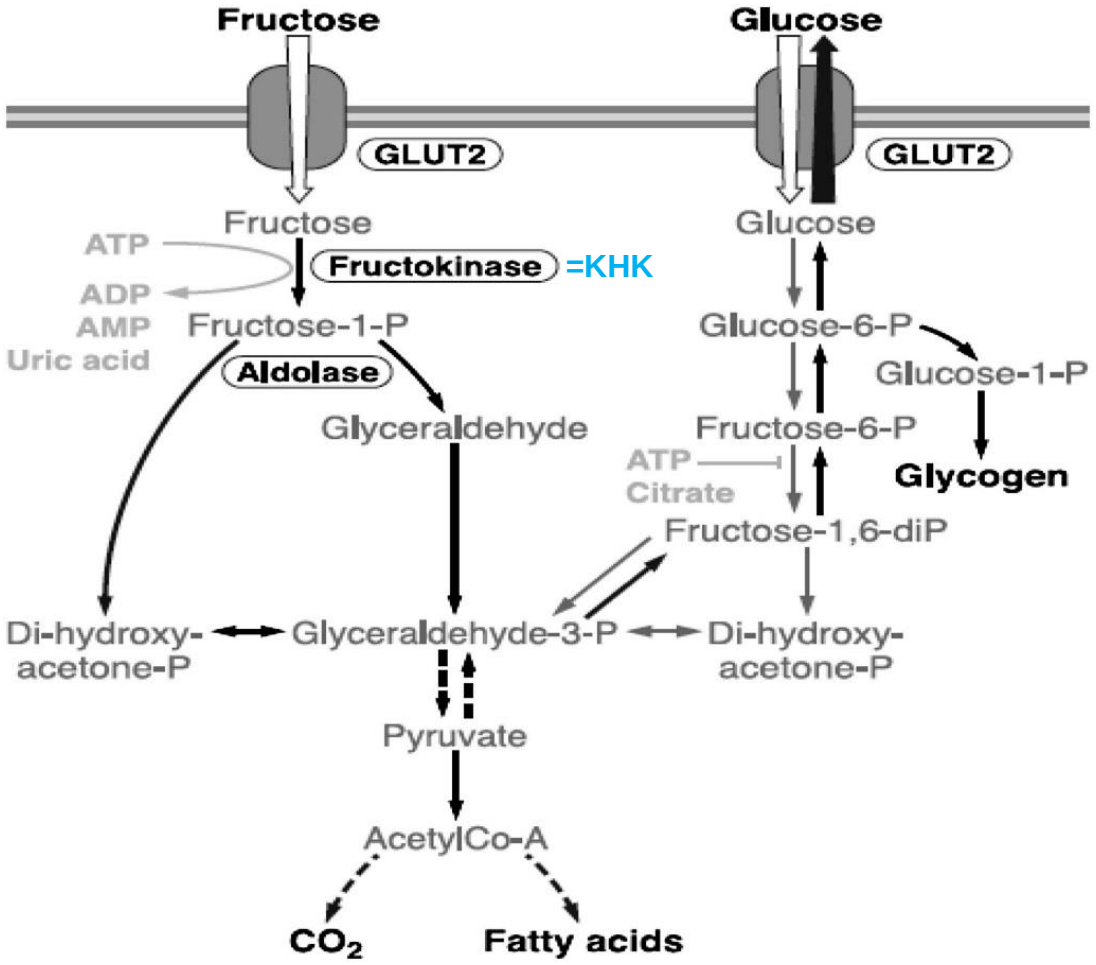


Hannou et al. JCI review, 2018

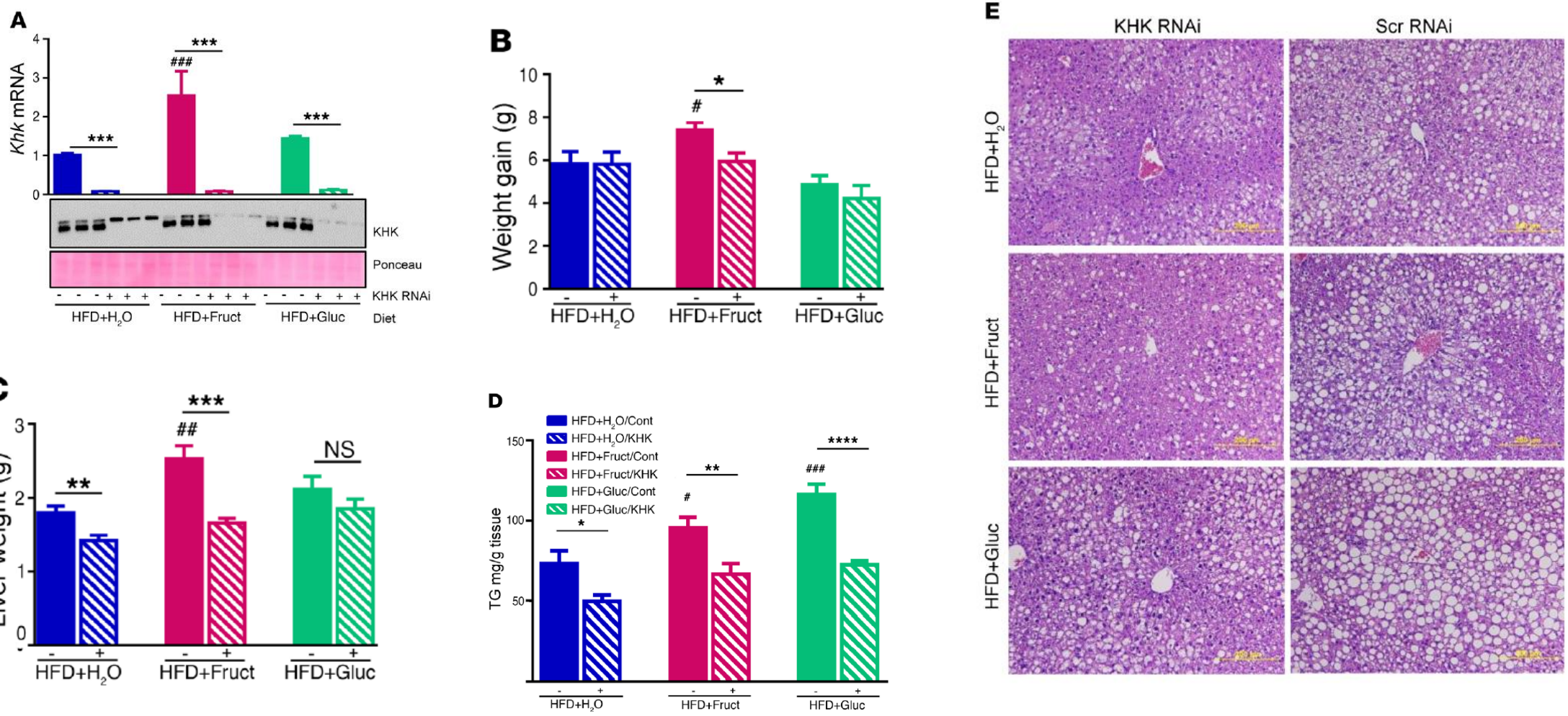
Ketohexokinase (KHK), a Target for Metabolic Syndrome and Type 2 Diabetes

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



KHK siRNA is Protective in High Fat-High Fructose Diet



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

Additional Opportunities from Liver-directed Investigational RNAi Therapeutics

Summary

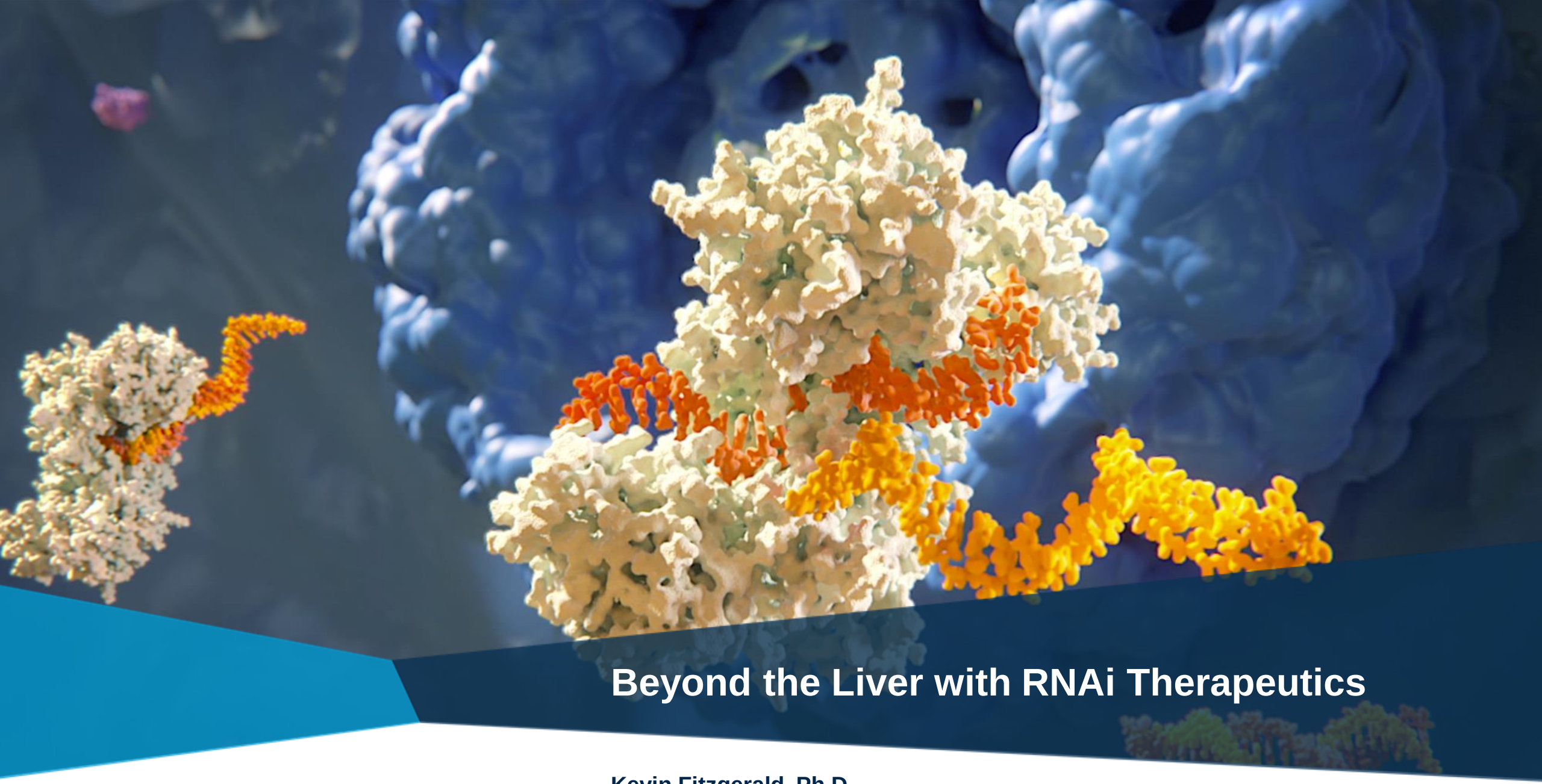
- Multiple attractive programs addressing areas of high unmet need
  - Lumasiran for recurrent renal stones
  - Cemdisiran for complement-mediated diseases
  - ALN-HBV (VIR-2218) for HBV infection
  - ALN-XDH for gout
  - ALN-KHK for metabolic syndrome and type 2 diabetes
- Reliance on genetically-validated 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

VOICES OF **PATIENTS & CAREGIVERS**

“My baby girl was on dialysis for about 15 hours a day for 2 years. She didn’t eat for the first 4 years of her life.”

Natalie, mother of three children diagnosed with PH1

Alnylam® PHARMACEUTICALS



Beyond the Liver with RNAi Therapeutics

Kevin Fitzgerald, Ph.D.
Chief Scientific Officer

Alnylam® PHARMACEUTICALS

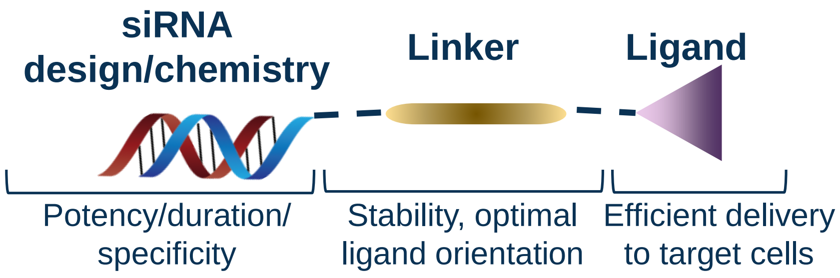
Alnylam Advancements in Conjugate-Based Delivery of siRNAs

siRNA Designs with Enhanced Potency and Stability May Extend to Extrahepatic Tissues

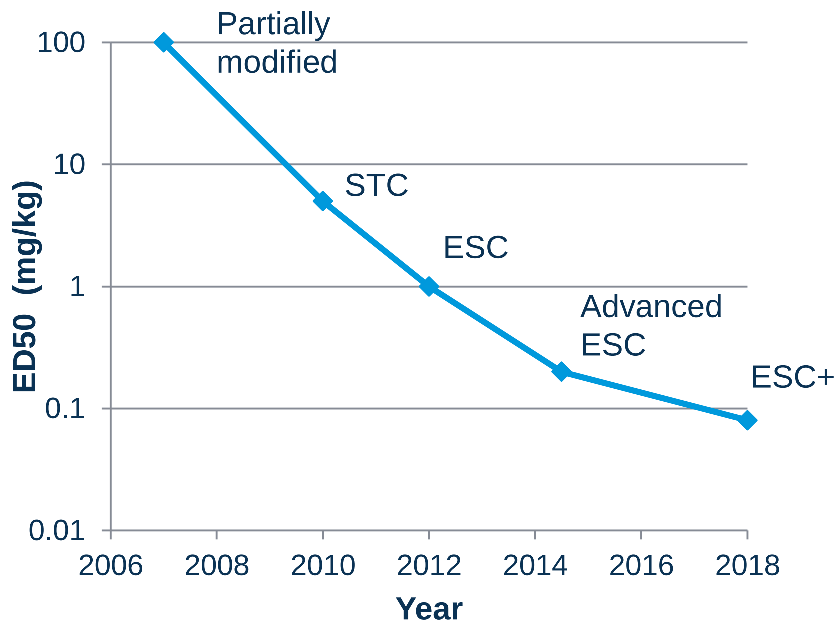
2004

2014

2018



Evolution of conjugate potency (mouse, SD ED_{50})



Over 20 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

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

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

CNS

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

EYE

Alnylam
- ALN-TTRoc

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

LUNG

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

RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent or Restore Neurodegenerative Disease

- Dominantly inherited neurodegenerative diseases include
  - Alzheimer's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal dementia
  - Huntington's disease
  - Parkinson's disease
  - Prion disease
  - Spinocerebellar ataxia
  - Many other orphan genetic diseases with CNS component

- Number of genetically validated targets known but no current disease modifying therapies for these devastating, life threatening disorders
- RNAi therapeutics directed to disease-causing, CNS-expressed genes represent next great frontier
- Based on pre-clinical studies, expect superior potency, duration and systemic safety profile vs. ASOs

RNAi Therapeutics for CNS Diseases

Platform Advantages to Address Unmet Needs

Wide biodistribution

Infrequent dosing

Validated safety

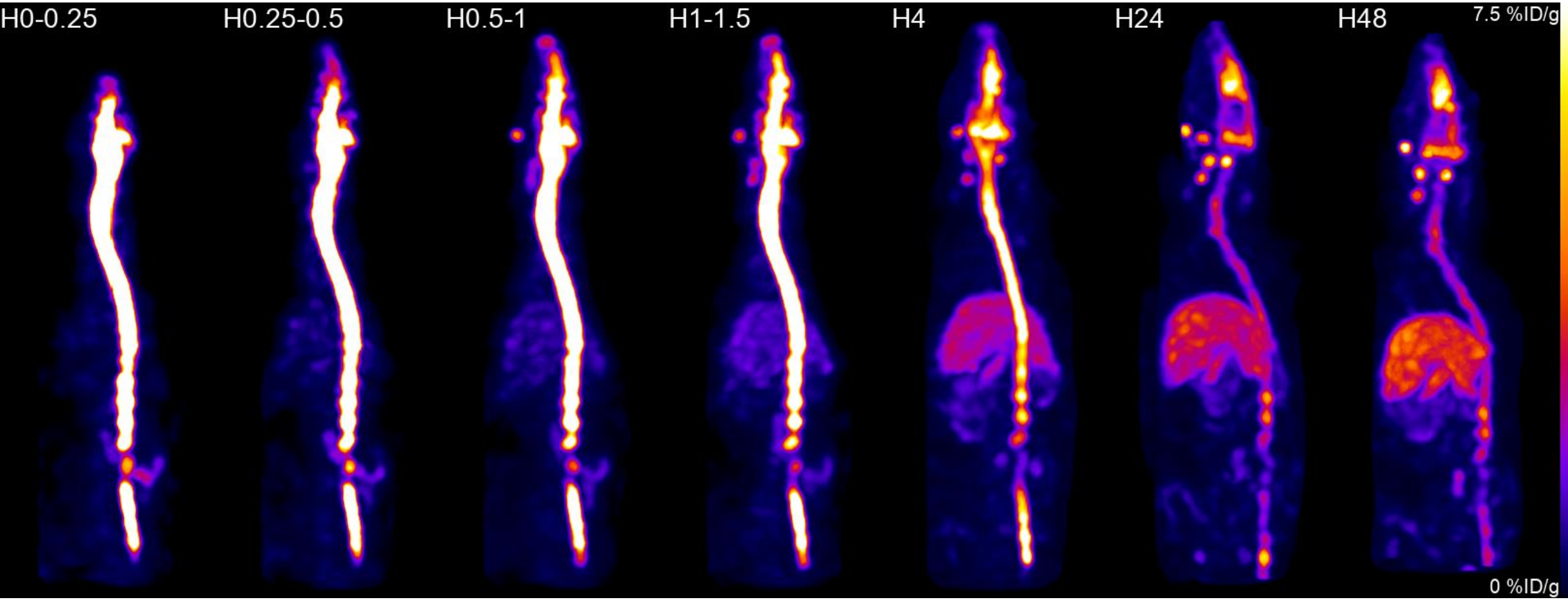
Broad range of cell types accessible

Dominantly inherited neurodegenerative diseases include

- Alzheimer's disease
- Amyotrophic lateral sclerosis (ALS)
- Frontotemporal dementia
- Huntington's disease
- Parkinson's disease
- Prion disease
- Spinocerebellar ataxia
- Many other orphan genetic diseases with CNS component

Wide Biodistribution of Novel siRNA Conjugates in CNS

Longitudinal SPECT Imaging (without CT)



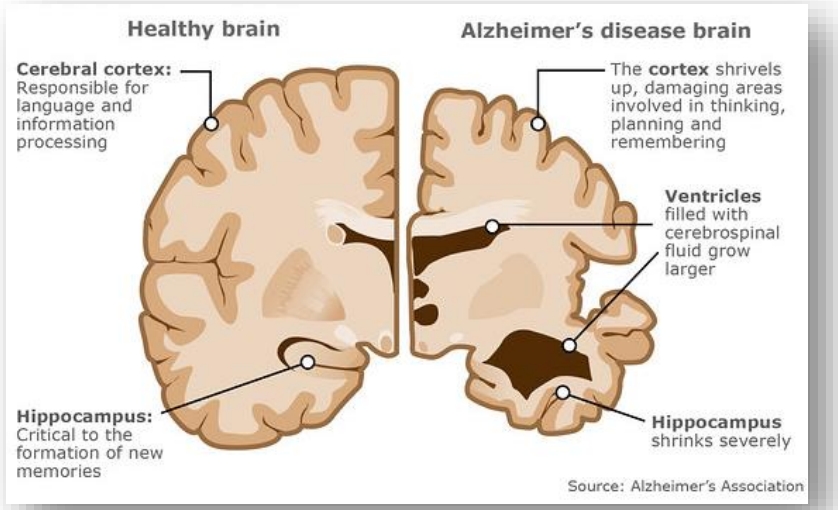
Conjugate ID 83: MIPs from 0-90 min dynamic SPECT and 30 min static SPECT at 4, 24 and 48 h post radio-tracer administration focusing on accumulation and retention at later timepoints.

SPECT: Single-photon emission computed tomography; MIP: Maximum intensity projection images

APP Targeting for Autosomal Dominant Alzheimer's Disease (ADAD)

ADAD

Patients develop rapidly progressive Alzheimer's-type dementia.



BURDEN

- ~50,000 affected globally.
- Mean age of onset 44 years with rapid progression over 6-8 years.

TARGET IDENTIFICATION

- All ADAD causative genes identified to date (*APP, PSEN1,* PSEN2) regulate APP protein metabolism by increasing production of amyloid products, including Aß42.
- Autosomal dominant, nearly 100% penetrant genetic syndrome.

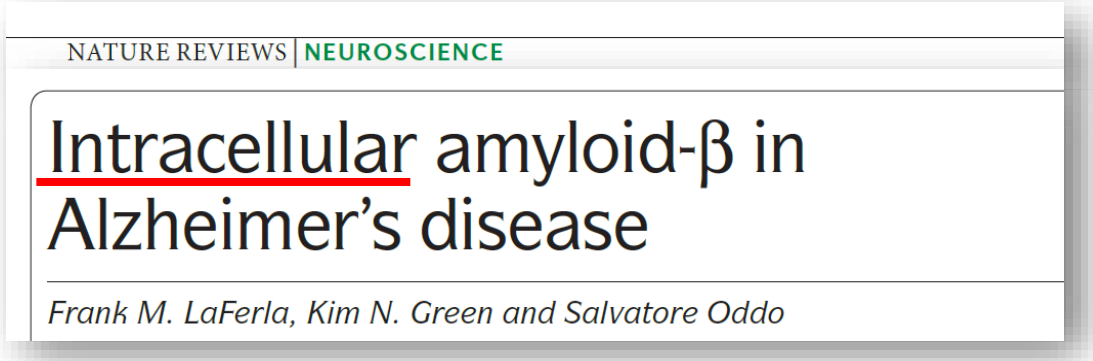
THERAPEUTIC HYPOTHESIS

- Aß42 is made in neurons and aggregates in the intracellular and extracellular brain parenchyma.
- RNAi-mediated knockdown of *APP* transcript in neurons will lower production of Aß42, halting aggregation and plaque formation.

OPPORTUNITY

- Application of Alnylam's CNS platform to reduce parenchymal *APP*-derived amyloid with no existing disease-modifying treatment.
- Potential for expansion into sporadic Alzheimer's disease.

What About the Role of INTRAcellular Aβ in Alzheimer's Pathogenesis?


NATURE REVIEWS | NEUROSCIENCE

Intracellular amyloid-β in Alzheimer's disease

Frank M. LaFerla, Kim N. Green and Salvatore Oddo


PNAS

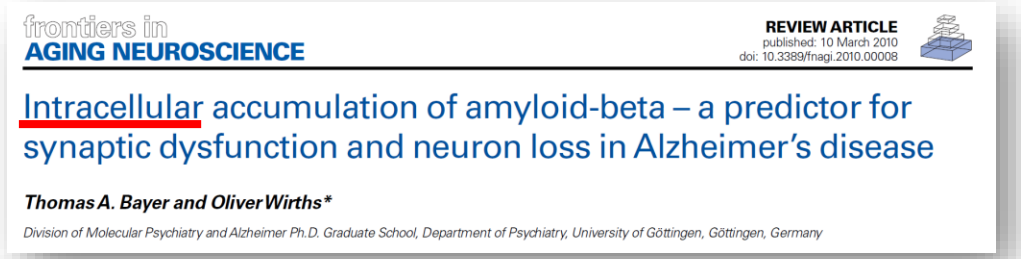
Mechanism of amyloid plaque formation suggests an intracellular basis of Aβ pathogenicity

Ralf P. Friedrich[a,1,3], Katharina Tepper[a,b,1], Raik Rönicke[c], Malle Soom[a], Martin Westermann[d], Klaus Reymann[c], Christoph Kaether[a], and Marcus Fändrich[a,b,e,2]


RESEARCH Open Access

Intracellular amyloid β oligomers impair organelle transport and induce dendritic spine loss in primary neurons

Tomohiro Umeda[1,2], Elisa M. Ramser[3], Minato Yamashita[1], Koichi Nakajima[4], Hiroshi Mori[2,5], Michael A. Silverman[3*] and Takami Tomiyama[1,2*]

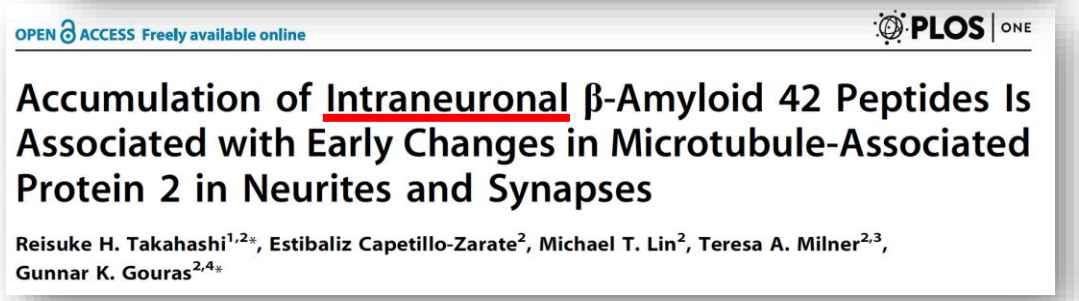

frontiers in AGING NEUROSCIENCE

REVIEW ARTICLE
published: 10 March 2010
doi: 10.3389/fnagi.2010.00008

Intracellular accumulation of amyloid-beta – a predictor for synaptic dysfunction and neuron loss in Alzheimer's disease

*Thomas A. Bayer and Oliver Wirths**

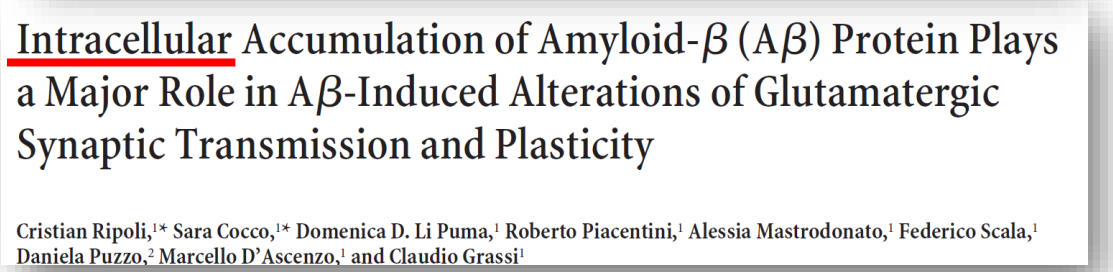
Division of Molecular Psychiatry and Alzheimer Ph.D. Graduate School, Department of Psychiatry, University of Göttingen, Göttingen, Germany


OPEN ACCESS Freely available online

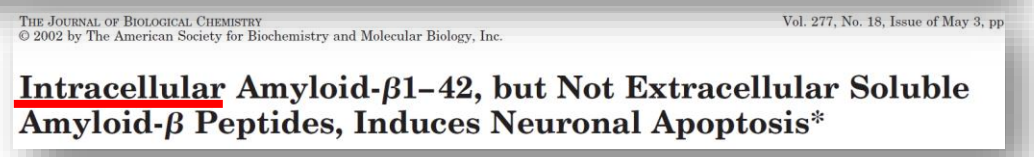
PLOS ONE

Accumulation of Intraneuronal β-Amyloid 42 Peptides Is Associated with Early Changes in Microtubule-Associated Protein 2 in Neurites and Synapses

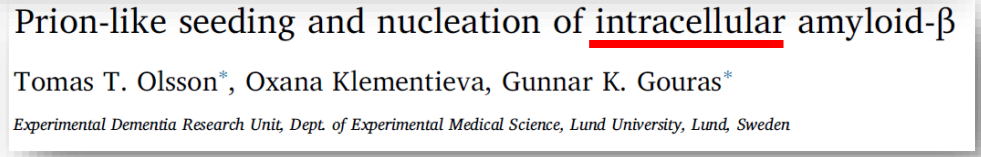
Reisuke H. Takahashi[1,2]*, Estibaliz Capetillo-Zarate[2], Michael T. Lin[2], Teresa A. Milner[2,3], Gunnar K. Gouras[2,4]*


Intracellular Accumulation of Amyloid-β (Aβ) Protein Plays a Major Role in Aβ-Induced Alterations of Glutamatergic Synaptic Transmission and Plasticity

Cristian Ripoli,[1]* Sara Cocco,[1]* Domenica D. Li Puma,[1] Roberto Piacentini,[1] Alessia Mastrodonato,[1] Federico Scala,[1] Daniela Puzzo,[2] Marcello D'Ascenzo,[1] and Claudio Grassi[1]


THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 277, No. 18, Issue of May 3, pp
© 2002 by The American Society for Biochemistry and Molecular Biology, Inc.

Intracellular Amyloid-β1–42, but Not Extracellular Soluble Amyloid-β Peptides, Induces Neuronal Apoptosis*


Prion-like seeding and nucleation of intracellular amyloid-β

Tomas T. Olsson*, Oxana Klementieva, Gunnar K. Gouras*

Experimental Dementia Research Unit, Dept. of Experimental Medical Science, Lund University, Lund, Sweden

1. LaFerla, et al. Nat Rev Neurosci 8, 499–509 (2007)
2. Bayer et al. Front Aging Neurosci. 2010
3. Ripoli et al Neurobioilogy of Disease 2014
4. Umeda et al. Acta Neuropathologica Communications (2015)
5. Friedrich et al PNAS 2010
6. Kienlen-Campard et al 2002
7. Olsson et al. Neurobiology of disease 2018
8. Takahashi et al. PLOS One 2013

Pathological Effects of Intraneuronal Aβ

ALN-APP Mechanism Lowers all APP Species Intra/Extracellular

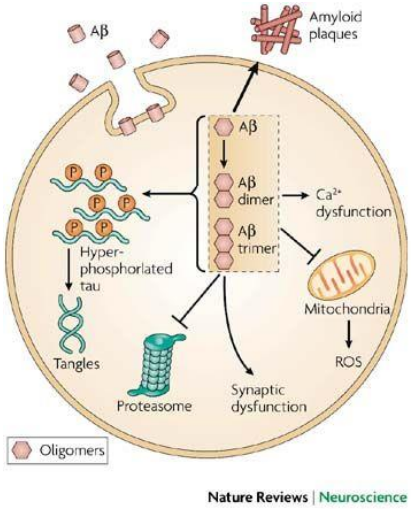
Intracellular Aβ contributes to pathology by causing:

- tau hyperphosphorylation
- proteasome dysfunction
- mitochondrial dysfunction
- calcium dysfunction
- synaptic dysfunction

Aβ can exist in at least 5 assembly states

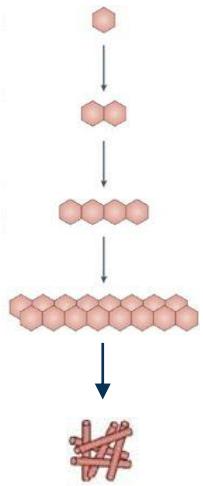
- monomers
- oligomers
- protofibrils
- fibrils
- plaques

It remains unclear which of the Aβ assembly states contributes to disease pathogenesis.



Nature Reviews | Neuroscience

Antibodies only reduce extracellular Aβ, while ALN-APP reduces intra-neuronal Aβ thought to contribute to pathogenesis.

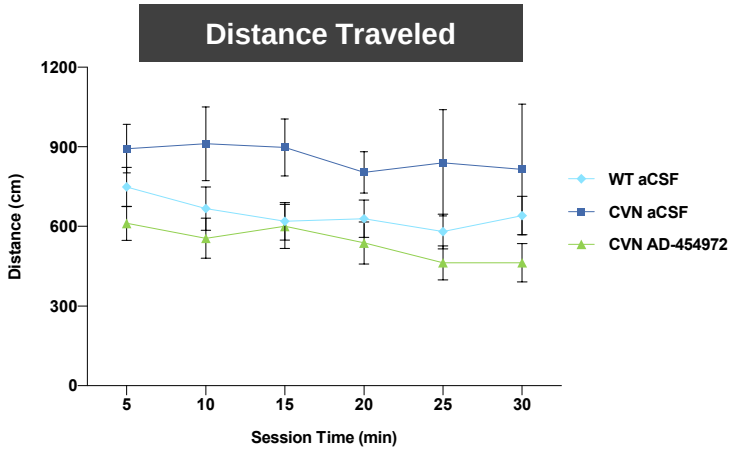


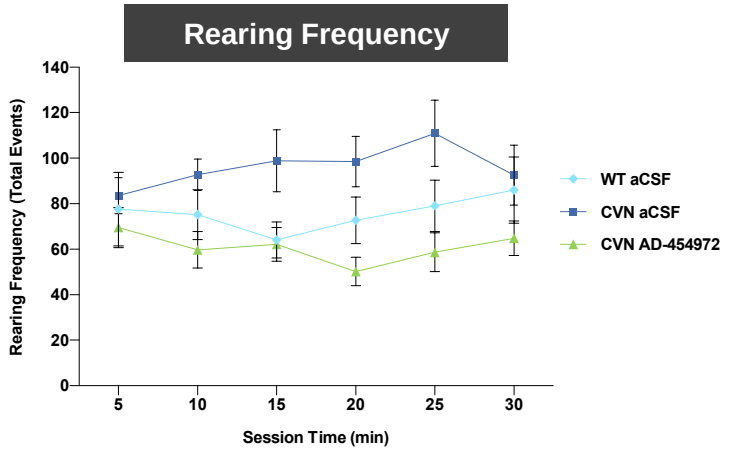
Antibodies only bind one or few Aβ conformations, while ALN-APP predicted to lower all Aβ assembly species.

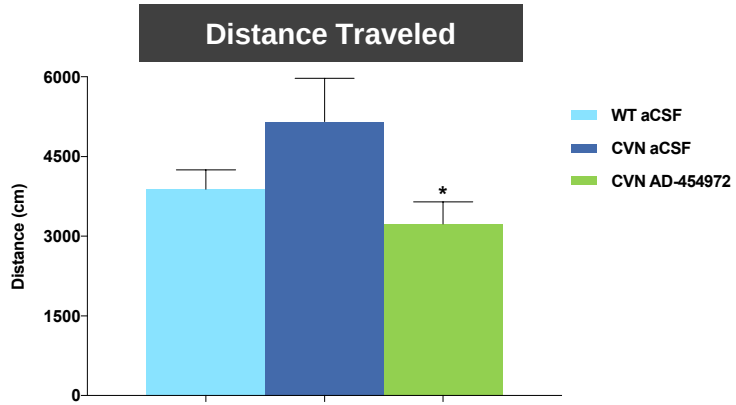
LaFerla et al. Nat. Reviews Neurosci

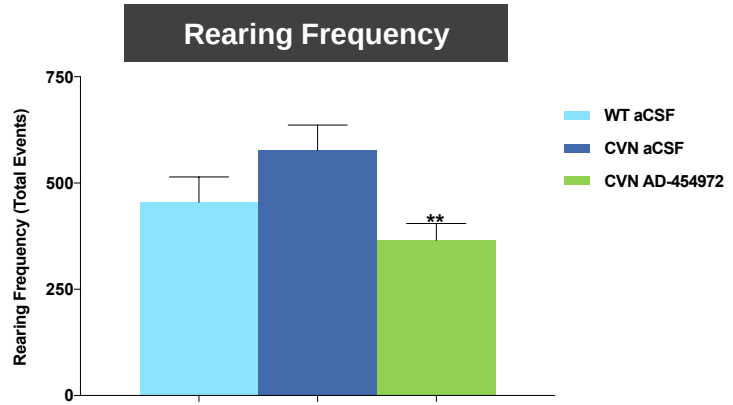
Silencing of Human APP Showed Reduced Anxiety in Open Field Test

Phenotypic Analysis of APP siRNA Treated CVN Mice Following Disease Onset







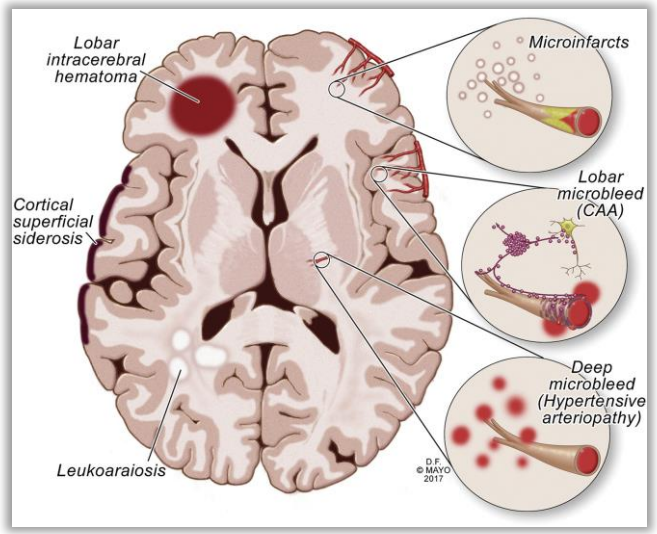


- Disease onset occurs at 4 months of age.
- Single ICV treatment at 6 months.
- Phenotypic observations were taken at 9 months of age.
- Statistically significant reduction in anxiety observed in treated animals in open field test.

APP Targeting for Cerebral Amyloid Angiopathy (CAA)

hCAA

Patients present with stroke-like presentation (intracerebral hemorrhage).



BURDEN

- 100% of affected individuals share a common ancestor from the Netherlands.
- Mean age of onset 54 years.

TARGET IDENTIFICATION

- Missense substitution in *APP* (p.Glu693Gln) increases production of Aß40 and causes 100% of known cases of Dutch-type cerebral amyloid angiopathy.
- Autosomal dominant, 100% penetrant genetic syndrome.

THERAPEUTIC HYPOTHESIS

- Aß40 is made in neurons but then undergoes extracellular transit before deposition in the perivascular space.
- RNAi-mediated knockdown of *APP* transcript in neurons will lower production of Aß40, halting toxic protein build-up.

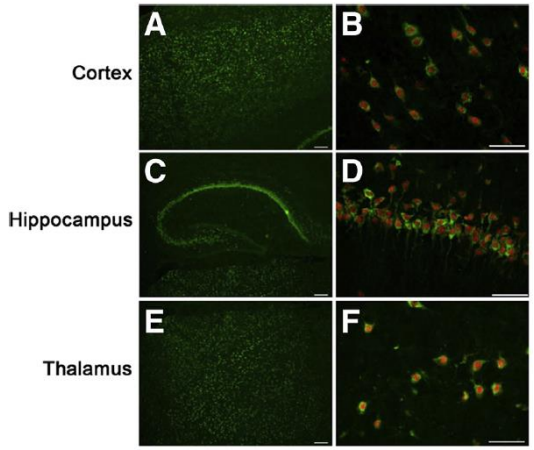
OPPORTUNITY

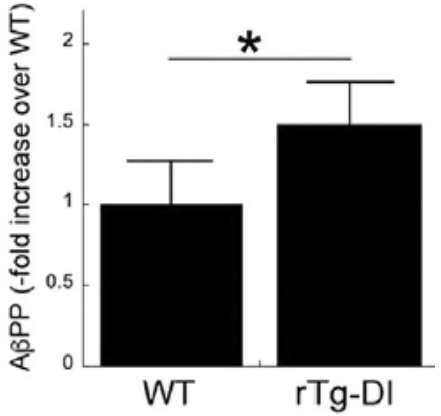
- Application of Alnylam's CNS platform to reduce perivascular *APP*-derived amyloid with no existing disease-modifying treatment.
- Expansion into sporadic CAA, a very common age-related cause of hemorrhagic stroke.

Model for Cerebral Amyloid Angiopathy (CAA)

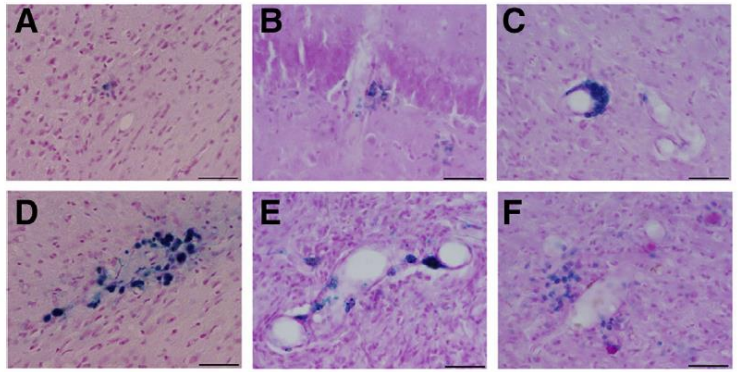
rTg-DI Rat Model – APP[1]

Human APP Expression

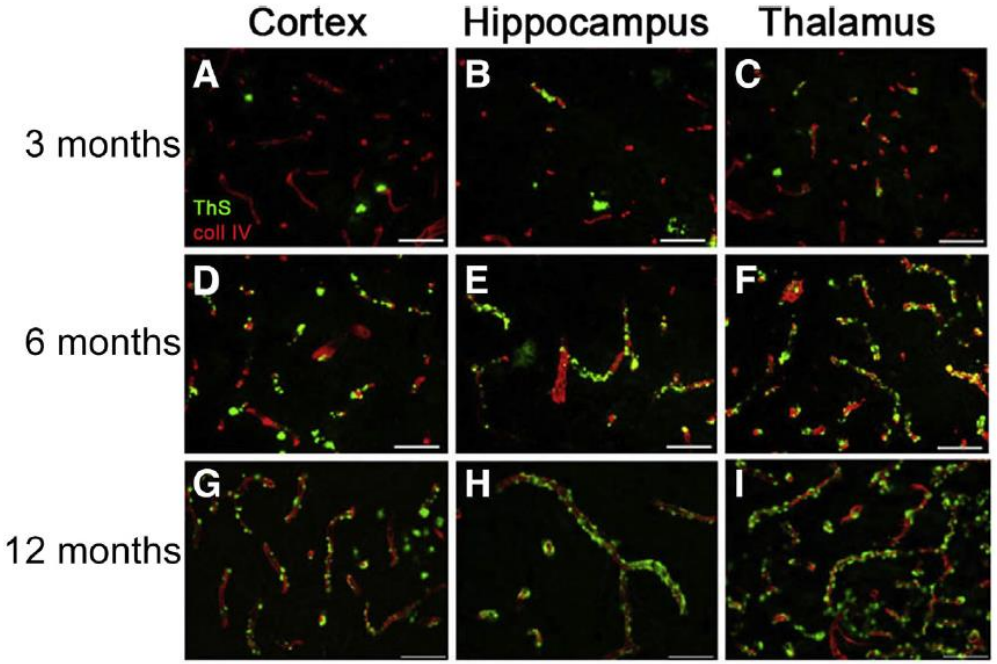




Microhemorrhages in Cortex, Hippocampus and Thalamus



Progressive Accumulation of Microvascular Amyloid[2]



Davis et al (2018) The American Journal of Pathology, Vol. 188, No. 12

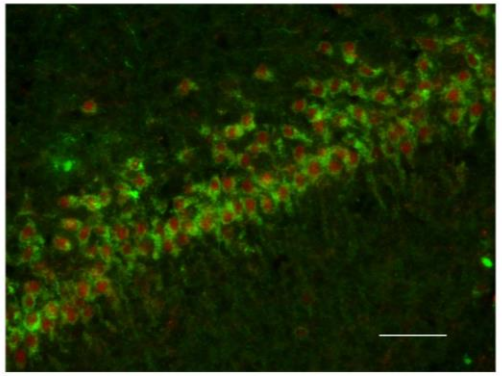
[1] Swedish K670N/M671L, Dutch E693Q, and Iowa D694N

[2] Van Nostrand lab, URI

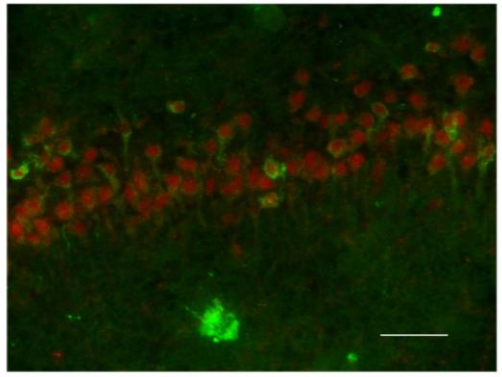
Complete Elimination of Human APP Protein in Rat hCAA Model

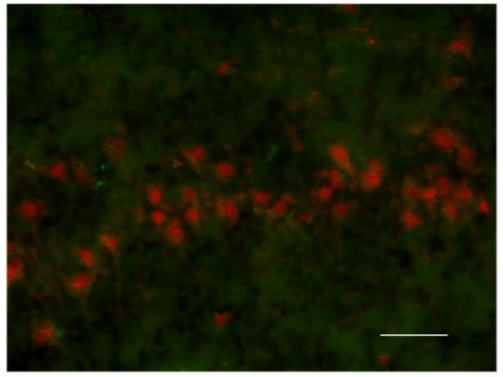
Single IT Dose of 0.9 mg in rTg-DI Rat – Day 28 in Hippocampus

ACSF-CTRL



siRNA Treatment





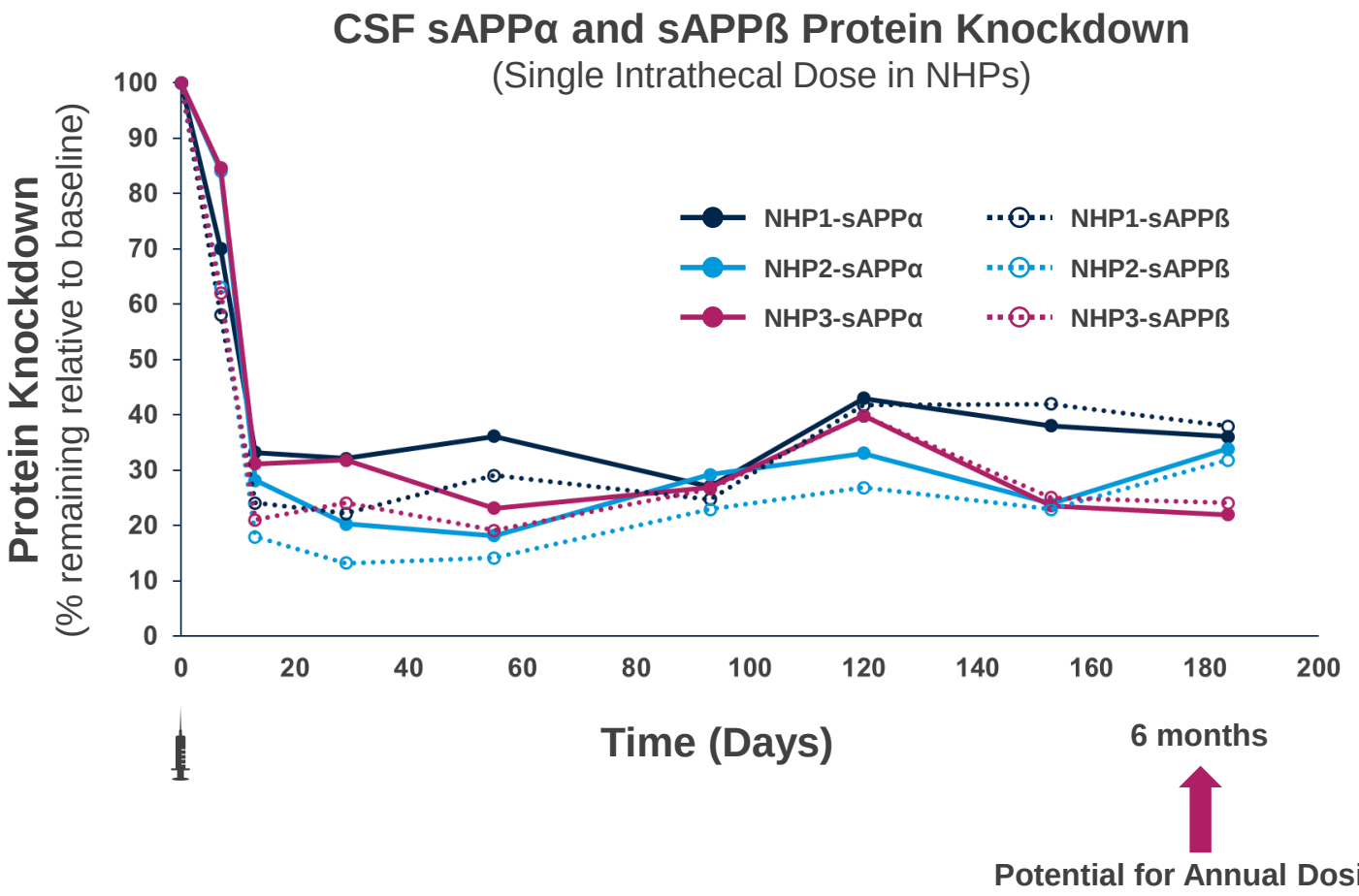
Detection Antibodies

- NeuN (red)
- hAPP (green)

Van Nostrand lab, URI

APP Program Status

ALN-APP: 2021 CTA Program



ALN-APP

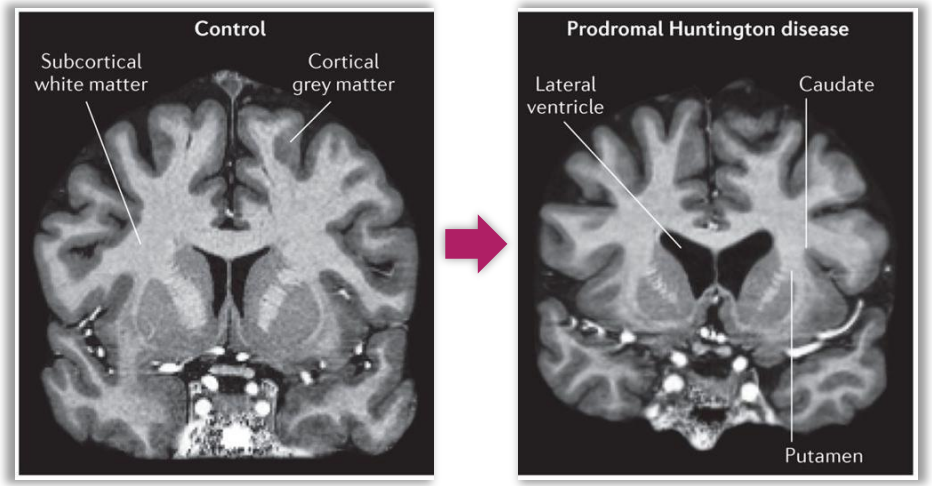
ONGOING WORK & EXPECTED TIMELINES

- DC selected
- Regeneron opted-in
- CTA filing in mid-2021
- Potential POC data 2022

HTT Targeting for Early Manifest Huntington's Disease

HTT

Patients present with progressive motor, cognitive and psychiatric decline.



BURDEN

- Affecting ~30,000 in U.S. with disease duration of 15-20 years.

TARGET IDENTIFICATION

- Autosomal dominant, gain-of-function genetic disease.
- 100% age-related penetrance.
- Trinucleotide repeat expansion in exon 1 of the huntington gene (*HTT*).

THERAPEUTIC HYPOTHESIS

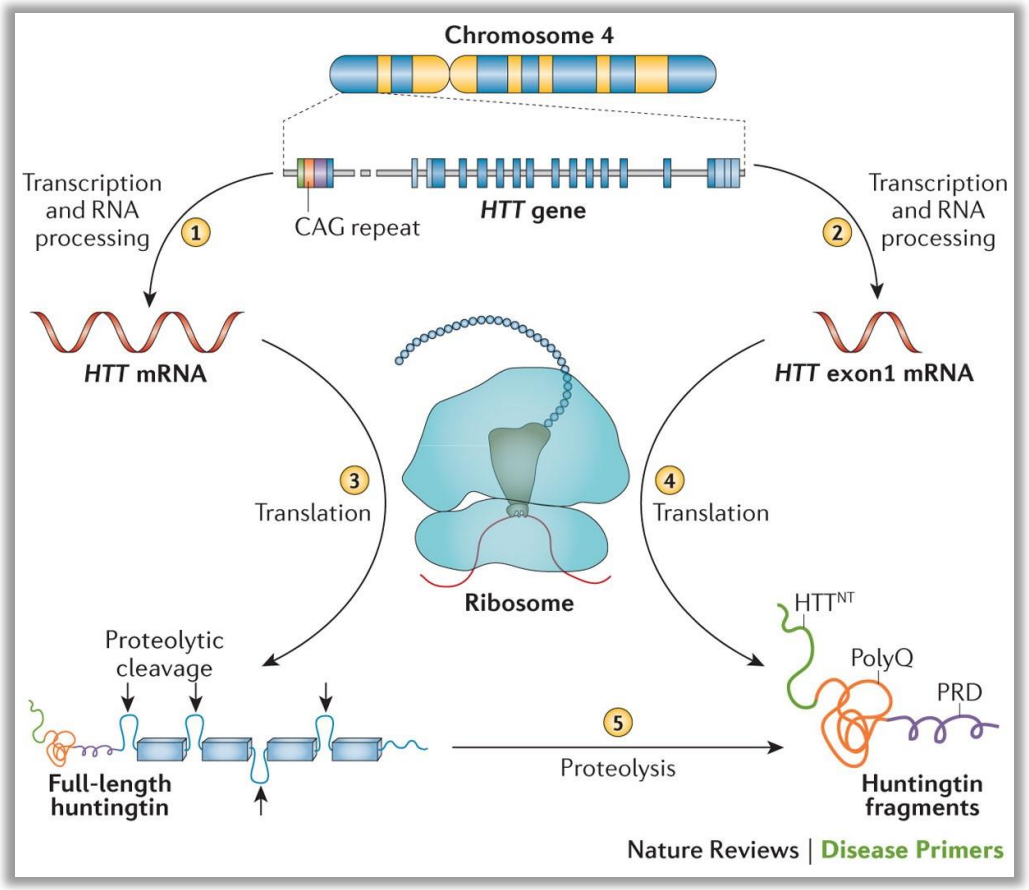
- RNAi-mediated knockdown of *HTT* transcript in neurons will reduce both RNA-induced and protein-induced neuronal toxicity, halting disease progression.

OPPORTUNITY

- Application of Alnylam's CNS platform to develop a therapeutic for a devastating progressive neurodegenerative condition.
- Potential differentiation over competition via exon 1 targeting strategy, targeting a pathogenic isoform that contributes to disease progression.

HTT Program Status

ALN-HTT: Advanced Preclinical Program



ALN-HTT

ONGOING WORK & POTENTIAL TIMELINES

- Finalize DC selection
- Advance toward IND

Tabrizi, S. J. et al. (2015) Huntington disease. Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.5

Over 20 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

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

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

CNS

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

EYE

Alnylam
- ALN-TTRoc

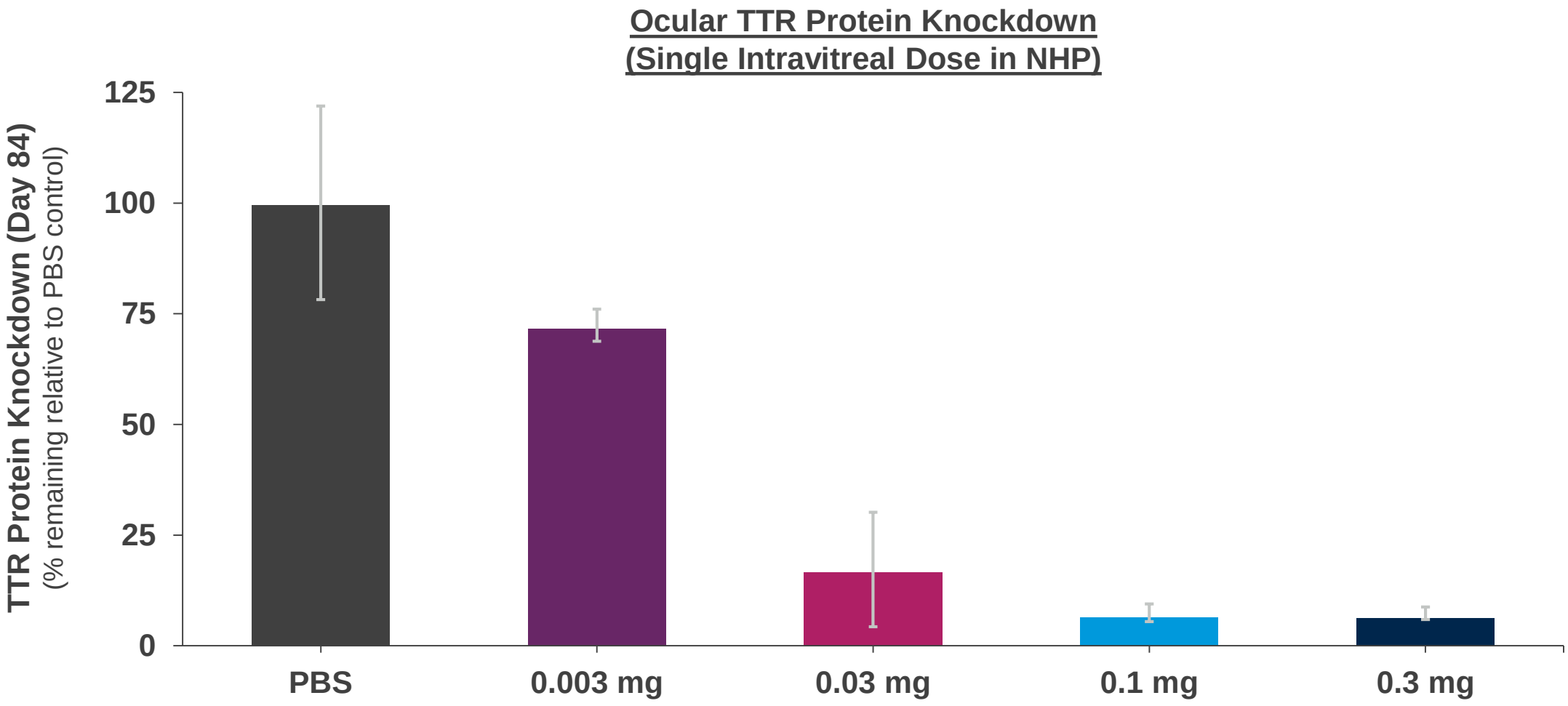
Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

LUNG

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

Ocular Program Update

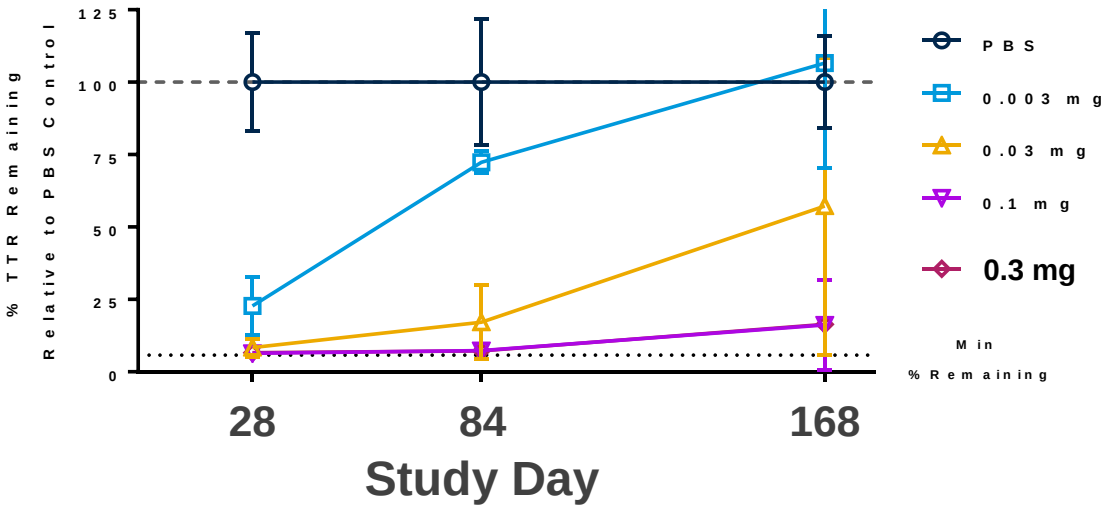
NHP Potency with Potential for Infrequent Dosing with Low ug Doses per Eye



Potent, Dose Dependent, Durable Activity After Single IVT Dosing in NHP Eye

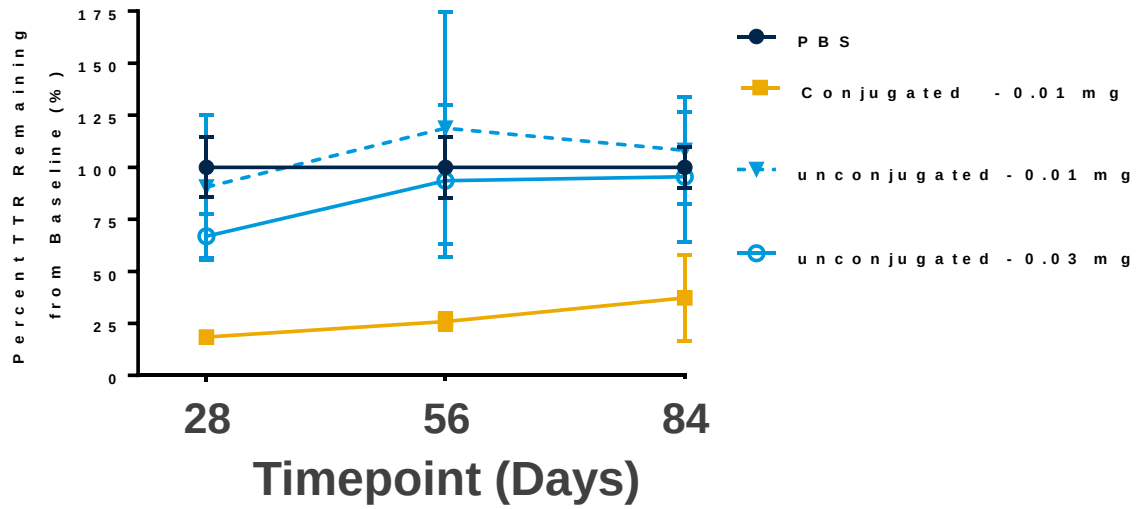
Durability Data Support q6M Dose Regimens

TTR Protein in Aqueous Humor



- Dose-dependent efficacy and duration up to 0.003 mg
- Persistent low siRNA levels in aqueous humor in line with observed duration

Conjugated vs. Unconjugated



- Unconjugated siRNA showed reduced potency; also reflected in reduced exposure in vitreous (~10-fold lower)

Over 20 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

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

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

CNS

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

EYE

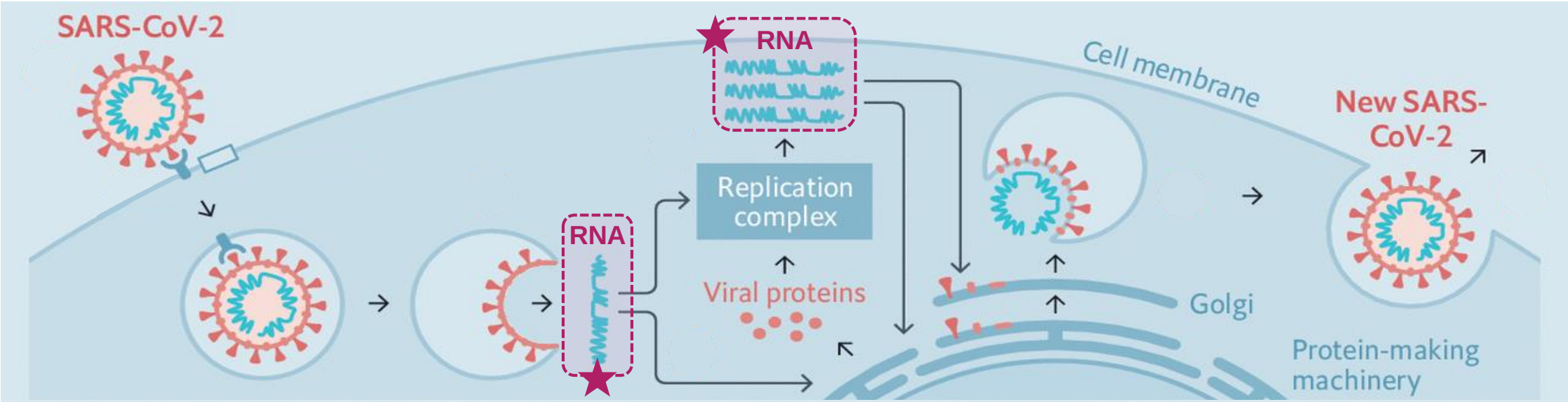
Alnylam
- ALN-TTRoc

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

LUNG

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

ALN-COV, an Investigational RNAi Therapeutic for COVID-19



Provides a unique and distinct antiviral strategy for the treatment of COVID-19

- RNAi mechanism of action results in degradation of SARS-CoV-2 viral RNA genome

Direct administration of ALN-COV to lungs, the key site of viral replication and disease manifestations

- Early delivery of a potent antiviral agent directly to the site of replication has the potential to prevent progression to severe pulmonary disease and decrease time to clinical recovery

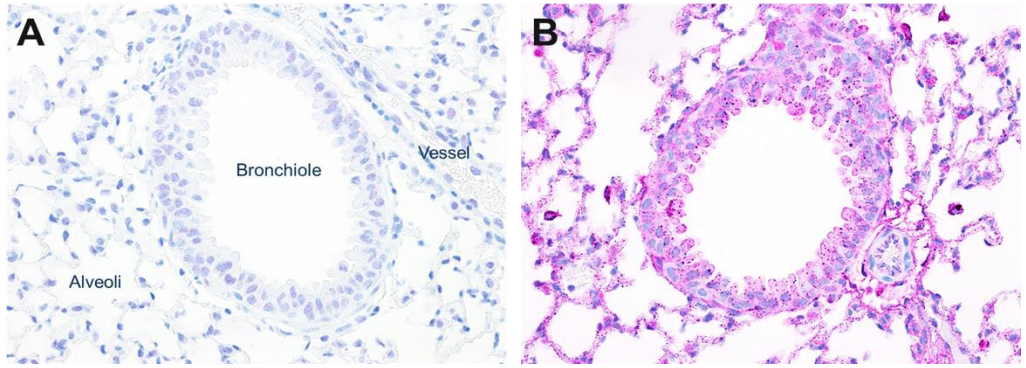
Initial development plan focused on the treatment of patients with mild to moderate COVID-19

- Potential for development in targeted prophylactic setting

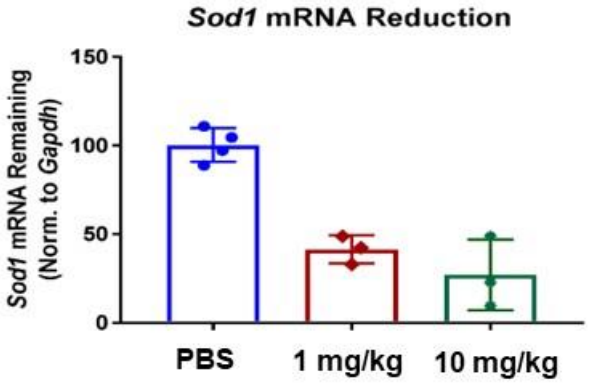
Chemistry Advances Enable Robust Tissue Distribution with Potent and Durable Gene Knockdown in Lung

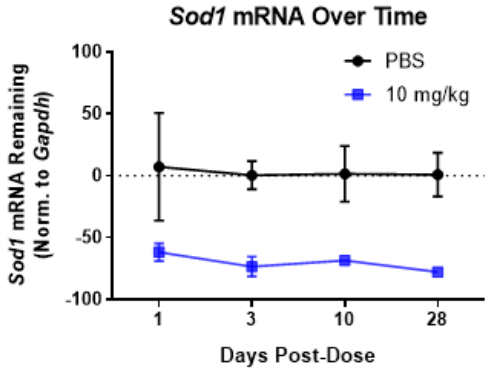
Surrogate siRNA Targeting Endogenous Target (Sod1) and Ectopic Target (ACE2)

Sod1 siRNA Distribution in the Mouse Lung Measured by IHC

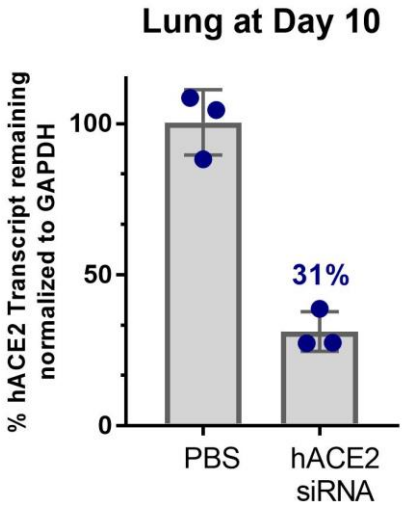


(**A**) PBS-treated animal on Day 10 post dose. (**B**) 10 mg/kg *Sod1* siRNA on Day 10 post dose. siRNA is magenta. Blue is hematoxylin counterstain.





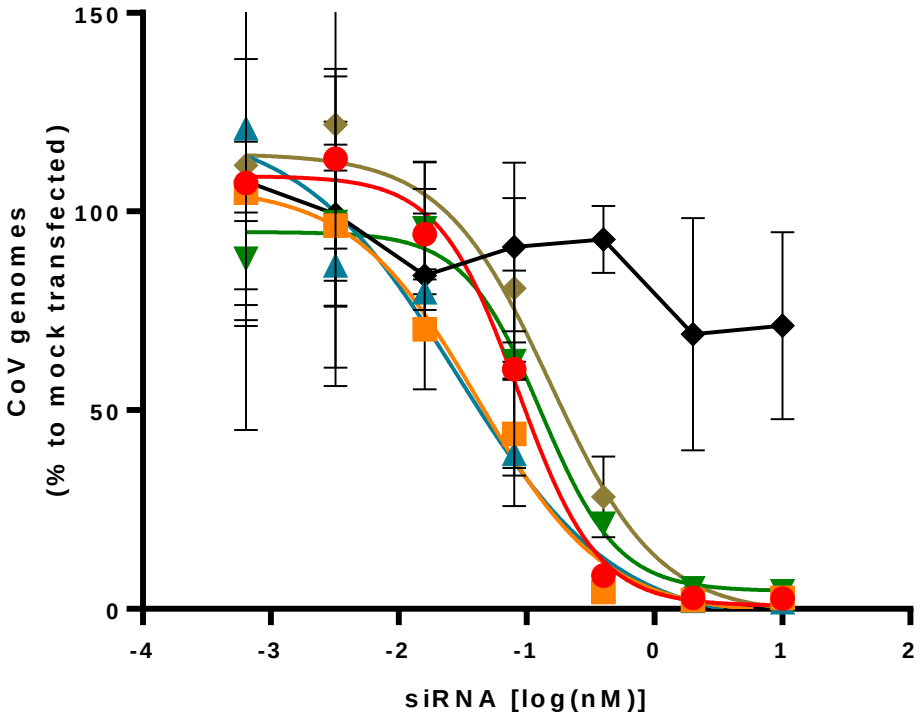
hACE2 mRNA Reduction in Lung Following a Single 10mg/kg Dose



ALN-COV Comprises Two siRNAs from Top 5 Candidates

Two siRNAs Utilized to Mitigate Risk of Viral Escape

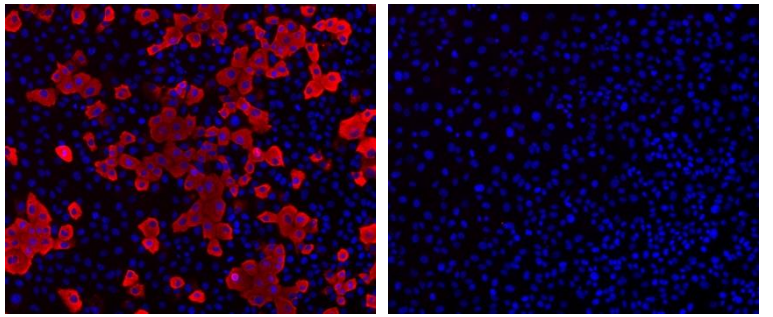
Top 5 Candidates (qPCR)



IFA

SARS-CoV-2 nucleocapsid protein (red stain)

Control siRNA (10 nM) siRNA 1 (10 nM)



siRNA	EC_{50} EC_{95} (pM; PCR)	EC_{50} EC_{95} (pM; IFA)	Genome Reactivity* (0 mm)	Genome Reactivity* (1 mm)
siRNA 1	42 1183	66 763	99.91%	100.00%
siRNA 2	86 702	118 608	99.89%	99.98%

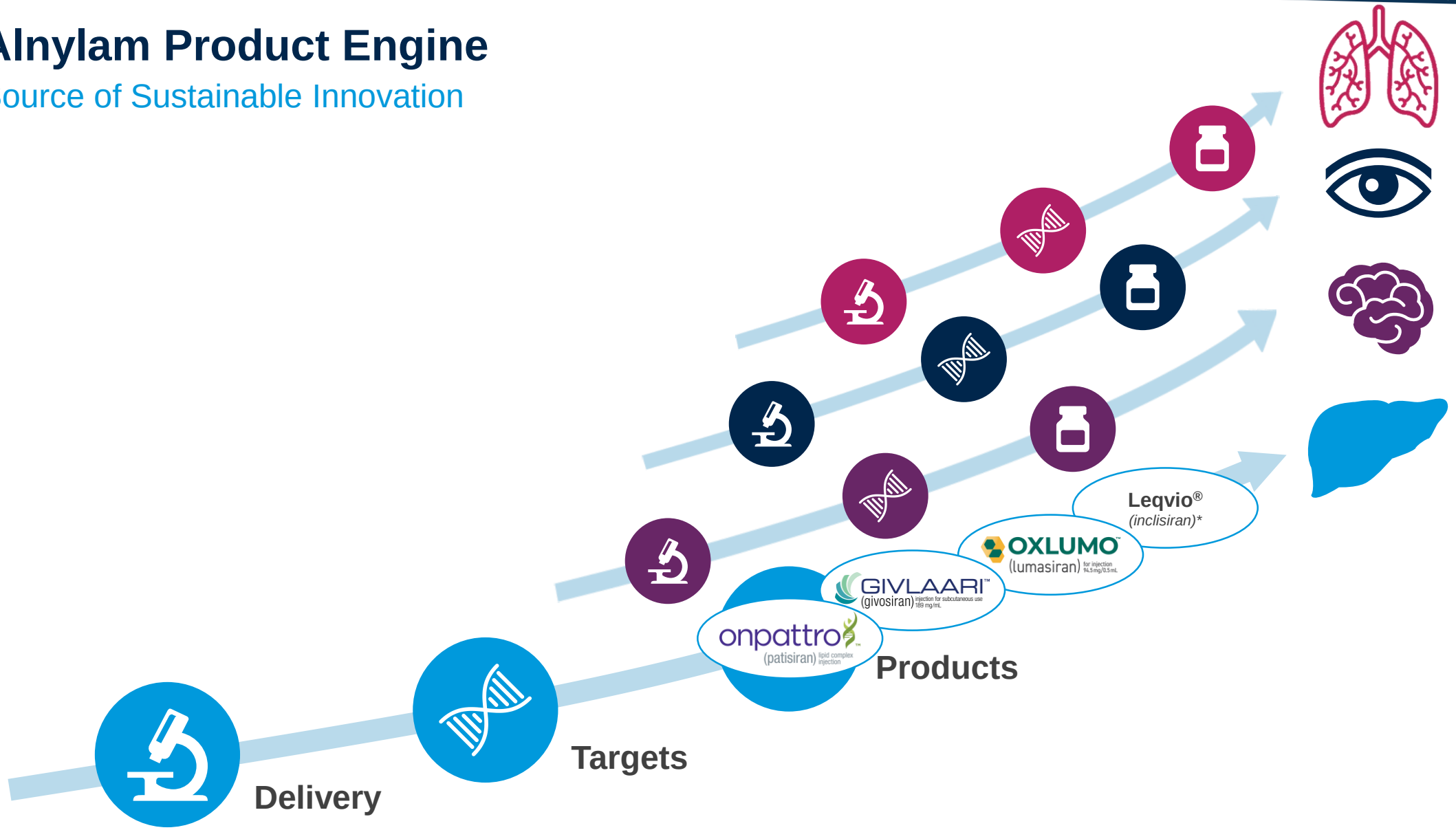
*N=4386 genomes analyzed

Lung Targets from Human Genetics

Gene	Indication	Human Genetics Support	Location and Cell Type
Target 1	Asthma	✓	Epithelium
Target 2	Asthma	✓	Epithelium
Target 3	Idiopathic pulmonary fibrosis	✓	Epithelium
Target 4	Nasal polyps	✓	Epithelium, immune cells
Target 5	COPD	Preliminary	Epithelium

Alnylam Product Engine

Source of Sustainable Innovation



* Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics

VOICES OF **PATIENTS & CAREGIVERS**

“The day after my mother’s funeral, my doctor confirmed that my last electromyogram and rectal biopsy were positive for hATTR. I arrived home and told my father, “Papa, Mum has gone, but the disease hasn’t. I’m not a caregiver anymore—now I have become the patient.”

Catilena, living with hATTR

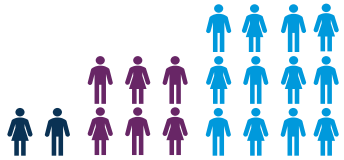
Alnylam® PHARMACEUTICALS

Transitioning to a Self-Sustainable Financial Profile

Jeff Poulton
Chief Financial Officer

Alnylam PHARMACEUTICALS

Key Drivers – Alnylam 2021 and Beyond



Robust commercial platform fundamental to near-term opportunity in rare indications, with leverageable capabilities supportive of transition to larger market indications

Sustainable R&D innovation and platform advances fuel value creation through organic means

Financial sustainability critical to building top biotech…

Commitment to Financial Self-Sustainability

Becoming a Profitable, Self-Sustainable Company Remains a Top Alnylam Priority

Path to profitability continues to be dictated by two key levers

- **Topline growth**
  - Rapid succession of product launches creates potential for significant near-term revenue growth
  - Potential for meaningful royalty revenue from partnered assets in large and orphan indications
  - Collaboration revenues from strategic partnerships
  - Deep mid and early-stage pipeline fuels long-term growth for years to come
- **Disciplined investment**
  - Continued investment in proven, organic R&D platform to drive long-term topline growth
  - Strategic investment in large indication late-stage programs and promising mid-stage assets with significant upside potential
  - Continue to leverage partnerships, driving R&D innovation while sharing in costs & risk
  - Disciplined SG&A investment, leveraging ONPATTRO® (patisiran) global commercial infrastructure to support future launches

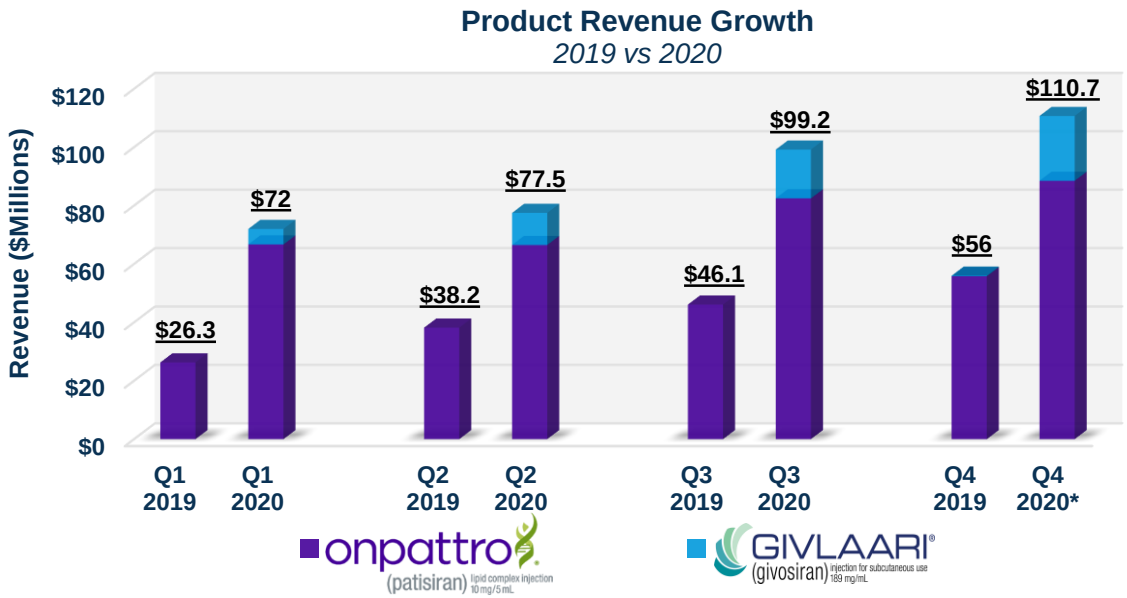
Alnylam is on a path to self-sustainability

- **Anticipate 2019 was our peak non-GAAP operating loss year**

Topline Growth – Progress Over Last 12 Months

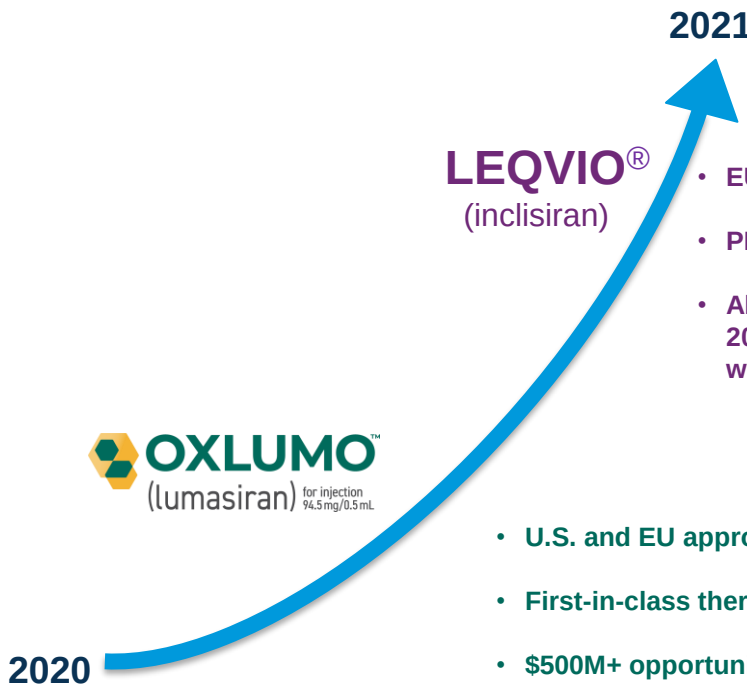
Advancing Toward Profitability Through Commercial Excellence and New Product Launches

Previously Launched Products



Geographic Expansion across EU, LATAM, Asia

New Revenue Sources



LEQVIO® (inclisiran)

- EU approval – December 2020
- PDUFA action date – December 2020
- Alnylam entitled to royalties of up to 20% on global sales (shared 50% with Blackstone)

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

- U.S. and EU approval – November 2020
- First-in-class therapeutic
- $500M+ opportunity in PH1
- Potential expansion into recurrent renal stones could broaden future opportunity

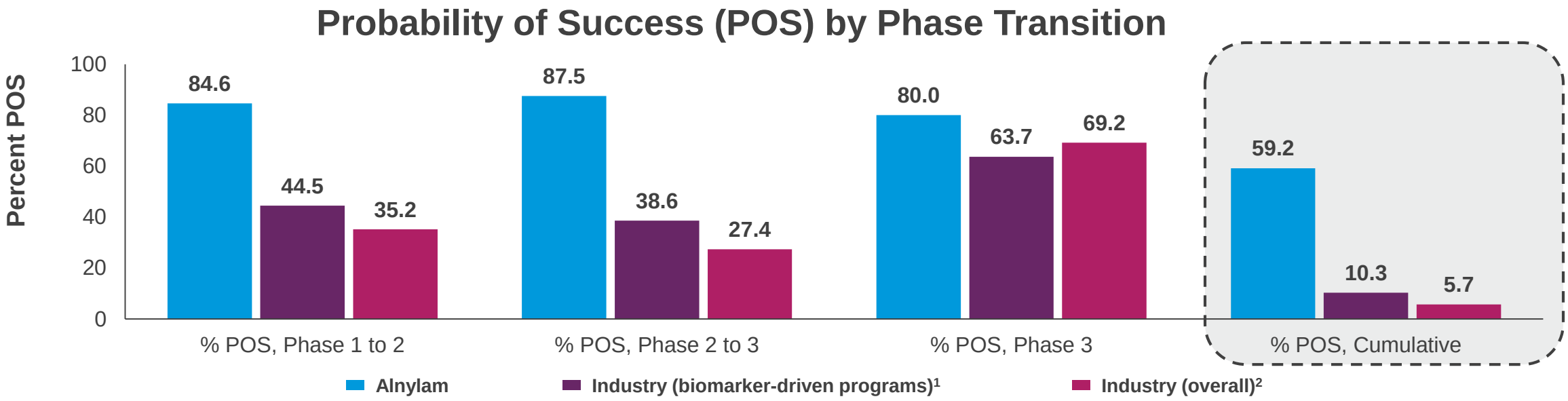
*Q4 2020 product revenue based on consensus estimates. All consensus estimates current as of December 8, 2020.

Disciplined Investment – Progress Over Last 12 Months

Supporting Near and Long-Term Topline Growth with Investment in Organic Pipeline Engine

R&D investment fuels sustainable long-term growth

- Revenue growth from potential 'second wave' of approved RNAi therapeutics to come from current R&D spend
  - Better than industry average probability of success underpins increasing platform investment
  - Advancing programs in large indications including hypertension, hepatitis B, and NASH
  - Expanding beyond the liver into ocular and CNS targets via collaboration with Regeneron
  - Ramping up late-stage investment entering 2021 to support TTR franchise expansion opportunity



Past rates of Alnylam and industry respectively may not be predictive of the future

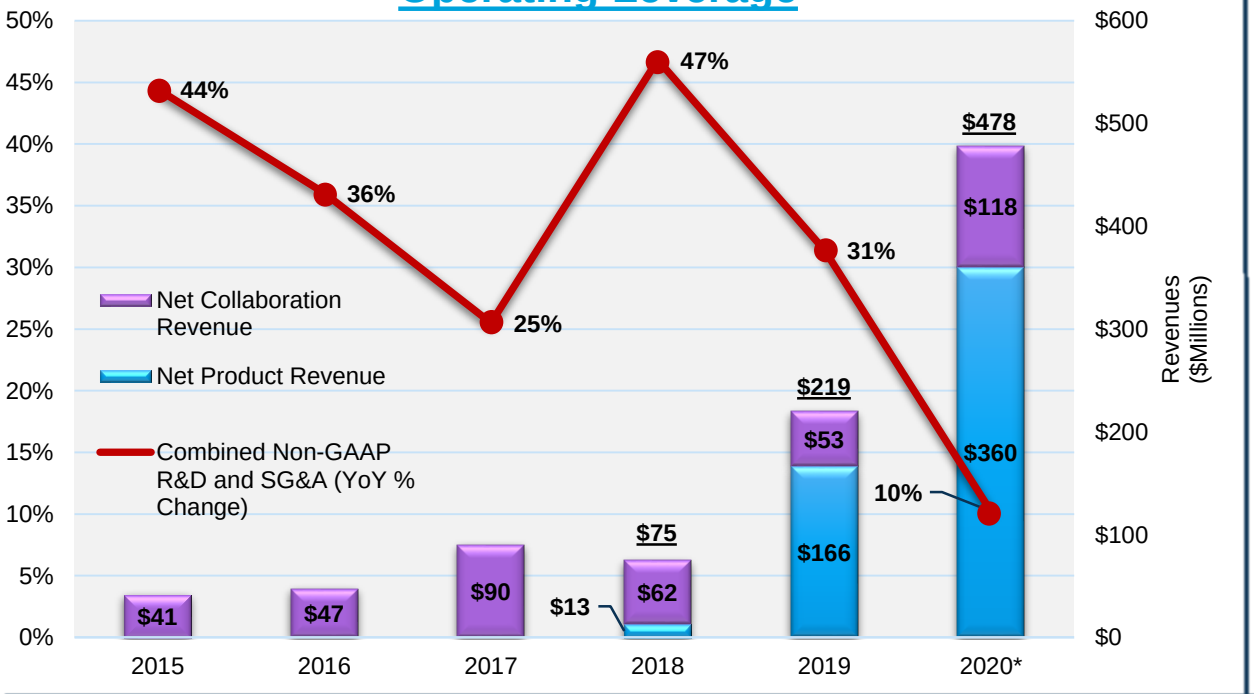
[1] Alnylam programs biomarker-driven at all stages of development (100%); figures include ALNY-originated molecules now being developed by partners

[2] Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

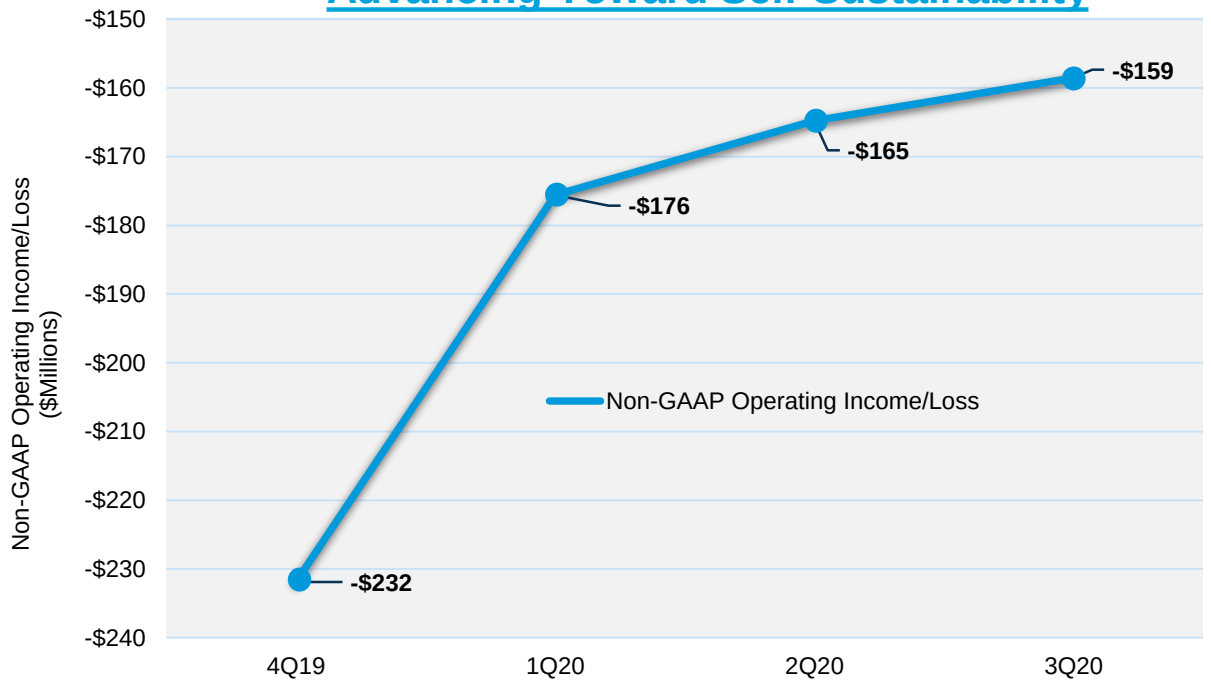
Disciplined Investment – Progress Over Last 12 Months

Supporting Near and Long-Term Topline Growth with Leverageable Infrastructure

Operating Leverage



Advancing Toward Self-Sustainability



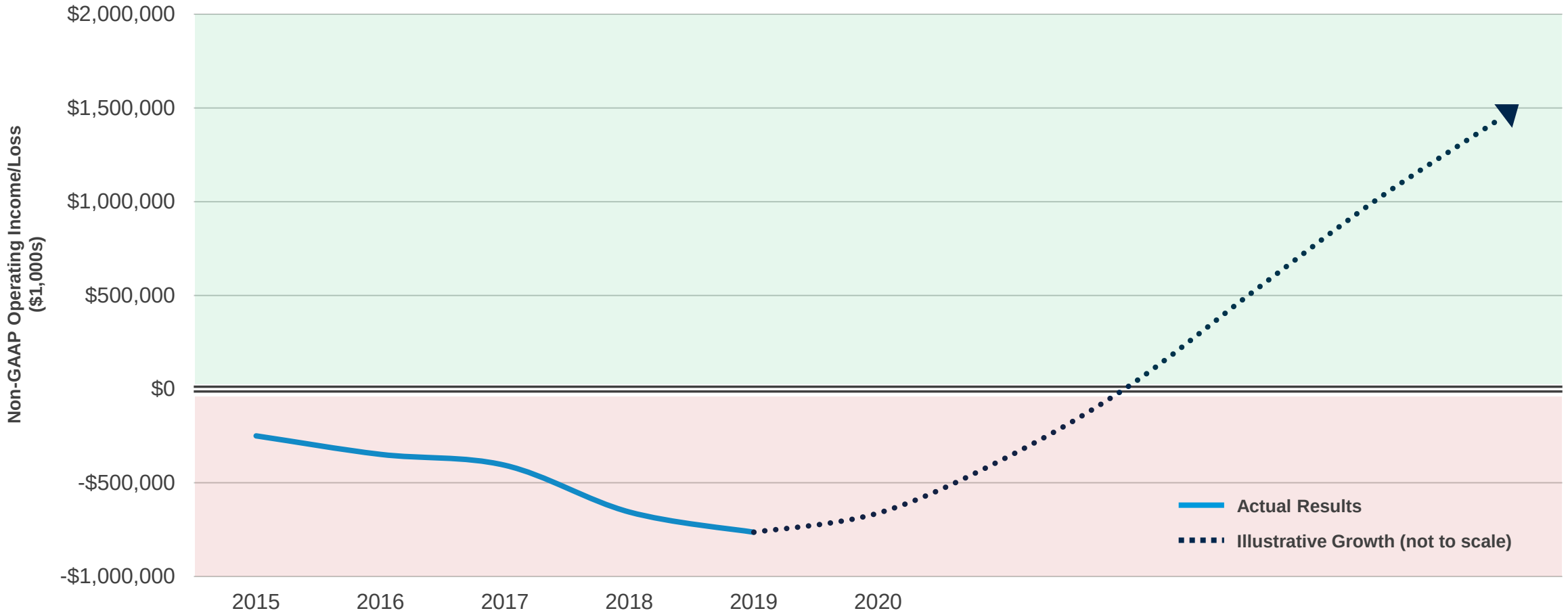
SG&A expense discipline to maximize value

- Ensure operational excellence commercializing wholly-owned programs
  - Commercial foundation established in US, EU, Asia, and LATAM with direct presence in 24 countries
  - Leveraging global infrastructure to support successive product launches
  - Maintain lean corporate G&A infrastructure to support business

*2020 net product and collaboration revenue based on consensus estimates. 2020 combined non-GAAP R&D and SG&A year over year % change calculated using consensus for FY20 combined Non-GAAP R&D and SG&A. All consensus estimates current as of December 2, 2020.

Alnylam Entering Period of Projected Growth

2019 Expected to be Peak Non-GAAP Operating Loss Year



	2015	2016	2017	2018	2019	2020
# Late Stage Programs:	2	1	4	6	6	6
# Commercial Products:	0	0	0	1	2	4

Blackstone Strategic Financing

Landmark financing arrangement led by Blackstone Life Sciences, worth $2 billion

- Secures Alnylam's bridge towards self-sustainable financial profile
  - Enables independence from equity markets
  - Strengthened cash position bolsters Alnylam efforts to build top-tier biopharmaceutical company
- Alnylam retains 50% of inclisiran royalty*
  - Allows for significant financial benefit from drug's potential commercial success
  - Largest ever royalty monetization for a non-approved product
- High quality partner in Blackstone
  - Leading private equity firm with strong commitment to Life Sciences and to value creation through advancement of innovative medicines for patients
  - Additional components of transaction demonstrate Blackstone's confidence in Alnylam's future and alignment with long-term vision

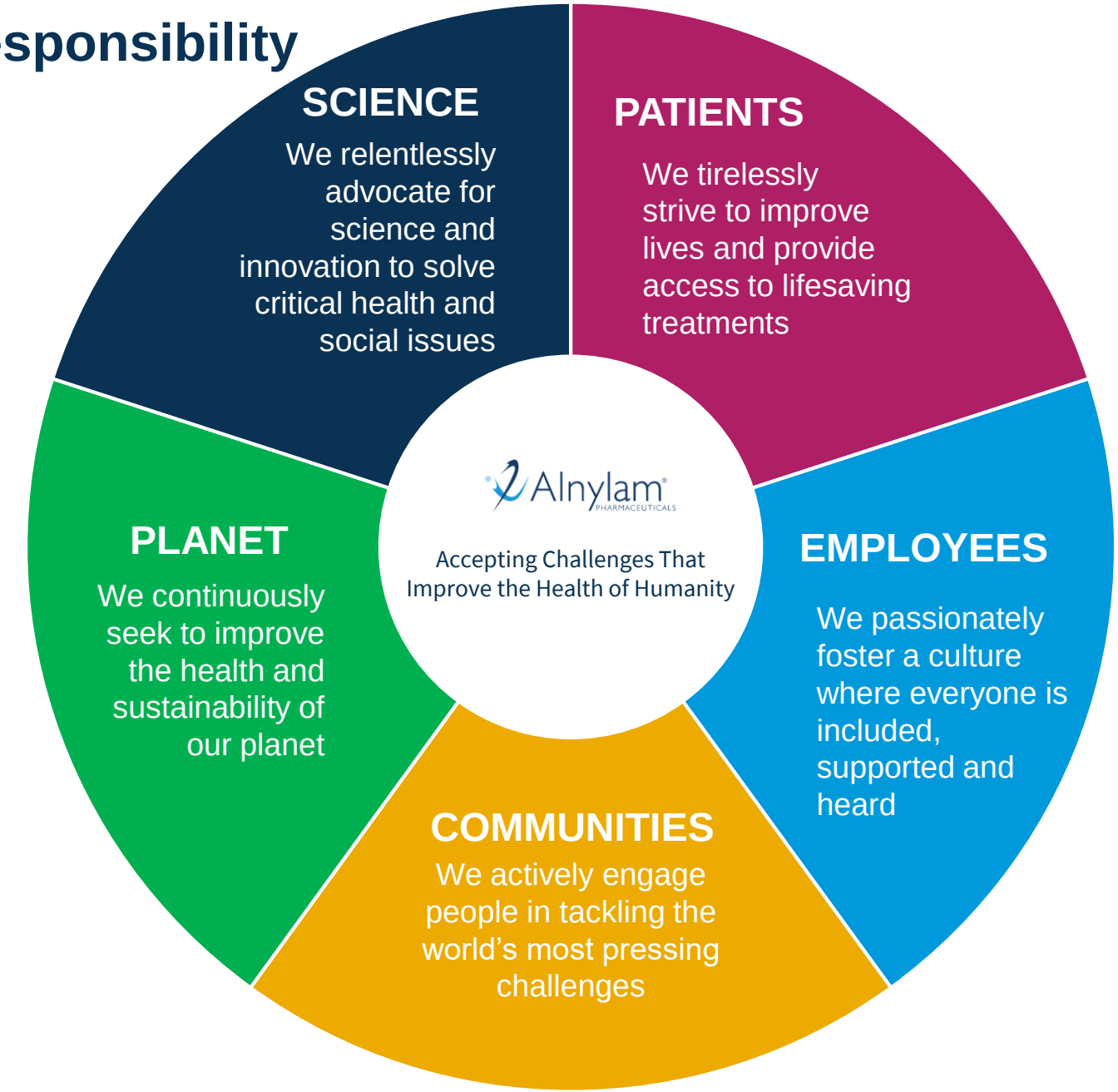
If Blackstone royalty proceeds through end of 2029 < $1B, Alnylam retained share declines to 45% beginning in 2030.
Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics

Achieving Self-Sustainability with Responsibility

Accepting Challenges That Improve the Health of Humanity

We take on bold challenges that improve the health of humanity, acting every day as relentless advocates for science, patients, employees, communities and our planet.

Initial CSR Summary Report Anticipated Early ‘21



Building a Top-Five Biotech

Potential for Significant Transformation of Alnylam over Next 5 Years

2020

- Rare Diseases
- 4 — Approved Products
- Initial Indications
- 6 — Late Stage Programs
- 4 — STArs
- ~20 Markets
- ~1K — Employees
- CMOs

2025

- Prevalent Diseases
- 6+ — Approved Products
- Multiple Indications
- 10+ — Late Stage Programs
- 4+ — STArs
- Global
- ~2.5K — Employees
- Norton + CMOs

Top 5 independent, global biopharma company admired for its dedication to **patients**, corporate **culture**, scientific **innovation**, social **responsibility**, and commercial **excellence** with numerous RNAi products across orphan and large disease areas

VOICES OF **PATIENTS & CAREGIVERS**

“With ONPATTRO, I can do those ‘extra’ little things, like taking my daughter to the park.”

Joe, treated with ONPATTRO®

Alnylam® PHARMACEUTICALS

Alnylam PHARMACEUTICALS