ProQR®

DEVELOPING RNA-EDITING MEDICINES

for patients in need

Nasdaq: PRQR

April 2025

Forward-looking statements

This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to", "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. Such forward-looking statements include, but are not limited to, statements regarding our strategy and future operations, statements regarding the potential of and our plans with respect to our technologies and platforms (including Axiomer™), our preclinical model data, our pipeline targets, our other programs and business operations, our current and planned partnerships and collaborators and the intended benefits thereof, including the collaboration with Lilly and the intended benefits thereof, including the upfront payment, equity investment, and milestone and royalty payments from commercial product sales, if any, from the products covered by the collaboration, as well as the potential of our technologies and product candidates; our updated strategic plans and the intended benefits thereof, our plans to seek strategic partnerships for our ophthalmology assets, and our financial position and cash runway. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this presentation. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, the risks, uncertainties and other factors in our filings made with the Securities and Exchange Commission, including certain sections of our annual report filed on Form 20-F. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies and other development activities by us and our collaborative partners whose operations and activities may be slowed or halted due to shortage and pressure on supply and logistics on the global market; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; the ability to secure, maintain and realize the intended benefits of collaborations with partners, including the collaboration with Lilly; the possible impairment of, inability to obtain, and costs to obtain intellectual property rights; possible safety or efficacy concerns that could emerge as new data are generated in research and development; general business, operational, financial and accounting risks; and risks related to litigation and disputes with third parties. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future, except as required by law.

ProQR development pipeline

	TARGET	DISCOVERY	NON-CLINICAL	CLINICAL	NEXT MILESTONE	ESTIMATED POPULATION
DEVELOPMENT PIPELINE						
AX-0810 *for Cholestatic diseases*	NTCP				CTA filing in Q2 2025	~100K patients
AX-2402 *for Rett syndrome*	MECP2 R270X				Candidate selection in 2025	~5K patients
AX-1412 *for Cardiovascular disease*	B4GALT1				Scientific update in mid 2025	~200M patients
AX-2911 *for MASH*	PNPLA3				Candidate selection in 2025	~8M patients
DISCOVERY PIPELINE						
AX-1005 *for CVD*	Undisclosed					~200M patients
AX-0601 *for obesity and T2D*	Undisclosed					~650M patients
AX-9115 *for rare metabolic condition*	Undisclosed					
AX-2403 *for Rett syndrome*	MECP2 R168X					~6K patients
AX-2404 *for Rett syndrome*	MECP2 R255X					~5K patients
AX-2405 *for Rett syndrome*	MECP2 R294X					~6K patients
AX-2406 *for Rett syndrome*	MECP2 R133H					
AX-3875 *for rare metabolic & CNS disorder*	Undisclosed					
AX-4070 *for rare CNS disorder*	Undisclosed					
PARTNERED PIPELINE						
10 targets (option to expand to 15)	Undisclosed	*Progress undisclosed*				Lilly

[1]Approximately 100K people affected with Primary Sclerosing Cholangitis and Biliary Atresia in US and EU5. [2]Approximately 200 million people suffer from too high a level of cholesterol in US and EU5. SLC10A1 is the gene that encodes for NTCP protein. CVD: Cardiovascular Diseases, NASH: Nonalcoholic steatohepatitis, T2D: Type 2 Diabetes. | References: Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999; Tsao CW, et al. Circulation. 2022;145(8):e153–e639. World Health Organization, World Gastroenterology Organization

Catalyst overview

4 trial readouts expected in 2025-2026, cash runway into mid-2027

AX-0810 for Cholestatic disease

- CTA submission Q2 2025
- Top-line data Q4 2025

AX-2402 for Rett Syndrome

- Clinical candidate selection in 2025
- Anticipated trial start and top-line data in 2026

AX-1412 for Cardiovascular disease

- Non-clinical data update in mid 2025

AX-2911 for MASH

- Clinical candidate selection in 2025
- Anticipated trial start and top-line data in 2026

Partnerships

- Opportunity to earn up to $3.75B in milestones in the Lilly partnership
- Opportunity to receive a $50 M opt-in fee from Lilly for expansion to 15 targets
- Opportunity for other strategic partnerships

Axiomer™ advancing
to value inflection

INNOVATIVE ADAR-ENABLED RNA EDITING SCIENCE DRIVING ADVANCEMENT OF AXIOMER™

supported by robust IP estate

HIGH IMPACT STRATEGIC PARTNERSHIPS

Eli Lilly, Rett Syndrome Research Trust

PIPELINE WITH TRANSFORMATIVE POTENTIAL FOR DISEASES WITH HIGH UNMET MEDICAL NEEDS

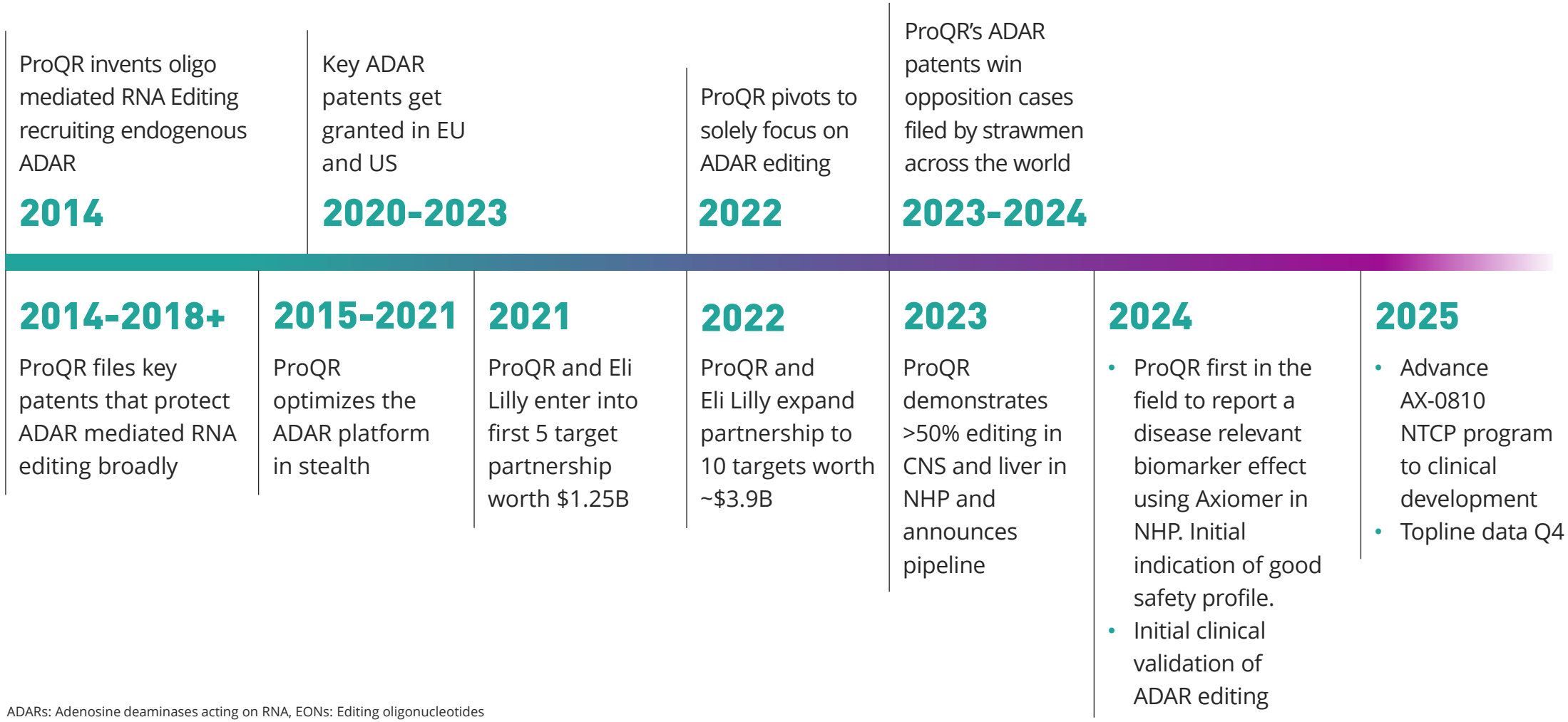
Across rare and common liver and CNS disease

EXPERIENCED TEAM DRIVING EXECUTION

RUNWAY INTO MID 2027

***€ 149.4 million** cash and cash equivalents as of end of 2024, providing runway into mid-2027*

ProQR's Axiomer™ ADAR journey since 2014

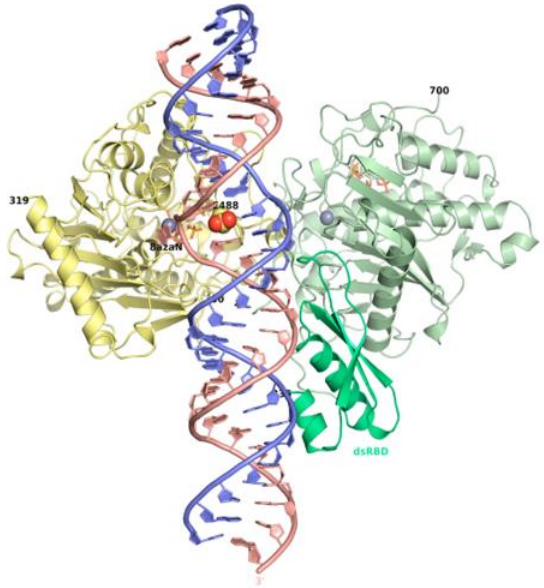


ADARs: Adenosine deaminases acting on RNA, EONs: Editing oligonucleotides

Axiomer™ EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

ADAR *(Adenosine Deaminase Acting on RNA)*

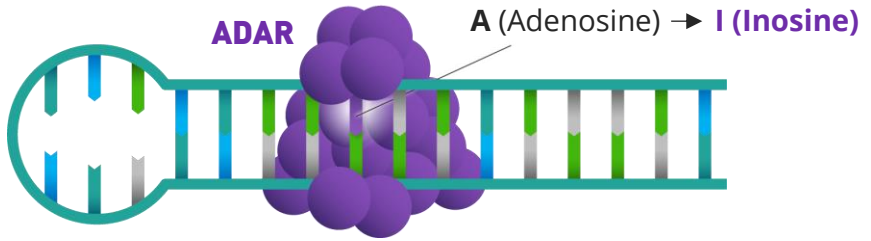


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing *(A-to-I)*

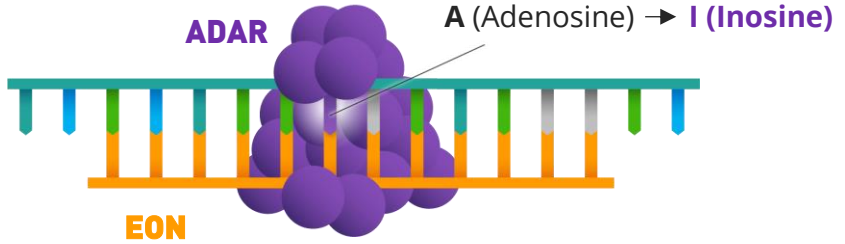
Natural ADAR editing *(A-to-I)*

RNA
Double stranded

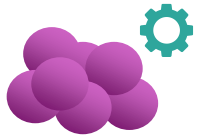
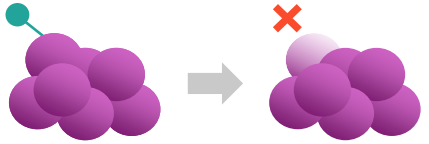


Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*

RNA+EON
Double stranded



Creating a new class of medicines with broad therapeutic potential

Correction	Protein modulation		
			
Mutations correction Thousands of G-to-A mutations, many of them described in literature	**Alter protein function or include protective variants** Modified proteins achieving loss- or gain-of-functions that help addressing or preventing diseases	**Disrupt >400 different types of PTMs** Regulate protein activity, change localization, folding, preventing immune escape or slowing down degradation	**Change protein interactions** Changes localization, folding, protein function or prevents immune escape of glycosylated tumor antigens
Mutation correction leading to protein recovery	Variant resulting in a dominant negative effect	Reduction of protein phosphorylation altering protein function	Variant impacting protein interaction with sugar

AX-0810 Program

Targeting NTCP to address cholestatic diseases unmet medical need at the root cause

AX-0810 RNA editing therapy targeting NTCP for cholestatic diseases

Cholestatic diseases have high unmet medical need. Patients accumulate bile acids in liver leading to fibrosis and ultimately liver failure.

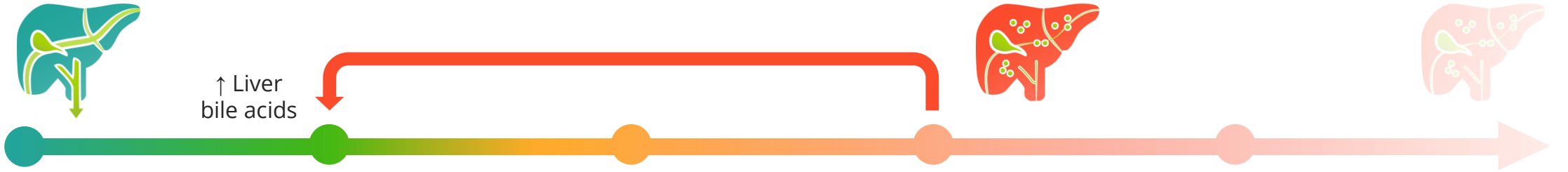
Initial indications are **Primary Sclerosing Cholangitis** affecting adults and Congenital **Biliary Atresia** affecting pediatrics early in life.
Both conditions have no approved therapies and may require liver transplantation.[1,2]

- **Biliary Atresia** is projected to affect ~20,000 pediatric individuals in US and EU.
- **Primary Sclerosing Cholangitis** is projected to affect more than 80,000 individuals in US and EU.

AX-0810 is a unique therapeutic approach leading to a potentially disease modifying therapy by targeting the NTCP channel which is responsible for majority of bile acid re-uptake in liver cells.

[1]Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; [2]Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999

NTCP modulation leads to positive effect on different mechanism involved in cholestasis



NTCP MODULATION

Restores Bile Acids Balance

Protect hepatocytes by lowering bile acid levels and decrease hepatic bile production through downregulating effects

Reduces Inflammation

Prevents bile leakage and infiltration, limiting liver cell damage and release of proinflammatory mediators

Slows Fibrosis Progression

Stops cholangiocyte senescence and proliferation, reducing fibro-inflammatory responses

Zeng J, Fan J, Zhou H. Cell Biosci. 2023 Apr 29;13(1):77; Trauner M, Fuchs CD. Gut 2022;71:194–209; Halilbasic E, Claudel T, Trauner M. J Hepatol. 2013 Jan;58(1):155-68.

NTCP variants reduced bile acids uptake into liver in health population research

Healthy population discovered with NTCP variants that reduces bile acids uptake into liver[1-4]

Ethnicity-dependent Polymorphism in Na+-taurocholate Cotransporting Polypeptide (*SLC10A1*) Reveals a Domain Critical for Bile Acid Substrate Recognition*

Richard H. Ho‡§¶, Brenda F. Leake‡, Richard L. Roberts‖, Wooin Lee‡, and Richard B. Kim‡**

d D Viruses and Bile Salts
on Molecular Determinants on Sodium
Polypeptide

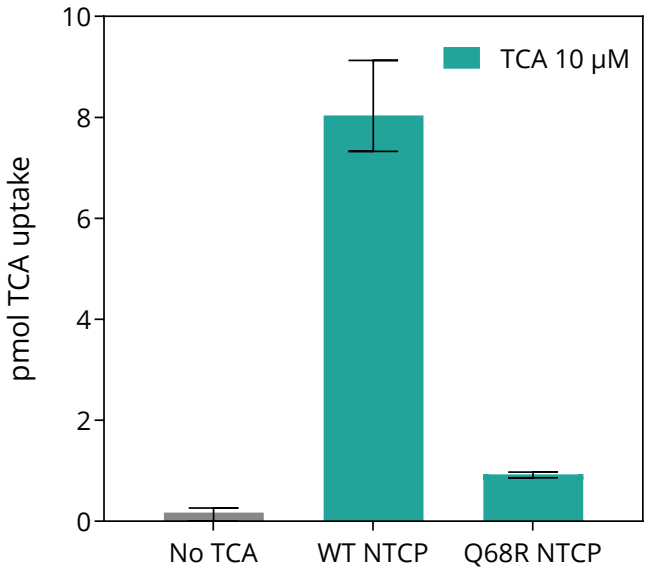
[1]Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-22; [2]Vaz FM, et al. Hepatology. 2015 Jan;61(1):260-7; [3]Schneider AL, et al. Clin Res Hepatol Gastroenterol. 2022 Mar;46(3):101824; [4]Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069.

NTCP modulation validated *in vitro, vivo* and clinic

Reducing liver bile acids toxic overload via NTCP modulation is a key driver for hepatoprotective effects

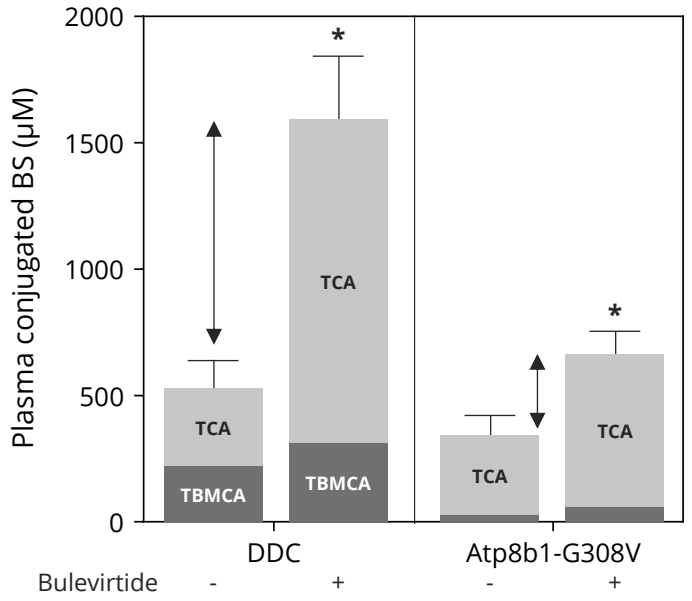
BAs uptake (TCA) in vitro

n=3, mean±SEM



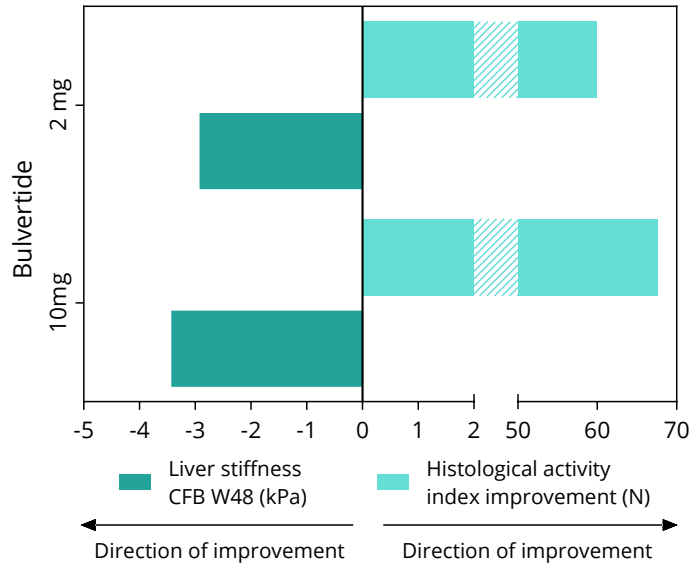
Q68R NTCP variant leads to modulation of bile acids re-uptake

3-fold increase *in conjugated BA* **2-fold increase** *in conjugated BA*



NTCP modulation demonstrated effectivity in cholestatic disease model[1]

Bulevirtide 2 and 10 mg



Clinical PoC with bulevirtide in Ph3 Hepatitis D trial. **Improvement** occur in patients, **even without virologic response**[2-4]

Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. NTCP channel is a known transporter for bile acids and hepatitis virus from bloodstream to the liver.

1. Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069; 2. Wedemeyer H, et al. N Engl J Med. 2023 Jul 6;389(1):22-32; 3. Wedemeyer H, J Hepatol. 2024 Oct;81(4):621-629.; 4. Dietz-Fricke C, JHEP Rep. 2023 Mar 15;5(4):100686.

NTCP modulation approach broadly validated

Reducing liver bile acids toxic overload via NTCP modulation is a key driver for hepatoprotective effects

HUMAN GENETICS

Healthy population discovered with NTCP variants that reduces bile acids uptake into liver[1-3]

IN VITRO

NTCP variant leads to an 8-fold decrease of bile acids re-uptake *in vitro*

IN VIVO

NTCP modulation demonstrated effectivity in mouse cholestatic disease model, with 2- to 3-fold change in conjugated bile acids[4-5]

IN CLINIC

Clinical PoC with bulevirtide in Ph3 Hepatitis D trial, for which liver improvement occur in patients, even without virologic response[6-8]

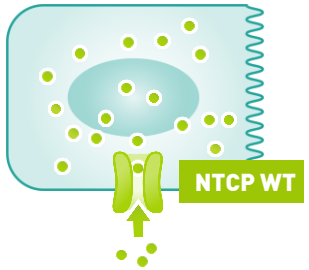
Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. NTCP channel is a known transporter for bile acids and hepatitis virus from bloodstream to the liver.

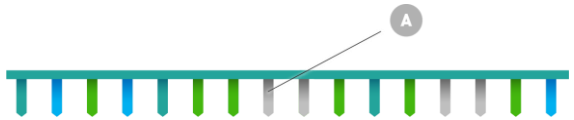
[1]Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-22; [2]Vaz FM, et al. Hepatology. 2015 Jan;61(1):260-7; [3]Schneider AL, et al. Clin Res Hepatol Gastroenterol. 2022 Mar;46(3):101824; [4]Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069; [5]Salhab A, et al. Gut. 2022 Jul;71(7):1373-1385; [6]Wedemeyer H, et al. N Engl J Med. 2023 Jul 6;389(1):22-32; [7]Wedemeyer H, J Hepatol. 2024 Oct;81(4):621-629.; [8]Dietz-Fricke C, JHEP Rep. 2023 Mar 15;5(4):100686.

Human genetics validates NTCP modulation as strategy for cholestatic disease

LIVER WITH CHOLESTATIC DISEASE

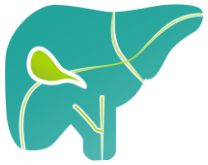
High concentration of bile acids in hepatocytes

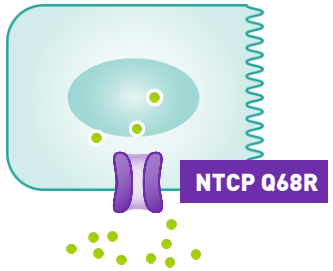


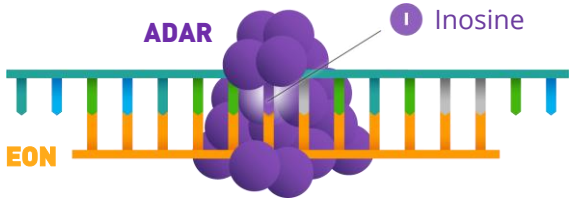


AX-0810 STRATEGY FOR DISEASED LIVER

AX-0810 modifies the NTCP channel to limit bile acids uptake while preserving all other functions of the channel







- The AX-0810 program introduces a variant in individuals with cholestatic disease to lower bile acids concentration in hepatocytes by a single A-to-I change
- The AX-0810 program is designed to be a disease modifying treatment
  - To alleviate symptoms in PSC and BA
  - To limit inflammation and fibrosis linked to bile acid toxicity
  - To prevent or delay the development of cirrhosis, organ failure and need for transplant

BA, Biliary atresia; PSC, Primary Sclerosing Cholangitis

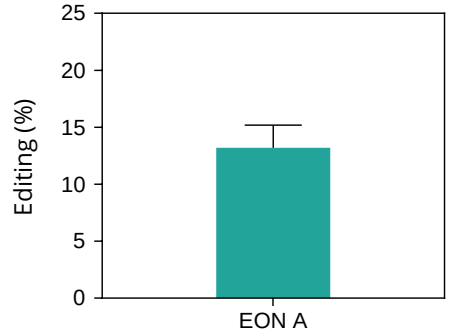
EON mediated editing demonstrates consistent editing of NTCP and impact on biomarker *in vivo*

MICE *in vivo*

EDITING EFFICIENCY

NTCP RNA Editing in Humanized Mice

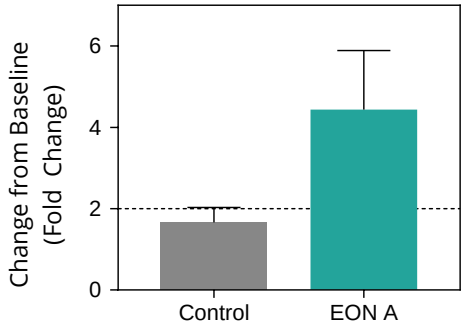
(N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25, ddPCR)



PLASMA TOTAL BILE ACIDS

Plasma TBA in Humanized Mice

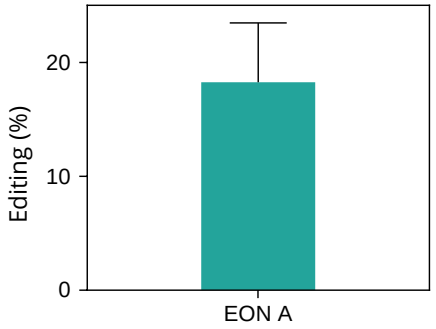
(N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25)



NHP *in vivo*

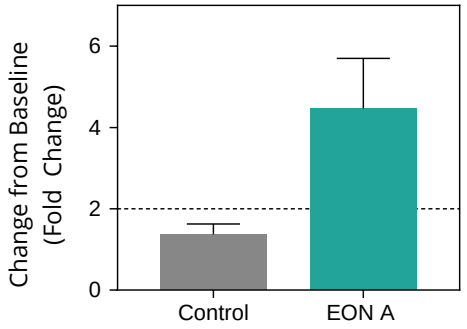
NTCP RNA Editing in NHP

(N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D46, ddPCR)



Plasma TBA in NHP

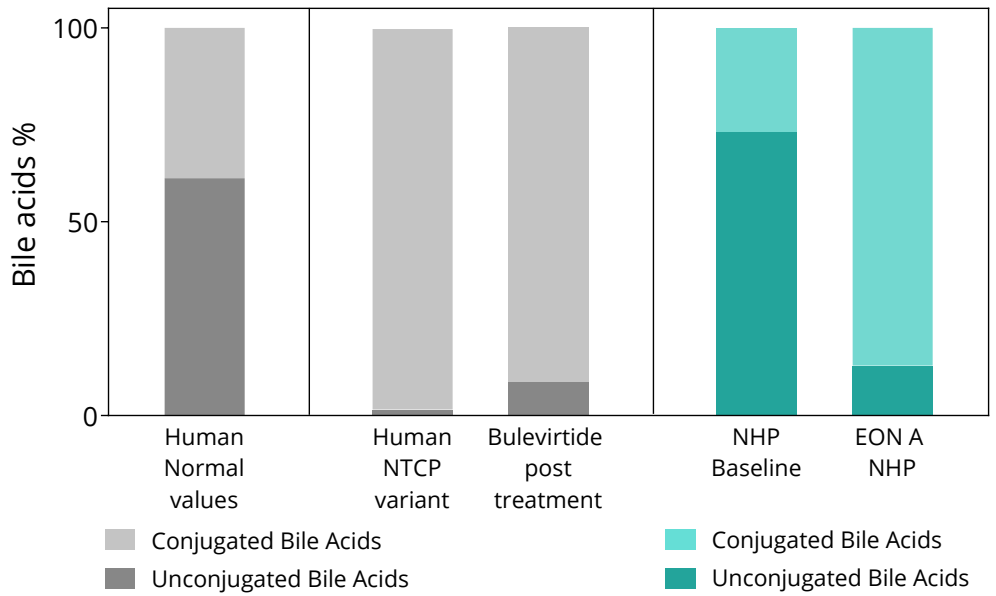
(N=1, 1-4mg/kg, 4 doses, LNP formulation IV, up to D39)



- EON A results in consistent editing data in humanized mouse model and NHP *in vivo* with approx. 15% editing reaching expected NTCP modulation
- Reaching >2-fold changes in biomarkers - expected impact on plasma bile acids levels following NTCP EON treatment

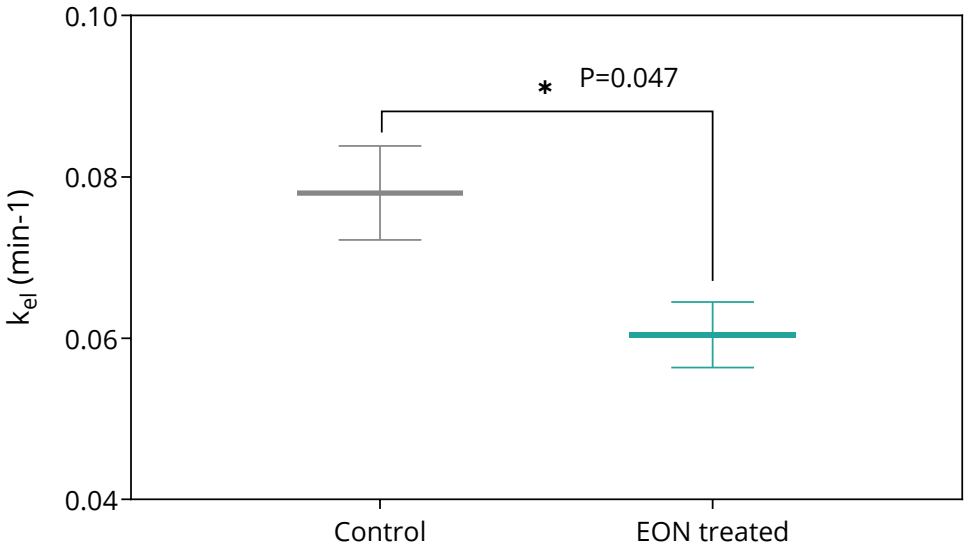
PoC in NHP on bile acid profile and TUDCA elimination

Change in Plasma BA Profile



TUDCA elimination rate from plasma in NHP

Exploratory study, early generation EON, n=5-7, 10mg/kg, 4 doses, SC, D51



- Conjugated bile acids are transported by NTCP back to the liver, change in plasma BA profile confirms NTCP specific modulation
- High confidence on NTCP EON treatment to positively impact BA toxic load in the liver

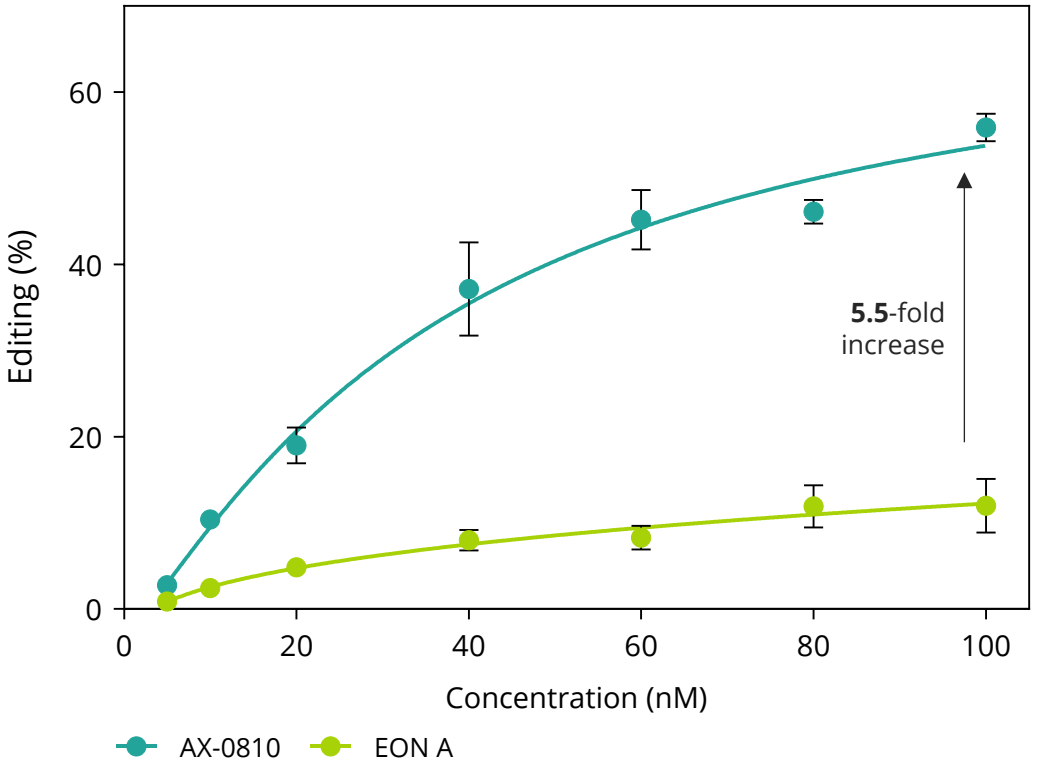
- TUDCA is a Tauro-conjugated bile acid specifically transported by NTCP from the plasma to the liver
- Decrease in TUDCA plasma clearance kinetics further confirm NTCP target engagement for EON treated NHP

Conditions in the NHP experiment on the left: N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D42, LC-MS/MS. Mao F, et al. J Biol Chem. 2019 Aug 2;294(31):11853-11862; Haag M, et al. Anal Bioanal Chem. 2015 Sep;407(22):6815-25.; Wedemeyer H, et al. N Engl J Med. 2023 Jul 6;389(1):22-32.

AX-0810 clinical candidate selected with enhanced potency and stability profile

AX-0810 clinical candidate has an enhanced potency profile over EON A in PHH

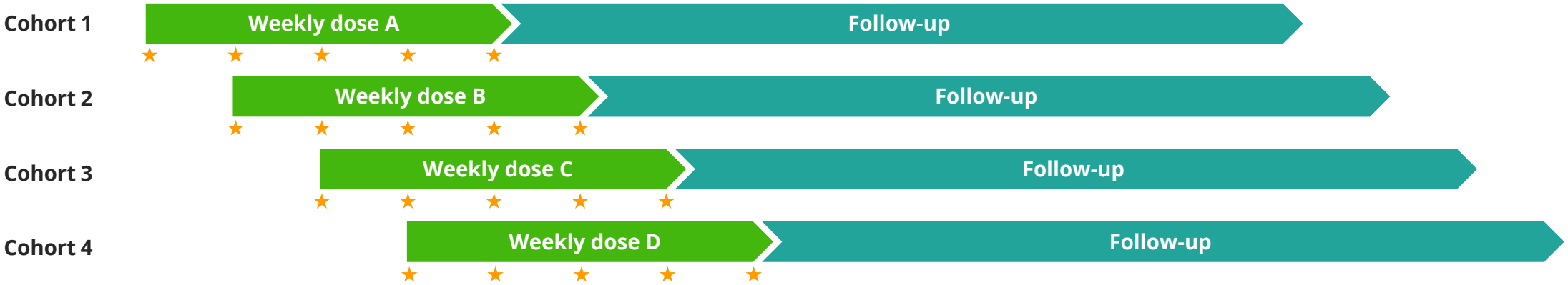
Transfection, n=3, 72 hours, dPCR, mean±SEM



- AX-0810 clinical candidate is a GalNAc conjugated EON
- 5.5-fold increase in potency over early generation NTCP editing oligonucleotide
- Improved stability profile *in vitro*
- Confirmed class safety, with no hepatotoxicity or immunostimulatory score

First in human trial of AX-0810 to establish target engagement

Integrated single/multiple ascending dose study design



Treatment

AX-0810 GalNAc conjugated editing oligo-nucleotide

Objectives

- Confirm target engagement as measured by biomarkers
- Assess safety, tolerability, and PK of AX-0810

Trial design

- Combined single and multiple ascending dose
- ≥60 heathy volunteers, 4 weeks dosing phase followed by 12 safety weeks follow-up
- 5 weekly subcutaneous injections
- Baseline and placebo-controlled design
- Standardized conditions for assessment of bile acids at multiple timepoints
- DMC safety reviews before proceeding to next dose and dose escalation

Key endpoints

- Change in bile acids levels and profile in plasma and urine, liver biomarkers
- Circulating RNA as exploratory endpoint

CTA submission in Q2 2025

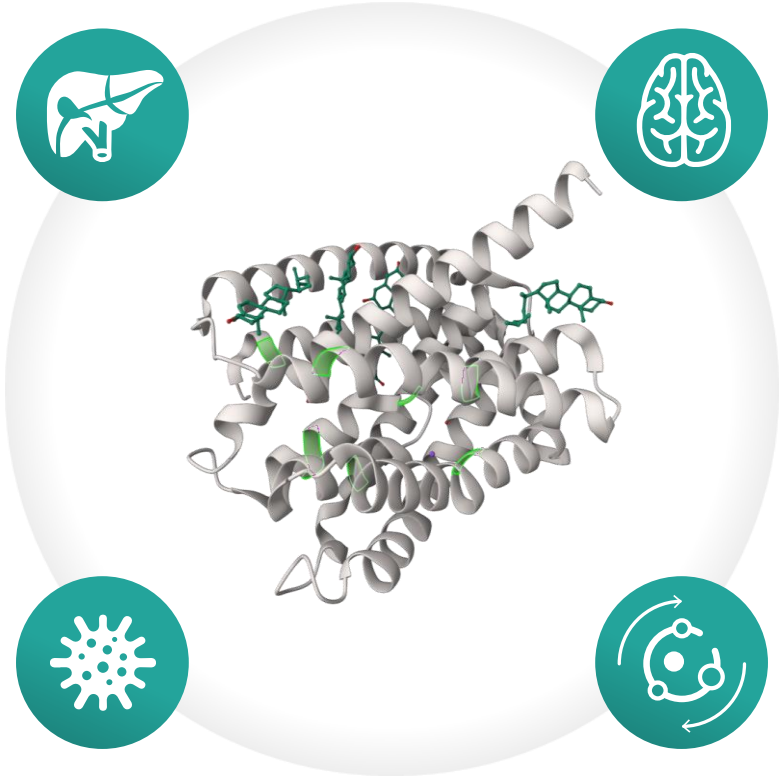
Top-line data in Q4 2025

NTCP and bile acids are involved in a variety of therapeutic areas

Providing opportunity across multiple indications

Cholestatic diseases

- Primary Sclerosing Cholangitis (PSC)
- Biliary Atresia
- Primary Biliary Cholangitis (PBC)
- Alagille syndrome
- Dubin-Johnson Syndrome
- Progressive Familial Intrahepatic Cholestasis (PFIC)
- Drug-Induced Cholestasis
- Alcoholic Liver Disease
- Secondary Biliary Cirrhosis
- Rotor syndrome
- Neonatal cholestasis



Neurological diseases

- Multiple Sclerosis
- Amyotrophic Lateral Sclerosis
- Neurological diseases
- Epilepsy
- Parkinson's Disease

Infectious disease

- Parasitic Infections
- Sepsis-Associated Cholestasis
- Viral Hepatitis: Hepatitis A, B, C, D, E

Metabolic diseases

- Hyperlipidemia
- Hypertension
- MASH
- Obesity
- Diabetes
- Lysosomal storage diseases
- Hyper-cholesterolemia
- ASCVD

AX-2402 Program

Targeting MECP2 to restore protein functionality in Rett Syndrome, a severe neurodevelopmental disorder

AX-2402 RNA editing therapy targeting MECP2 for Rett Syndrome

RETT SYNDROME RESEARCH TRUST

Rett Syndrome is a **devastating and progressive neurodevelopmental disorder** caused by variants in the transcription factor Methyl CpG binding protein 2 (*MECP2*). There is a **high unmet need for a disease modifying therapy**.

Nonsense variants lead to **severe phenotypes.** They represent more than one third **of Rett Syndrome** cases and are projected to affect **20,000 individuals** in US and EU.[1,2]

Rett Syndrome is **not a neurodegenerative disorder** and restoring levels of the MECP2 protein has shown to **reverse symptoms** in mice.[3]

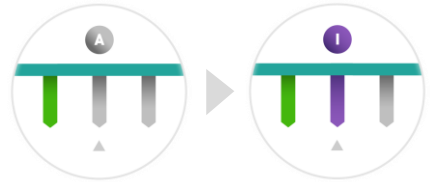
Axiomer has the potential to **restore the precise level of MECP2 protein regulatory function,** which is lacking in Rett Syndrome, and become a disease modifying therapy.

Rett Syndrome Research Trust partnership includes $9.2 M in funding; collaboration established in January 2024, expanded in December 2024

[1]Krishnaraj R, et al. Hum Mutat. 2017 Aug;38(8):922-93; [2]RSRT 2023 conference; [3]Guy J, et al. Science. 2007 Feb 23;315(5815):1143-7.

Axiomer™ has the potential to restore physiological levels of functional MECP2

AX-2402 correcting MECP2 R270X into WT-like R270W



GGGGCC>UGAAAGCCG

RETT syndrome

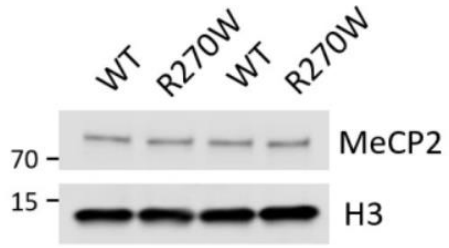
Postnatal microcephaly, stereotypic hand movements, ataxia, abnormal breathing, and growth retardation, social withdrawal, loss of speech, seizures

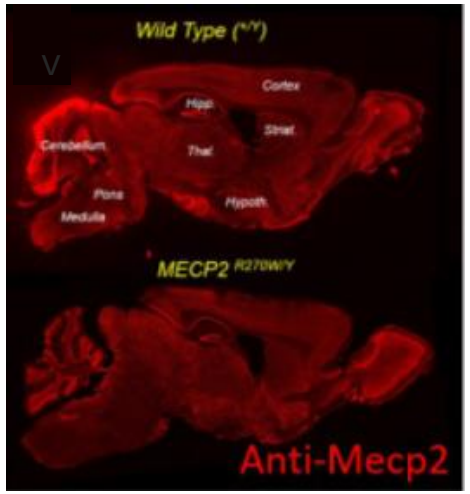
GGGGCUGA>GAAGCCG

WT like phenotype

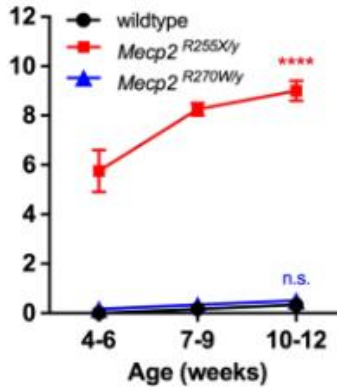
- MeCP2 protein restoration/recovery
- MeCP2 R270W (Arg > Trp) mouse model indistinguishable from wild type mice

R270W variant demonstrates wild-type like profile

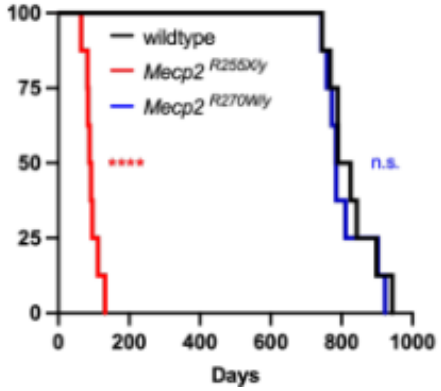




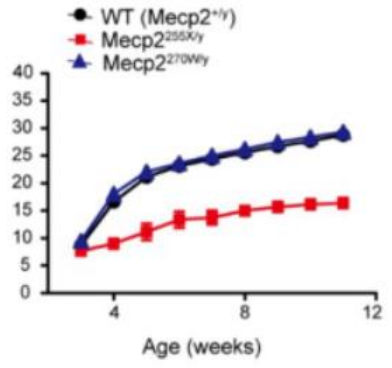
Severity score (0-12)



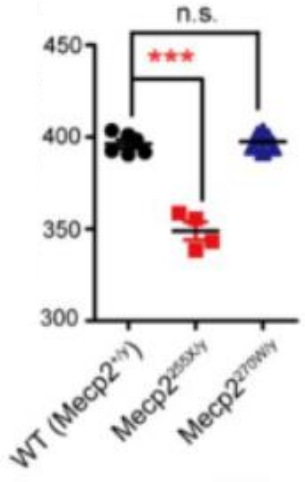
Probability of survival



Body weight (g)



Brain weight (mg)



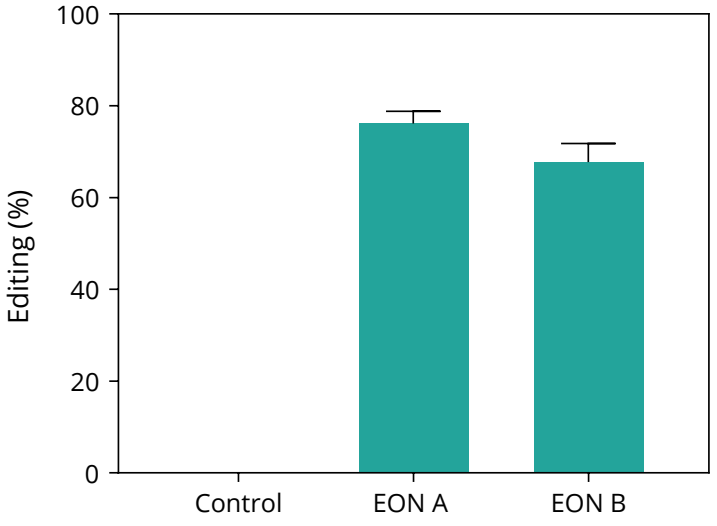
AX-2402 can restore physiological levels of functional MECP2 potentially reverting Rett syndrome into a WT like phenotype[1]

[1]Colvin, S. (2023) thesis. Massachusetts Institute of Technology. Figures adapted from: Colvin, S. (2023) thesis. Massachusetts Institute of Technology

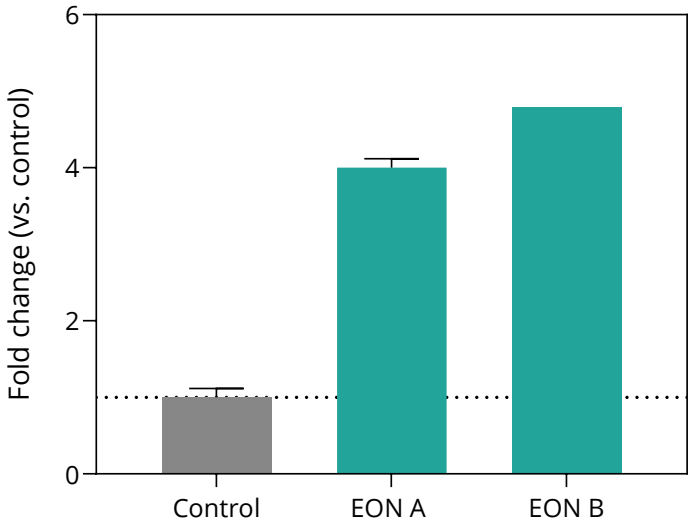
EON mediated editing in patient's cells increases mRNA levels and restores protein expression

PTC recoding leading to absent NMD mediated RNA degradation

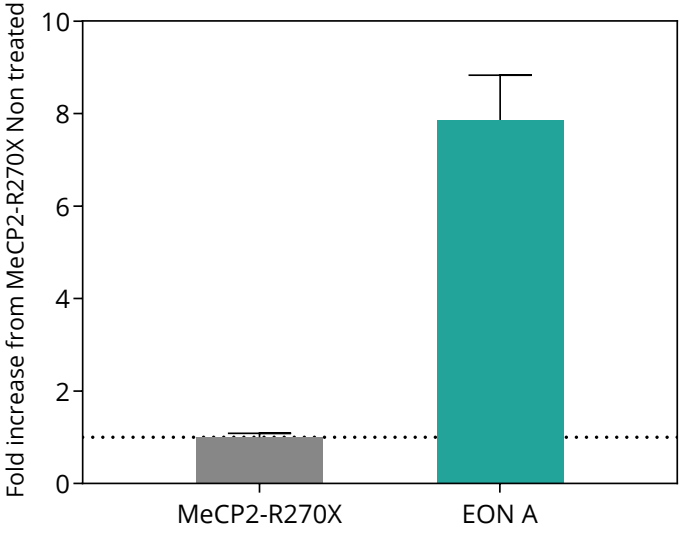
R270X MECP2 editing



MECP2 RNA levels



R270W MECP2 protein levels



Up to 80 % editing of R270X MECP2 in patient fibroblasts

Increased MECP2 RNA levels due to PTC recoding and NMD inhibition

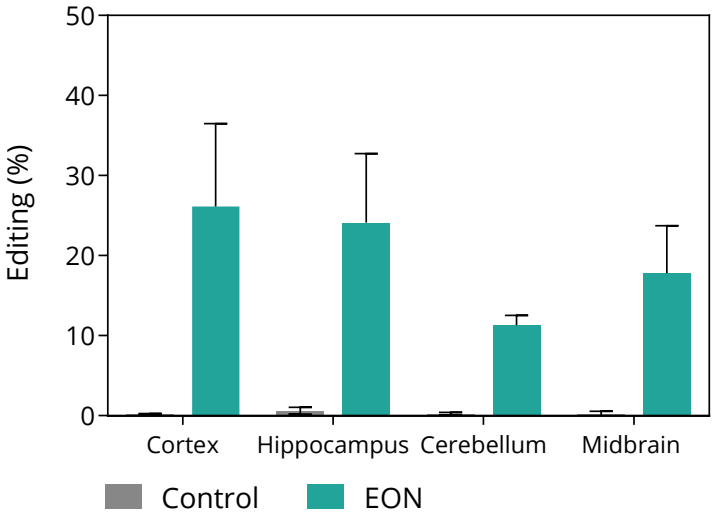
Increased R270W MECP2 protein levels

EON, Editing oligonucleotide; NT, Non-treated; TF, transfection, Conditions panel on the left and middle: 100 nM EON, transfection, 48h, N=2, mean±SEM. Conditions panel on the right: MeCP2-R270X-NanoLuc activity; 100 nM EON, transfection, 48h, N=8, mean±SEM.

Consistent CNS editing demonstrated across species

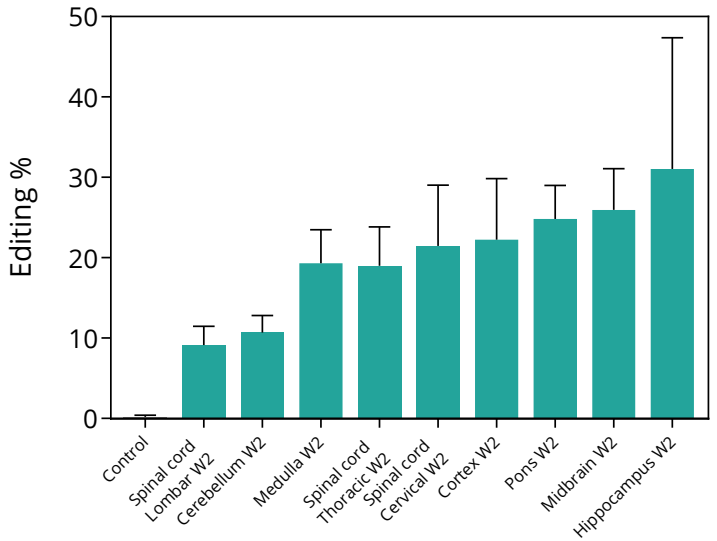
Mice *in vivo*

ICV, 250µg, undisclosed target, single dose, n=6, 4 weeks, ddPCR, mean, SD



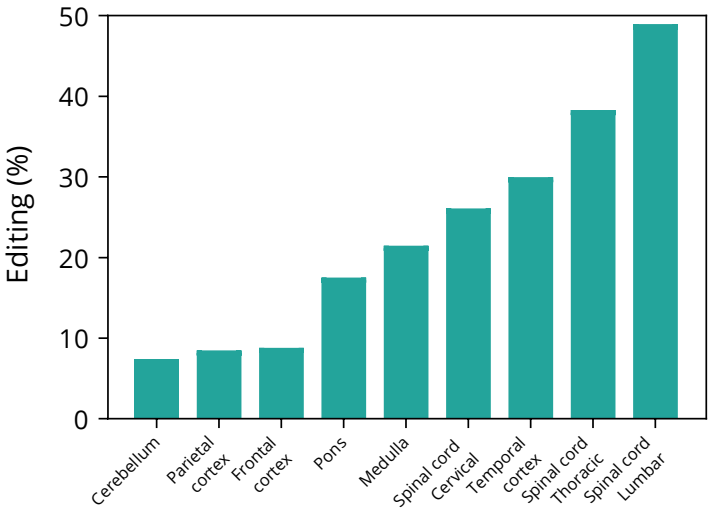
Rat *in vivo*

ICV, 500µg, APP, single dose, n=5, 2 weeks, ddPCR, mean, SD



NHP *in vivo*

IT administration, undisclosed target 12mg, single dose, n=3, 7 days, ddPCR*

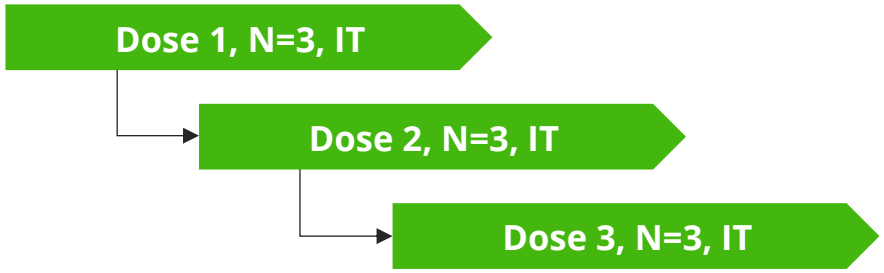


- Up to 40% editing *in vivo* leading to 26-fold change in protein function recovery in brain tissues of interest at 4 weeks with a single dose in mice model
- In rat, Axiomer EONs demonstrated up to 50% editing *in vivo* with sustained editing between W2 and W4 after single dose
- Up to 30% RNA editing reported in brain and approx. 50% in spinal cord in NHP in vivo

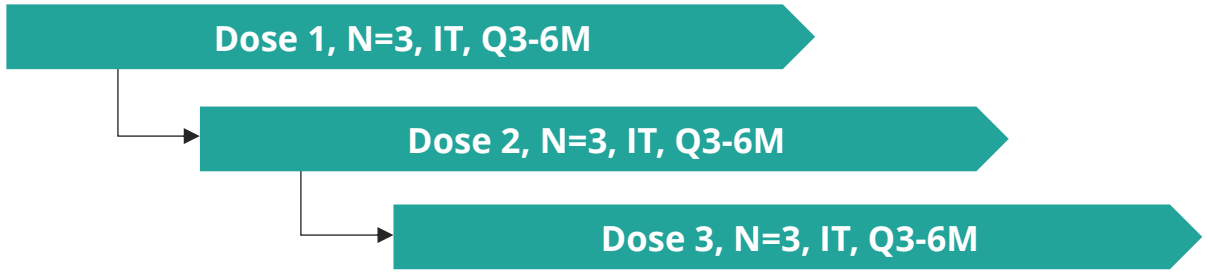
* Data of 2 NHPs not analyzable due to human error during injection procedure.

Preliminary clinical trial design

Single dose



Repeated dose



- Preliminary Phase 1/2 SAD & MAD design
- Up to 18 subjects with the R270X mutation
- Primary objective: safety, tolerability and pharmacokinetics
- Secondary objectives: target engagement and biomarkers

- Financially supported by $8.2 M funding provided by Rett syndrome Research Trust
- **Clinical candidate selection in 2025**
- **Top-line data expected in 2026**

AX-1412 Program

Targeting B4GALT1 to reduce the risk of cardiovascular diseases

AX-1412 RNA editing therapy targeting B4GALT1 for cardiovascular diseases

Leading causes of death in the world
~18 million people die from CVDs every year (**32% of all global deaths**) Despite therapies, the unmet medical need remains.

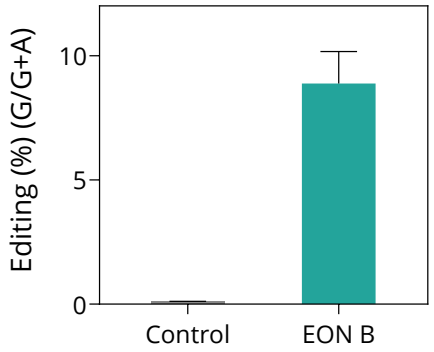
AX-1412 is designed to provide people with a protective genetic variant of B4GALT1 that is associated with **36%[1] reduction in the risk of cardiovascular disease**.

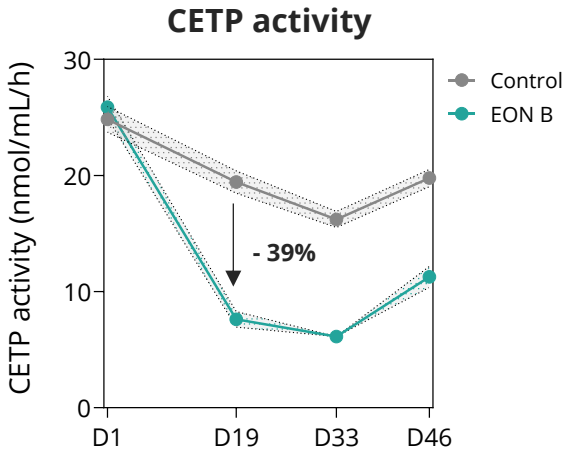
AX-1412 may become a **stand-alone cardiovascular therapy** that may also work **synergistically with standard of care** to further reduce risk of CVDs.

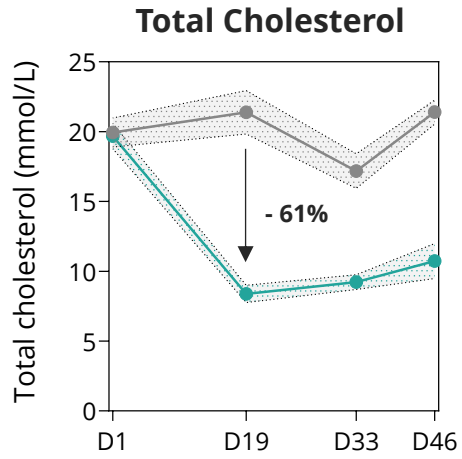
[1]Montasser ME, et al. Science. 2021 Dec 3;374(6572):1221-1227

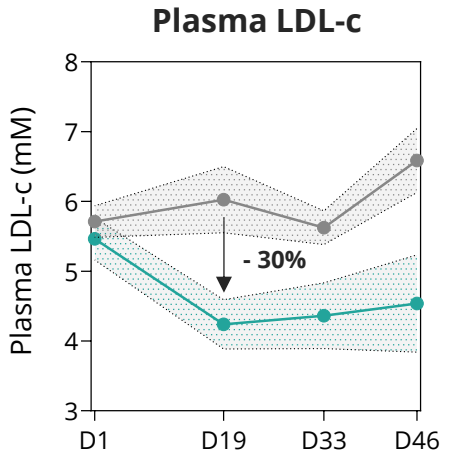
EON-mediated editing of B4GALT1 leads to meaningful effect on key biomakers in E3L.CETP Mice

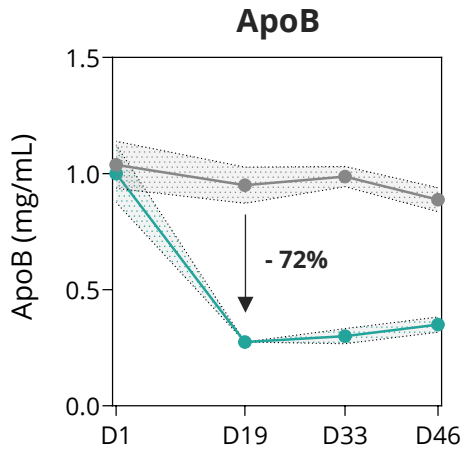
B4GALT1 editing and biomarkers in E3L.CETP mice *(N=10, 2mg/kg, LNP formulation, IV Q1W, D46, ddPCR)*

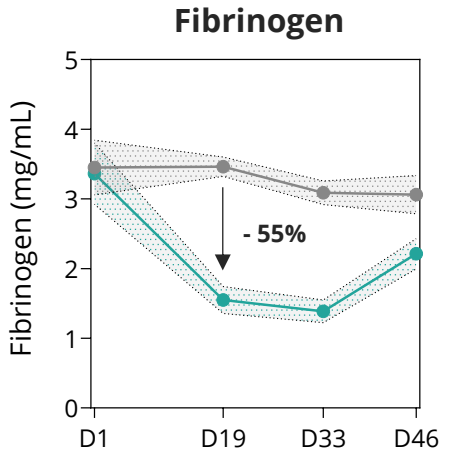












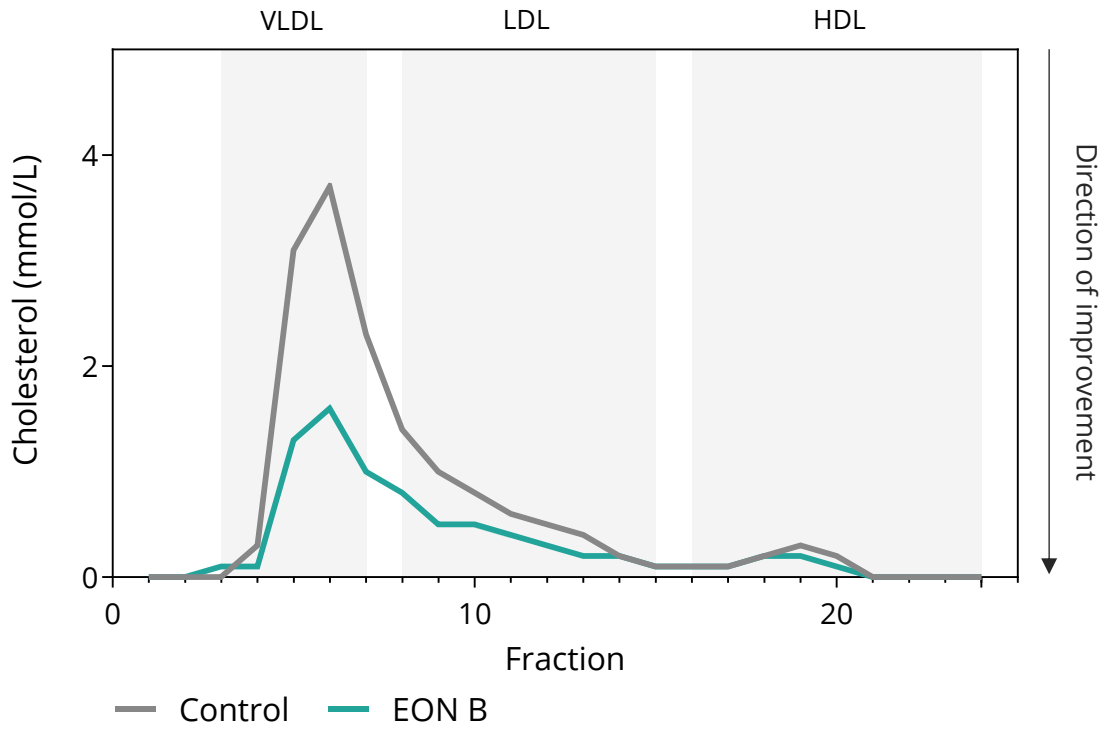
Following treatment with EON B, a marked reduction in total cholesterol, ApoB, and LDL-c by observed already at Day 19 confirms our approach to address cardiovascular diseases

B4GALT1 EON leads to a positive shift in lipoprotein profiles

Specifically targeting atherogenic lipoproteins

Impact on lipoprotein profile following editing of B4GALT1 in E3L.CETP mice

(N=10, 2mg/kg, LNP formulation, IV Q1W, D46)



- Treatment with EON B significantly decreases VLDL and LDL cholesterol compared to control
- These lipoproteins are associated with increased cardiovascular risk due to their role in atherosclerotic plaque formation
- HDL cholesterol which supports reverse cholesterol transport and is associated with reduced cardiovascular risk, remains unchanged

Summary & next steps

AX-1412 for CVD

EON-MEDIATED RNA EDITING OF B4GALT1

leads to the required reduction in galactosylation, reflecting the human genetics observed effect

LNP-DELIVERED EON EDITING OF B4GALT1

leads to editing and meaningful changes in biomarker effect on LDLC, CEPT, cholesterol and fibrinogen in an industry-standard in vivo disease model

FURTHER OPTIMIZATION OF A GALNAC DELIVERED EON ONGOING

to achieve a TPP desirable for CVD

UPDATE ON THE GALNAC OPTIMIZATION EFFORTS

expected in mid 2025

AX-2911 Program

Targeting PNPLA3 to address unmet medical needs in MASH

AX-2911 RNA-editing therapy to address Metabolic dysfunction associated steatohepatitis (MASH)

MASH and subsequent stages of liver disease **are very prevalent and still on the rise worldwide**. MASH individuals have a high unmet medical needs due to the **progressive** nature of the disease (cirrhosis and hepatocellular carcinoma) and **limited therapeutic options** available[1]

PNPLA3 (patatin-like phospholipase domain-containing 3) I148M is a variant **commonly reported** in the MASH population worldwide (20-60% of the patients) and is known as **associated risk factor**.[2,3] Approximately 8 million individuals in US and EU are homozygous for the 148M variant.

Axiomer EONs have the potential to change the Methionine into a Valine bringing the **PNPLA3 protein back to a WT-like functional conformation**.

[1]Sandireddy R, et al. Front Cell Dev Biol. 2024 Jul 16;12:1433857; [2]Romeo S, et al. Nat Genet. 2008 Dec;40(12):1461-5; [3]Salari N, et al. BMC Endocr Disord. 2021 Jun 19;21(1):125.

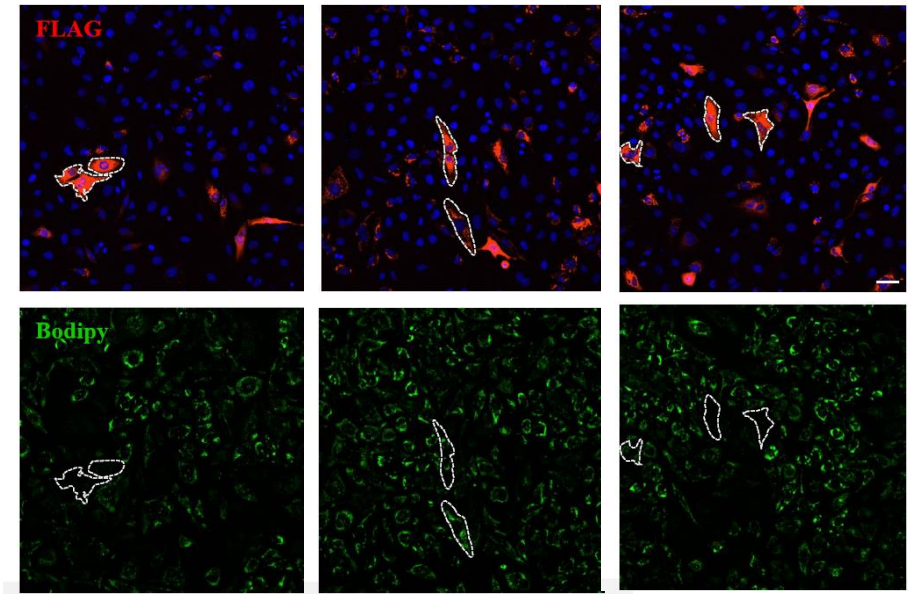
Axiomer™ creates a PNPLA3 protein with WT-like functionality

148I and 148V reports equivalence in lipid droplet sizes

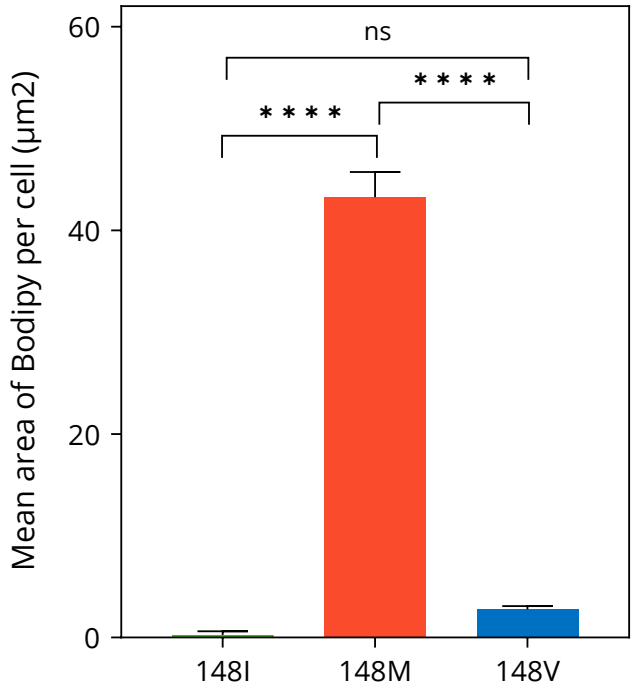
PNPLA3 148I
(WT)
Isoleucine (ATC)

PNPLA3 148M
(Mutant)
*Methionine (**A**TG)*

PNPLA3 148V
(Axiomer variant)
*Valine (**G**TG)*



Hoechst (nuclei), Bodipy (Lipids) and M2 anti-flag (PNPLA3)



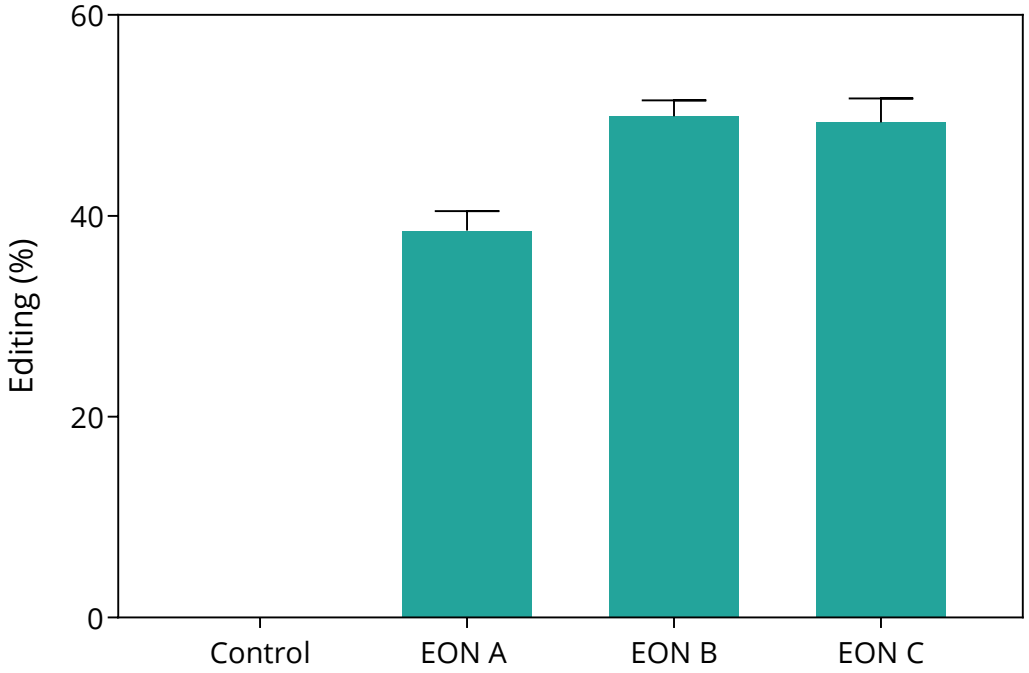
- The wild-type 148I shows smaller lipid droplets, reflecting normal lipid metabolism
- The 148M variant induces significantly larger lipid droplets, consistent with its pathogenic role in lipid metabolism disorders
- The corrected variant 148V results in wild-type like droplet sizes, suggesting a corrective effect on lipid accumulation, similar to 148I

Treatment conditions: HeLa cells, plasmid, transfection, 250uM linoleic acids, 24h, cell lipase activity by IF One-way ANOVA, ****, P<0.0001; Mean, SEM.

EON mediated PNPLA3 editing leads to over 50% RNA editing and change in lipid droplet

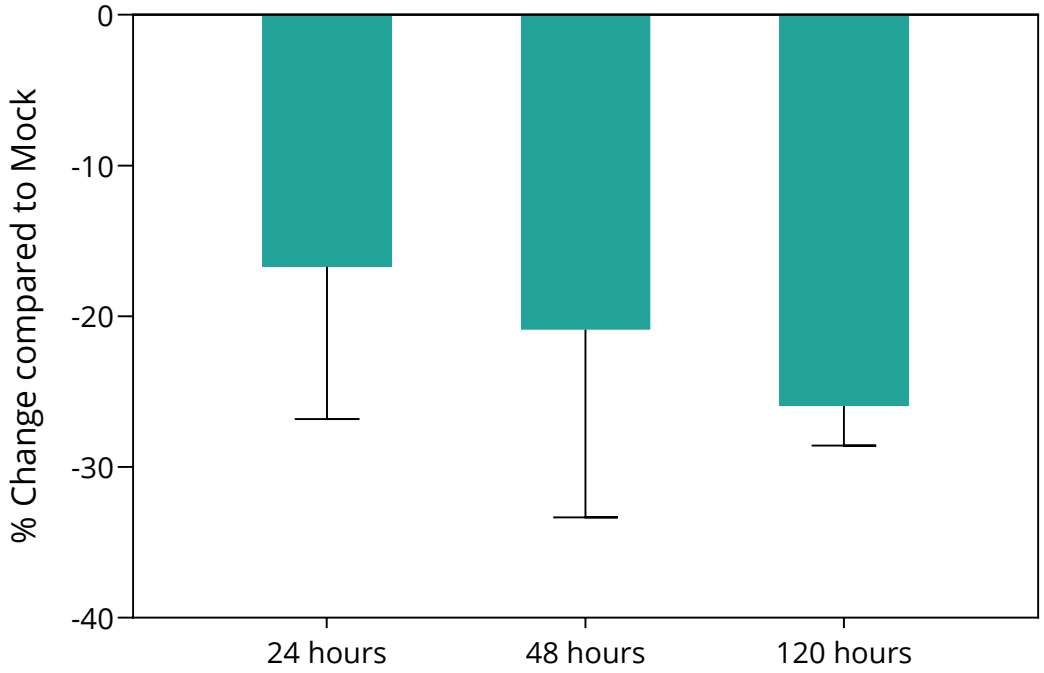
Editing of PNPLA3 in PHH

100nM EON, transfection, 72h, dPCR, mean, SEM, n=3



Change in intracellular lipid droplets post PNPLA3 148V EON treatment

Bodipy/DAPI stainings, 5µM EON, transfection, exposure to linoleic acid, mean, SEM, n=2



Summary & next steps

AX-2911 for MASH

CLINICAL CANDIDATE SELECTION

Final optimization of AX-2911 EONs ongoing for clinical candidate selection in 2025

SUBCUTANEOUS GALNAC-DELIVERY

expected with 3-6 monthly dosing interval

DEVELOPMENTAL ACTIVITIES

to start in 2025

CLINICAL TRIAL

to start in 2026

Well positioned

to advance Axiomer™

CLINICAL TRIAL RESULTS EXPECTED

across 4 trials in 2025 and 2026

- Clinical PoC data of NTCP trial in 2025
- Up to 4 clinical trials with data readouts in 2025/2026

RICH DISCOVERY PIPELINE

with potential for broad pipeline expansion

- Large number of potential therapeutic applications in discovery pipeline
- Broad applicability beyond current discovery pipeline

LEADING IP POSITION

- Axiomer™ is protected by >20 published patent families
- Continuously investing in expanding IP estate

VALIDATING STRATEGIC PARTNERSHIPS

- Eli Lilly collaboration valued up to $3.9B, with opportunity for near-term milestones
- Rett Syndrome Research Trust cofinancing of AX-2402 program
- Selectively form additional partnerships

STRONG BALANCE SHEET

- € 149.4 million cash and cash equivalents as of end of 2024
- Cash runway to mid-2027, excluding potential for additional BD-related upside

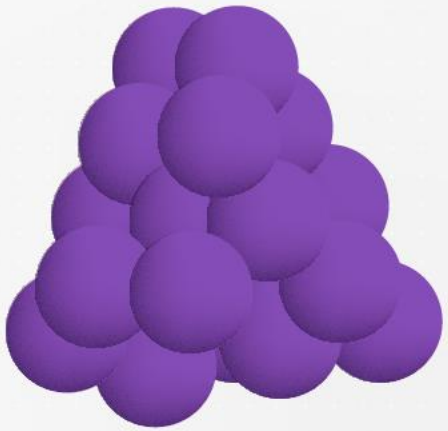
ProQR®

IT'S IN OUR RNA

Resource slides

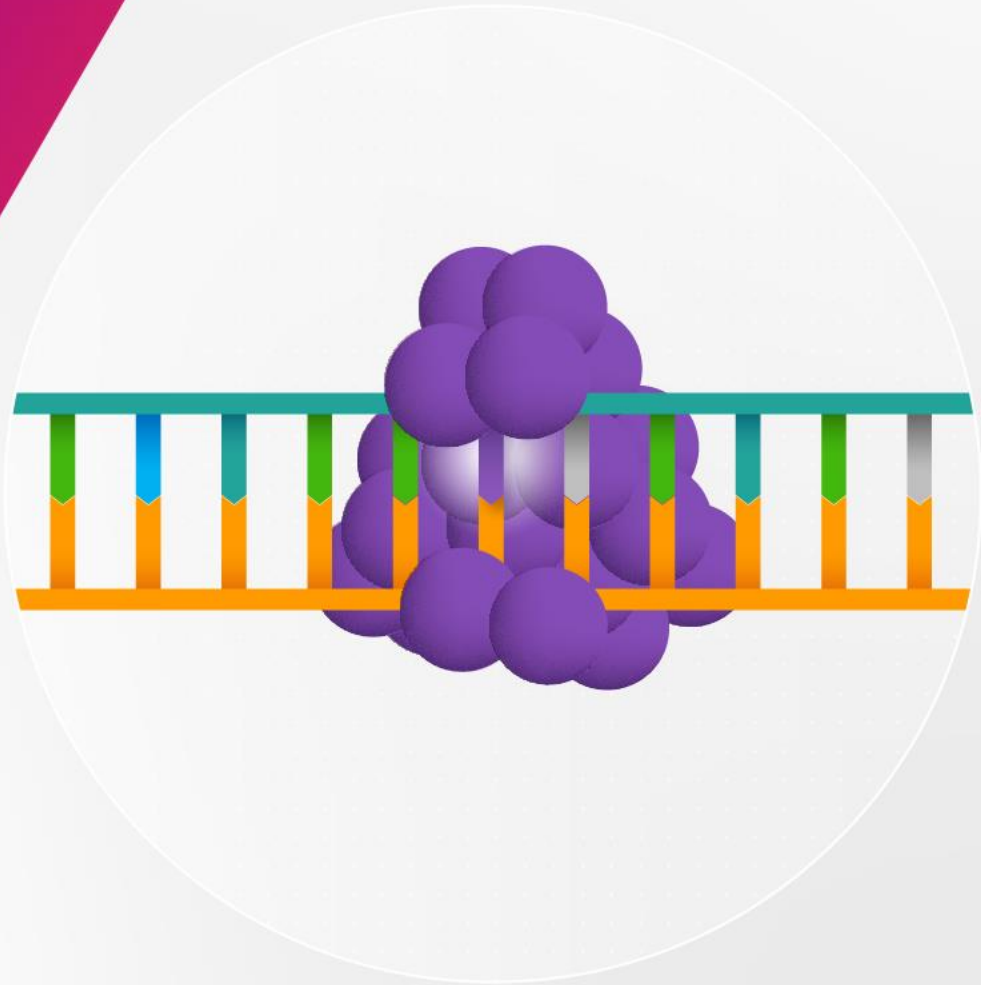
HOW DOES ADAR WORK?

Explained in 5 minutes



WHAT IS AXIOMER™?

Explained in 5 minutes



ProQR Leadership Team

Management Team

Daniel de Boer
Founder & CEO, Board Executive Director

Gerard Platenburg
Chief Scientific Officer, Board Executive Director

Dennis Hom
Chief Financial Officer

Cristina Lopez Lopez, MD, PhD
Chief Medical Officer

Sheila Sponselee
Chief People and Operations Officer

Board of Directors

James Shannon, MD
Chair

Alison Lawton

Begoña Carreño

Martin Maier, PhD

Bart Filius

Dinko Valerio

Theresa Heggie

Key Advisors

John Maraganore, PhD
Board advisor

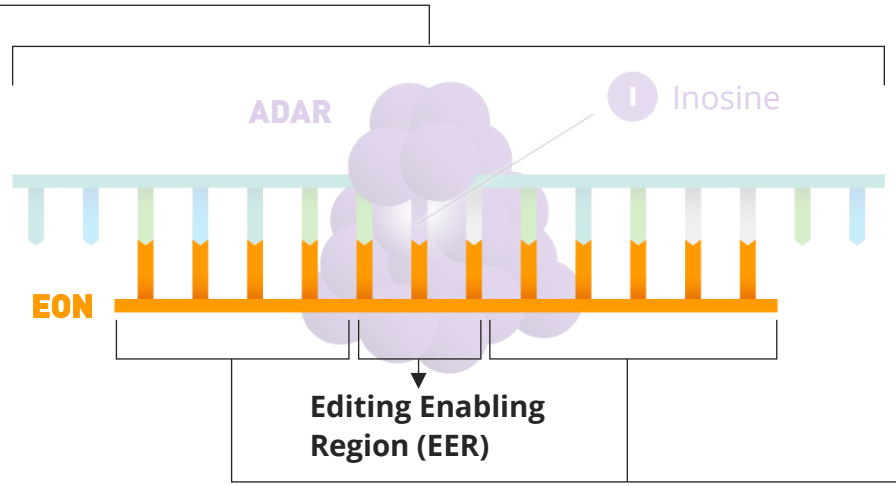
Peter A. Beal, PhD
ProQR Chief ADAR Scientist

Phillip D. Zamore, PhD
Scientific Advisory Board

Driving the development of optimized EONs for therapeutic use

Sequence defines target
RNA binding and provides stability

EON total length
Between ~25 - 30 nt



ADAR-binding region (ABR)
Backbone modifications enable ADAR binding, and disable off-target editing

Optimized sequence and chemistry define functionality

- Increase editing efficacy
- Bring metabolic stability
- Prevent off-target ('bystander') editing
- Ensure bioavailability (cell and tissue uptake)
- Offer safety and tolerability at therapeutic doses

ADAR: Adenosine deaminase acting on RNA, EON: Editing oligonucleotide, Nt: nucleotides

Leading IP supporting ADAR-mediated RNA editing platform technology

- Axiomer™ IP strategy commenced in 2014 with first patent application filings
- Currently 25 published patent families, comprising 33 national/regional patents
- Axiomer™ IP portfolio is constantly expanding
- Oppositions/appeals and several Third-Party Observations have been filed against a variety of applications and patents in the Axiomer™ IP portfolio, all by strawmen

ProQR Axiomer™ leading IP estate for ADAR-mediated RNA editing

- ProQR's Axiomer™ IP contains 3 early RNA editing platform patent families covering single-stranded oligonucleotides that recruit **endogenous** ADAR
- Oppositions/appeals and Third-Party Observations have been filed throughout these three patent families
- First (2014): oligonucleotides with a complementary (**targeting**) and a stem-loop (**recruiting**) portion
- Second (2016): oligonucleotides **without a stem-loop structure** but with **one or more mismatches** and chemical modifications
- Third (2016): oligonucleotides **without a stem-loop structure** but with specific chemical modifications in the '**Central Triplet**'

Overview of Axiomer™ related patents

Docket	Priority	Feature	Status	Remarks
1 (0004)	17DEC2014	Targeted RNA Editing using endogenous ADARs	Granted AU BR CA CN EP IL IN JP NZ US US ZA	Platform IP
2 (0013)	22JUN2016	Short EONs with wobble and/or mismatch base pairs	Granted AU IL JP KR US US US	Platform IP
3 (0014)	01SEP2016	Chemically modified short EONs	Granted AU CN EP IL JP KR NZ US US US ZA	Platform IP
4 (0016)	19JAN2017	EONs + protecting SONs (heteroduplex formation)	Granted US	Platform IP
5 (0023)	18MAY2018	PS linkages / chiral linkages (*e.g.,* PS, PN)	Published	Platform IP
6 (0025)	28JAN2019	Editing of PTC in exon 61 USH2A	Published	Target
7 (0026)	11FEB2019	Phosphonacetate linkages / UNA modifications	Published	Platform IP
8 (0029)	03APR2019	MP linkages	Published	Platform IP
9 (0031)	24APR2019	Editing inhibition	Published	Platform IP
10 (0032)	13JUN2019	Benner's base (dZ)	Published Granted CN ZA	Platform IP – with UC Davis (P Beal)
11(0035)	23DEC2019	Editing in exon 35 of ABCA4 for Stargardt disease	Published	Target
12 (0039)	23JUL2020	Split EONs	Published	Platform IP
13 (0045)	14FEB2022	PCSK9	Published	Target
14 (0046)	15JUL2022	5'-GA-3' editing	Published	Platform IP – with UC Davis (P Beal)
15 (0048)	15JUL2022	diF modification	Published	Platform IP
16 (0051)	21OCT2022	Heteroduplex Editing Oligonucleotide (HEON) complexes	Published	Platform IP
17 (0052)	24NOV2022	HFE	Published	Target
18 (0053)	09DEC2022	B4GALT1	Published	Target
19 (0054)	01DEC2022	ALDH2	Published	Target
20 (0055)	20JAN2023	AG1856 + (H)EONs	Published	Platform IP – with FU Berlin (A Weng)
21 (0057)	20FEB2023	ANGPTL3	Published	Target
22 (0058)	24MAR2023	KCC2	Published	Target
23 (0059)	24MAR2023	PNms linkages	Published	Platform IP
24 (0060)	27MAR2023	NTCP	Published	Target
25 (0061)	16JUN2023	RELN	Published	Target

ProQR Axiomer™ IP

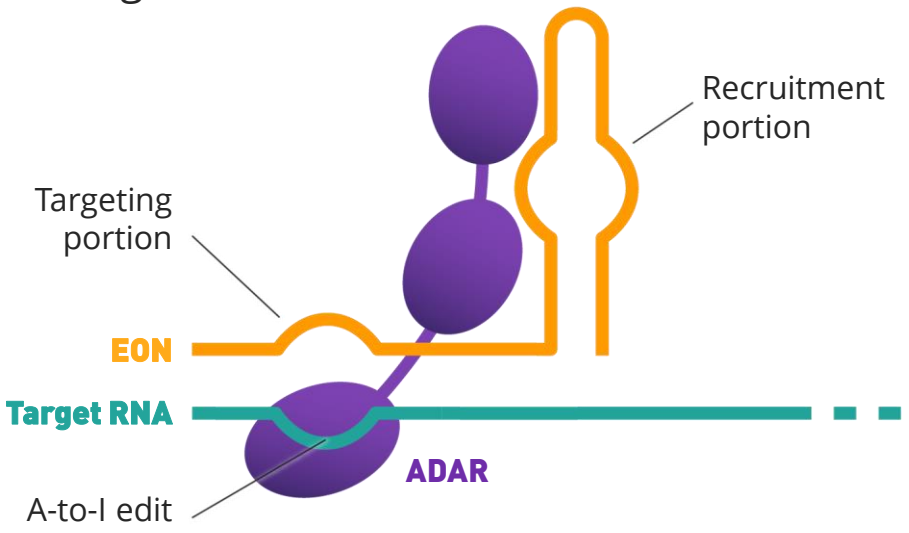
Broad coverage

- Axiomer™ patent claims are broad and cover:
  - **Any type of chemically modified oligonucleotide** aimed at RNA editing of **any possible target** and **any possible disease** using **endogenous** ADAR
  - Specific targets, including SERPINA1 (A1AT deficiency), IDUA (Hurler syndrome), LRRK2 (Parkinson's disease)
  - Oligonucleotides with chirally-controlled linkages
  - Oligonucleotides with all sorts of chemistries (also in the 'Central Triplet'), including **DNA**
- To note: claims directed to chemically modified oligonucleotides **do not cover viral delivery** of the oligonucleotide

Overview of key claims – 1

Granted claims in the 1st Axiomer™ patent family relate to (chemically modified) oligonucleotides that comprise:

- **A targeting portion** for binding to a target RNA incl. target adenosine
- **A recruitment portion** (hairpin structure) for recruiting **endogenous** ADAR to edit the target adenosine



EP 3 234 134 B1	Granted; appeal pending
US 10,676,737	Granted
US 11,781,134	Granted

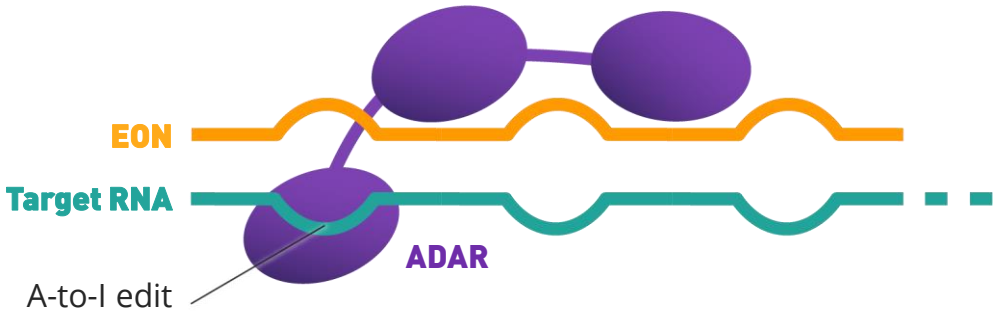
Claim 17 (US 11,781,134):

A method for making a change in a target RNA sequence in a human cell, comprising the steps of:

- introducing into the cell an oligonucleotide construct that is **sufficiently complementary** to bind by nucleobase pairing to the target RNA sequence, wherein the target RNA sequence comprises a target adenosine;
- allowing the formation of a double-stranded structure of the oligonucleotide construct with the target RNA sequence upon base pairing;
- allowing the double-stranded structure of the oligonucleotide and the target RNA sequence to recruit **an hADARl or hADAR2 enzyme naturally present in the cell;**
- allowing the hADARl or hADAR2 enzyme to perform deamination of the target adenosine to an inosine in the target RNA sequence.

Overview of key claims – 2

Granted claims in the 2nd Axiomer™ patent family relate to oligonucleotides that do **not** have a hairpin structure, but instead have one or more wobbles and/or mismatches, and chemical modifications in the base, ribose sugar and/or linkage to increase stability and are still able to recruit **endogenous** ADAR to edit the target adenosine.



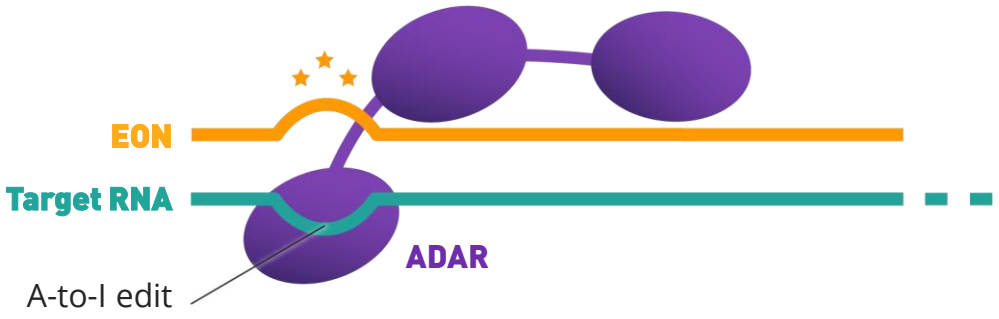
US 10,988,763	Granted
US 11,649,454	Granted
US 12,018,257	Granted

Target-specific claims are directed to:

- An AON capable of forming a double stranded complex with a target RNA in a cell, wherein: the target RNA encodes **alpha1- antitrypsin (A1AT)**, LRRK2, or the target RNA is encoded by the IDUA gene
- The AON is complementary to a target RNA region comprising a target adenosine
- The AON comprises one or more nucleotides with **one or more sugar modifications**
- The AON does not comprise a portion that is capable of forming an intramolecular stem-loop structure that is capable of binding an ADAR enzyme
- The AON is shorter than 100 nucleotides
- The AON **optionally comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10** mismatches, wobbles and/or bulges with the complementary target RNA region, and, wherein formation of the double stranded complex between the AON and the target RNA results in the deamination of the target adenosine by an ADAR enzyme **present in the cell**

Overview of key claims – 3

Granted claims in the 3rd Axiomer™ patent family relate to oligonucleotides that do **not** have a hairpin structure, but have **chemical modifications** in the base, ribose sugar and/or linkage to increase stability and are still able to recruit **endogenous** ADAR to edit the target adenosine.



EP 3 507 366 B1	Granted; appeal pending
US 10,941,402	Granted
US 11,851,656	Granted
US 12,203,072	Granted

Claim 1 (US 11,851,656):

An antisense oligonucleotide (AON) comprising a Central Triplet of 3 sequential nucleotides, wherein

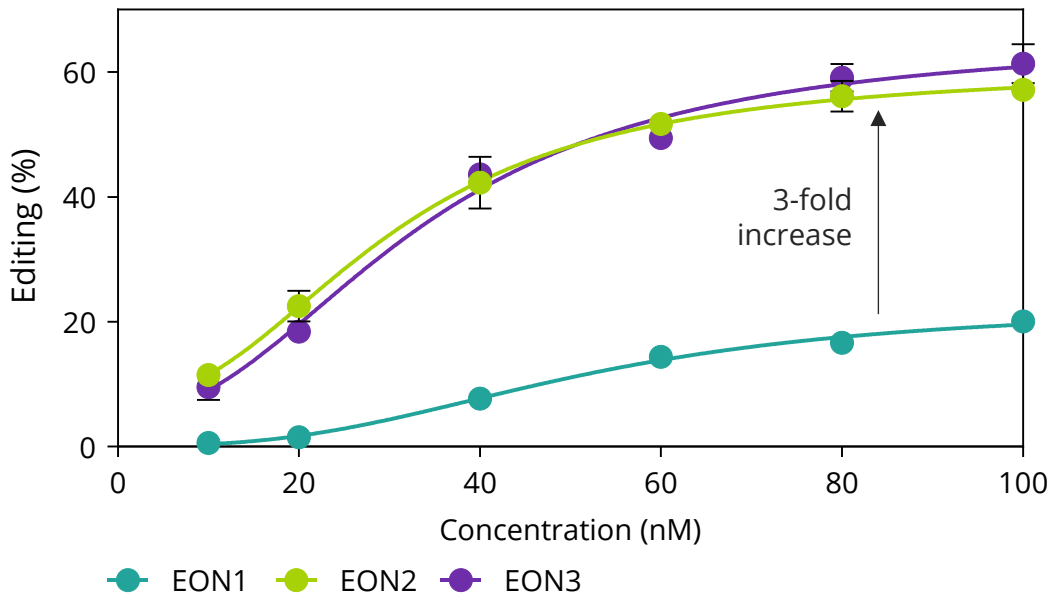
- the AON is capable of forming a double stranded complex with a target RNA molecule in a cell comprising a target adenosine;
- the nucleotide directly opposite the target adenosine is the middle nucleotide of the Central Triplet;
- 1, 2 or 3 nucleotides in the Central Triplet comprise **a sugar modification and/or a base modification** to render the AON more stable and/or more effective in inducing deamination of the target adenosine; with the proviso that the middle nucleotide does not have a 2'-O-methyl modification;
- the AON does not comprise a 5'-terminal O6-benzylguanosine;
- the AON does not comprise a portion that is capable of forming an intramolecular stem-loop structure that is capable of binding a mammalian ADAR enzyme present in the cell; and
- the AON can mediate the deamination of the target adenosine by the ADAR enzyme.

Axiomer™ EON treatment led to NTCP Q68R variant in WT hepatocytes

Editing of NTCP RNA modulates BAs reuptake in a dose dependent fashion

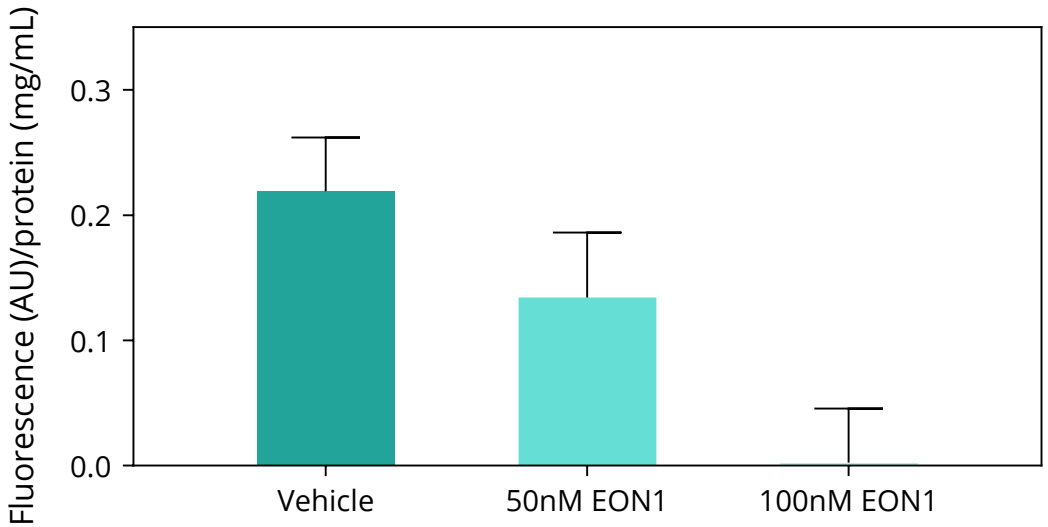
EONs targeting NTCP RNA optimization in PHH

Transfection, n=3, 72 hours, dPCR, mean±SEM



NTCP-mediated BAs uptake in HepaRG cells with Axiomer EON treatment

n=3, 50-100nM, 72 hours, mean±SEM



Leveraging expertise in EONs optimization, including adjustment of sequence and chemistry, lead to increased potency of EONs targeting NTCP RNA.

Early generation of EONs (EON1) induces a dose-response inhibition of BAs in vitro confirming its mediation by NTCP

BAs: Bile acids, NTCP: Na-taurocholate cotransporting polypeptide, BAs mentioned in this experiment are specifically Tauro-nor-THCA-24-DBD. *SLC10A1* is the gene that encodes for NTCP protein. Reference: Cnubben, N. et al. (2024) ASGCT 27th Annual meeting abstracts, Molecular Therapy. Volume 32, Issue 4, 1 – 889 (Abstract 705, p. 355)

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