ProQR®

DEVELOPING RNA-EDITING MEDICINES

for patients in need

Nasdaq: PRQR

December 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 “continue,” "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 business, technology, strategy, preclinical and clinical model data; our initial pipeline targets and the upcoming strategic priorities and milestones related thereto; the continued advancement of our lead development pipeline programs, including approved, ongoing and planned clinical trials; expectations regarding the planned Phase 1 clinical study of AX-0810 in NTCP for cholestatic diseases, including the planned trial design, implementation and initiation in the Netherlands, and our ability to recruit for and complete a Phase 1 clinical trial for AX-0810 in healthy volunteers; expectations regarding the safety and therapeutic benefits of AX-0810, including the planned dosing levels and their efficacy; the anticipated timing of initial Phase 1 clinical data for our lead program, AX-0810, in Q4 2025, and clinical updates across multiple programs in 2025; the continued development and advancement of our Axiomer™ platform; the therapeutic potential of our Axiomer RNA editing oligonucleotides and product candidates; the timing, progress and results of our preclinical studies and other development activities, including the release of data related thereto; our patent estate, including our anticipated strength and our continued investment in it; and the potential of our technologies and product candidates. 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 expressed or implied by 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 most recent annual report filed on Form 20-F. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies and clinical trials and other development activities by us and our collaborative partners whose operations and activities may be slowed or halted shortage and pressure on supply and logistics on the global market, economic sanctions and international tariffs; the likelihood of our preclinical and clinical programs being initiated and executed on timelines provided and reliance on our contract research organizations and predictability of timely enrollment of subjects and patients to advance our clinical trials and maintain their own operations; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; the potential for future data to alter initial and preliminary results of early-stage clinical trials; the unpredictability of the duration and results of the regulatory review of applications or clearances that are necessary to initiate and continue to advance and progress our clinical programs; 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; and risks related to macroeconomic conditions and market volatility resulting from global economic developments, geopolitical events and conflicts, high inflation, rising interest rates, tariffs and potential for significant changes in U.S. policies and regulatory environment. 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.

Axiomer™ advancing

to value inflection

EON-GUIDED ADAR RNA EDITING, INVENTED BY PROQR

Now translating Axiomer in clinic

Foundational IP estate securing long-term leadership in the field

DIFFERENTIATED PIPELINE FOR RANGE OF HIGH UNMET NEEDS

AX-0810 Phase 1 trial dosing

ProQR leading neurological application of RNA editing; robust and durable efficiency across regions of CNS

HIGH IMPACT STRATEGIC PARTNERSHIPS

With Eli Lilly, Rett Syndrome Research Trust

Accelerating development and creating meaningful value for patients

OVER A DECADE OF RNA THERAPY LEADERSHIP

With experienced team and further strengthened management to drive the future of ProQR

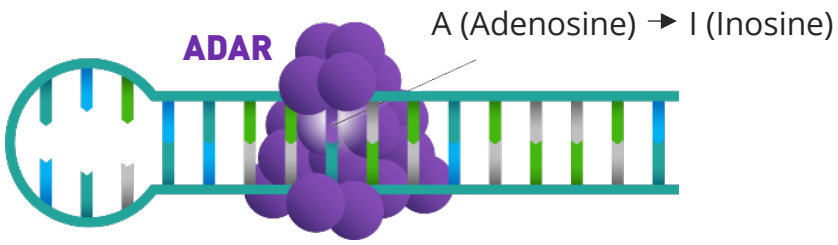
RUNWAY INTO MID 2027

Funding the clinical readout of multiple programs

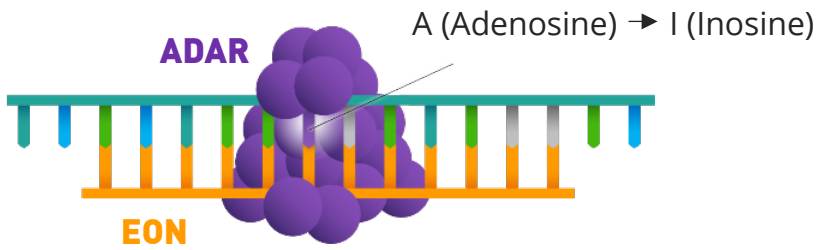
€ 106.9 million cash and cash equivalents as of end of Q3 2025

How Axiomer™ edits RNA

NATURAL ADAR EDITING



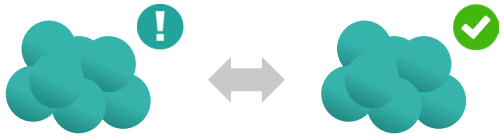
EDITING OLIGONUCLEOTIDE *(EON)-directed* EDITING



MODULATE

Modify protein function

CORRECT



Correct disease-causing mutations

PROTECT

Introduce protective variants

Pipeline horizons

Near term, next, and beyond

Near term

AX-0810 IN THE CLINIC

Axiomer in first-in-human (FIH) trial with AX-0810 targeting NTCP in **cholestatic disease;** Phase 1 trial dosing healthy volunteers to establish safety, PK, and target engagement

Next

AX-2402 RAPIDLY ADVANCING

Leading RNA editing CNS capability and first neuro pipeline program, AX-2402 for **Rett syndrome**, advancing rapidly – positioning ProQR at the forefront of neurological RNA editing medicines

Beyond

BROADER EXPANSION

Continued advancement of our platform, including earlier programs AX-1412 for **CVD** and AX-2911 for **MASH**, broadening the portfolio

Addressing unmet need in cholestatic diseases through NTCP modulation

Cholestatic diseases have high unmet medical need, especially **Primary Sclerosing Cholangitis** affecting adults (~80,000 patients) and Congenital **Biliary Atresia** affecting pediatrics early in life (~20,000 patients). Both conditions have no approved therapies and may require liver transplantation.[1,2]

Patients **accumulate bile acids** in liver leading to fibrosis and ultimately liver failure.

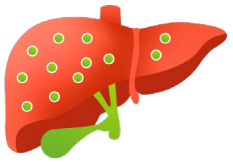
Learnings from human genetics and literature demonstrate that **modulation of the NTCP channel** responsible for majority of bile acids re-uptake in liver cells could lead to **hepato-protective effects**.

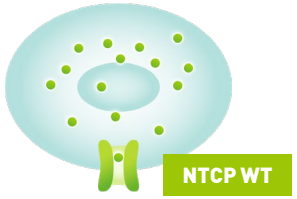
NTCP, sodium taurocholate co-transporting polypeptide. References: [1]Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; [2]Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999

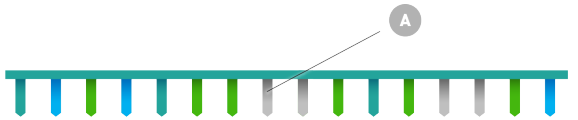
AX-0810: first-in-class RNA editing therapy targeting NTCP for cholestatic diseases

LIVER WITH CHOLESTATIC DISEASE

High concentration of bile acids in hepatocytes

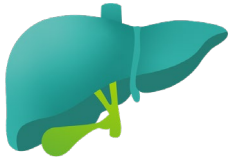


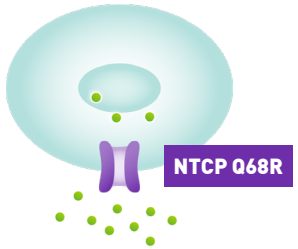


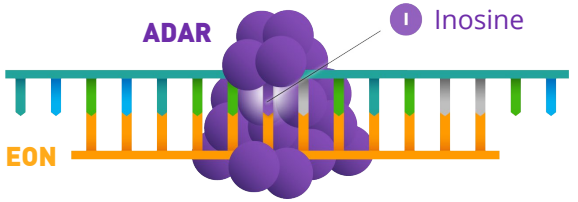


AX-0810 STRATEGY FOR DISEASED LIVER

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







- AX-0810 makes an A-to-I edit that mimics a variant to enable lower bile acids concentration in hepatocytes
- AX-0810 is designed to be a disease-modifying treatment

Therapeutic goals

- Reduce inflammation and fibrosis from bile acids toxicity
- Alleviate symptoms in PSC and BA
- Prevent or delay cirrhosis, organ failure, and transplant

ADAR, Adenosine Deaminase Acting on RNA; BA, Biliary atresia; EON, Editing Oligonucleotide; NTCP, sodium taurocholate co-transporting polypeptide; PSC, Primary Sclerosing Cholangitis; WT, Wild Type.

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 activity 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.

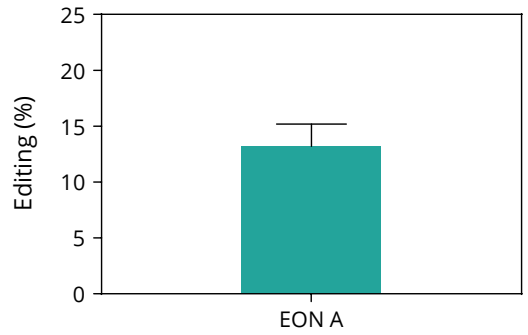
[1]Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-22; [2]Vaz FM, et al. Hepatology. 2015 Jan;61(1):260-7; [3]Schneider AL, et al. Clin Res Hepatol Gastroenterol. 2022 Mar;46(3):101824; [4]Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069; [5]Salhab A, et al. Gut. 2022 Jul;71(7):1373-1385; [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.

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

Editing efficiency | **Plasma total bile acids**

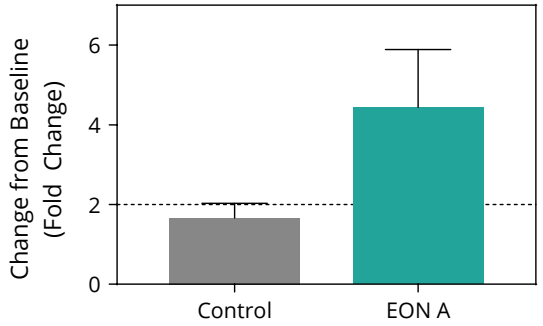
NTCP RNA Editing in Humanized Mice

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



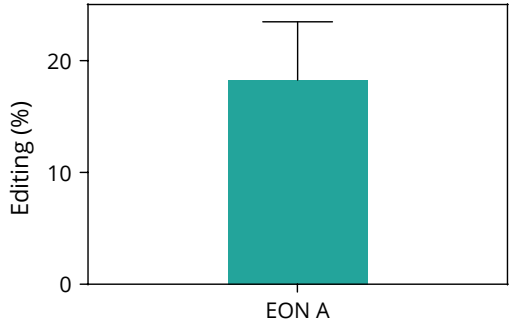
Plasma TBA in Humanized Mice

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



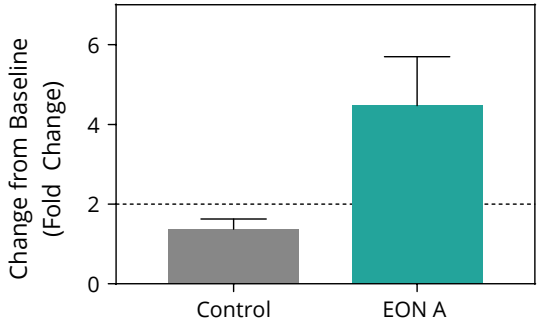
NTCP RNA Editing in NHP

(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)

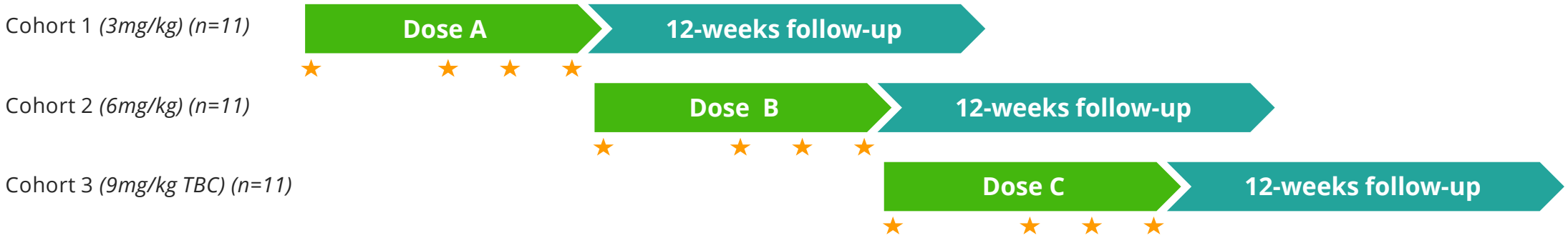


- EON A results in consistent editing data in humanized mouse model and NHP *in vivo* with approx. 15% editing reaching expected NTCP modulation
- Reaching >2-fold changes in biomarkers - expected impact on plasma bile acids levels following NTCP EON treatment

AX-0810 first-in-human (FIH) Phase 1 trial

Dosing healthy volunteers to assess safety, tolerability, PK, and biomarker-based target engagement of AX-0810

Multiple ascending dose (MAD) N=33 (24 on treatment, 9 on placebo)



DMC safety reviews before proceeding to next dose and dose escalation is sequential during the dosing phase

Treatment

AX-0810 GalNAc conjugated editing oligonucleotide

Objectives

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

Key endpoints

- Change in bile acids levels
- Bile acids profile
- TUDCA challenge
- Liver biomarkers

Phase 1 progressing

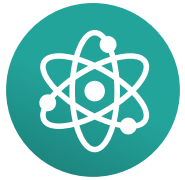
- Cohort 1 safety, tolerability, PK towards year end 2025/early 2026
- Target engagement data on all cohorts in H1 2026

CTA, Clinical Trial Application; DMC, Data Monitoring Committee; MAD, Multiple Ascending Dose; PK, Pharmacokinetics; TUDCA, Tauroursodeoxycholic acid; AX-0810 CTA has been approved in Europe (October 2025).

Clinically relevant biomarker strategy to inform future development

From target engagement to pharmacodynamics biomarkers

TARGET ENGAGEMENT



DISEASE RELEVANCE

MECHANISTIC PHARMACODYNAMIC

Total bile acids (TBAs) levels

Assess effect on bile acids transporter activity

Bile acids profile

Confirm NTCP specificity

Conjugated bile acids clearance (TUDCA)

Differentiate effect between doses to inform dosing regimen in disease population

NTCP, sodium taurocholate co-transporting polypeptide; TUDCA, Tauroursodeoxycholic acid.

Learnings from the FIH translating into the disease population

Healthy volunteers	Disease population
Plasma TBA from normal to ↑ with AX-0810	**Plasma TBA** From ↑ in cholestasis to ↑↑↑ with AX-0810
Plasma conjugated bile acids from normal to ↑ with AX-0810	**Plasma conjugated bile acids** from normal to ↑ with AX-0810
TUDCA challenge from normal clearance to ↓ with AX-0810	**TUDCA challenge** from ↓ clearance to ↓↓ with AX-0810
	Disease endpoints: ↓ ***Liver enzymes***
	Disease endpoints: ↓ ***Cholestasis markers***
	Disease endpoints: ↓ ***Fibrosis markers***

FIH, First in Human; TBA, Total Bile Acids.

AX-2402 RNA editing therapy targeting MECP2 for Rett Syndrome

Rett Syndrome is a **devastating** and **progressive neuro-developmental** 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 neuro-degenerative disorder** and restoring levels of the MECP2 protein has shown to **reverse symptoms** in mice.[3]

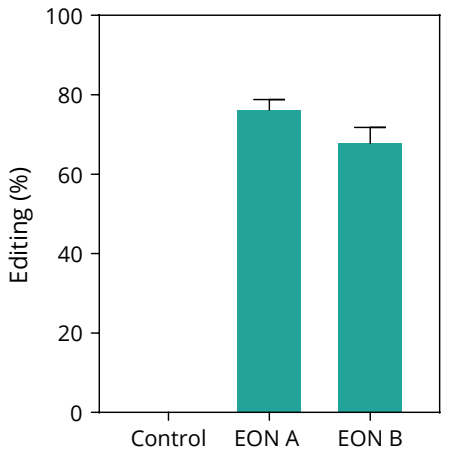
Axiomer has the potential to **restore** the precise **level of MECP2 protein regulatory function**, which is lacking in Rett Syndrome and become a disease modifying therapy.

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

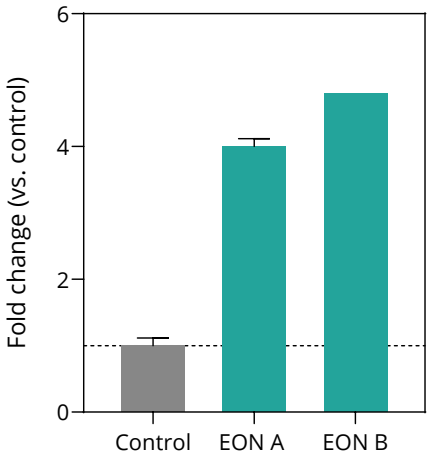
Editing increases mRNA levels and restores protein expression; Broad editing distribution in CNS

R270X MECP2 editing



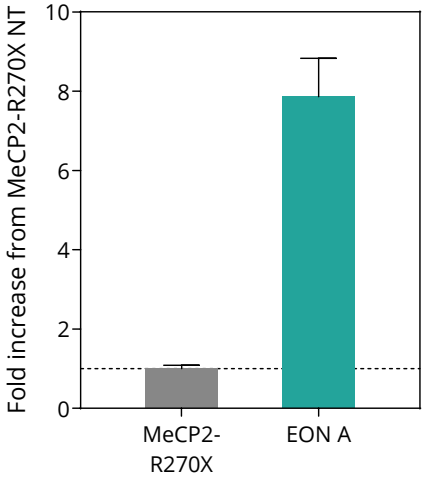
Up to 80 % editing of R270X MECP2 in patient fibroblasts

MECP2 RNA levels



Increased MECP2 RNA levels due to PTC recoding and NMD inhibition

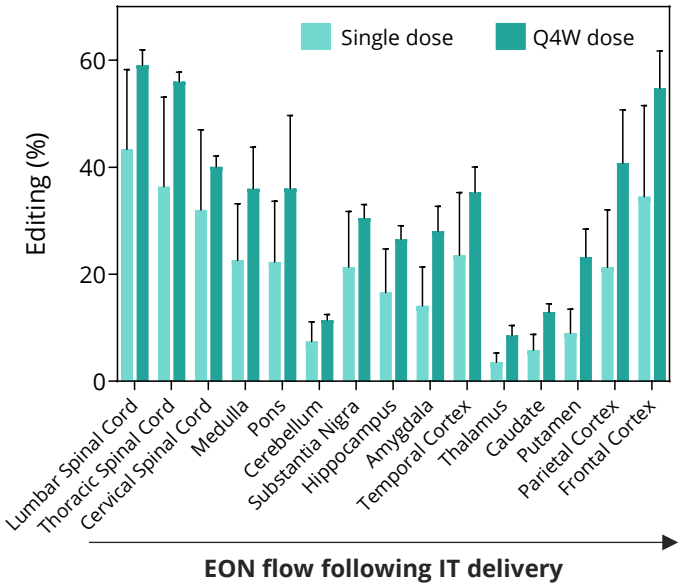
R270W MECP2 protein levels



Increased R270W MECP2 protein levels

RNA editing in NHP *in vivo*

IT administration, ACTB, 10.6mg, single dose (SD)/Q4W, N=2-3, 12 weeks, ddPCR, mean±SEM



Stable and prolonged editing efficiency in both superficial and deep brain regions

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.

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 cardio-vascular disease**.

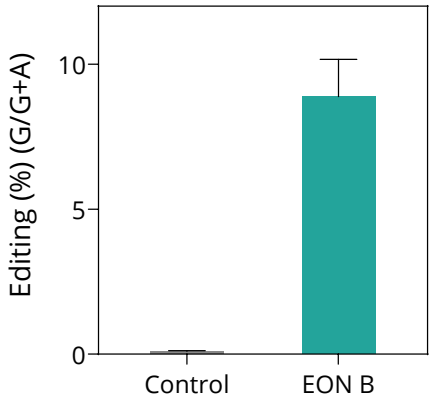
AX-1412 may become a **stand-alone cardio-vascular therapy** that may also work **synergistically with standard of care** to further reduce risk of CVDs.

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

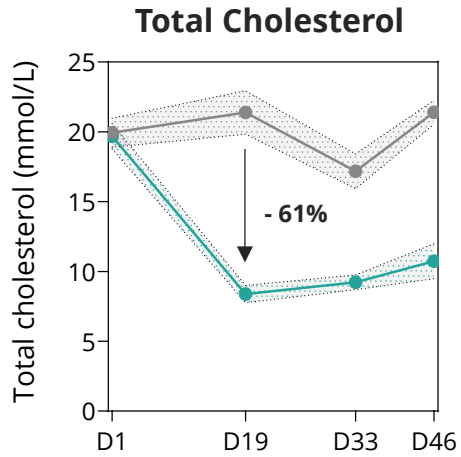
EON-mediated editing of B4GALT1 leads to meaningful effect on key biomakers in E3L.CETP Mice

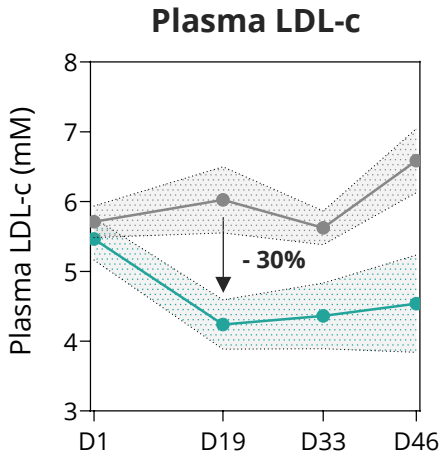
B4GALT1 editing and biomarkers in E3L.CETP mice

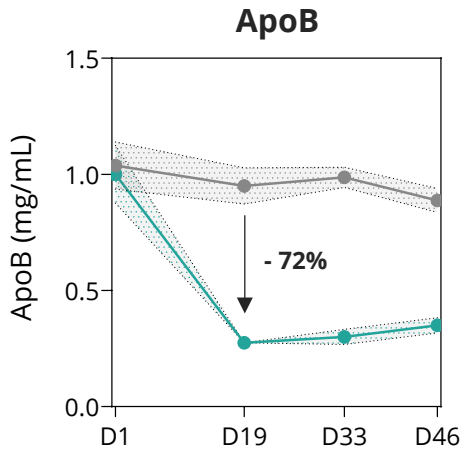
(N=10, 2mg/kg, LNP formulation, IV Q1W, D46, ddPCR)

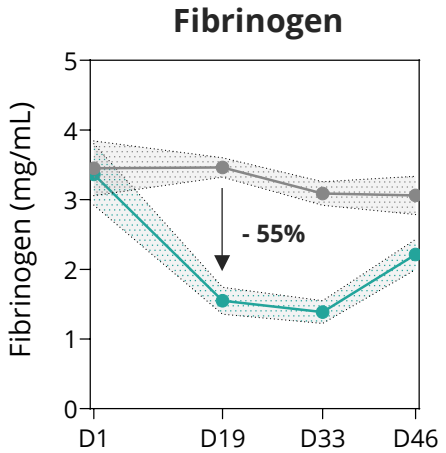


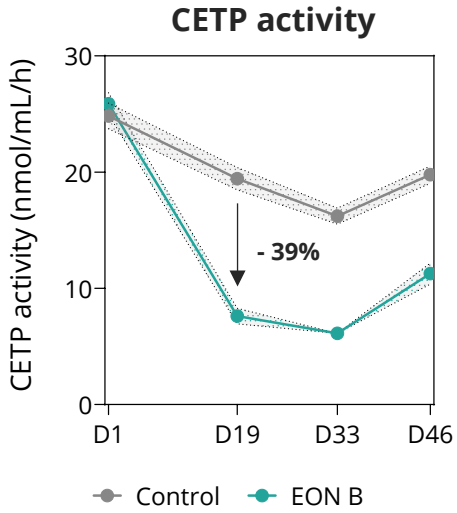
Treatment with EON B led to a reduction in total cholesterol, ApoB, and LDL-c confirming this therapeutic approach to address cardiovascular diseases











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] Approx. 8 million individuals in US and EU are homo-zygous 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.

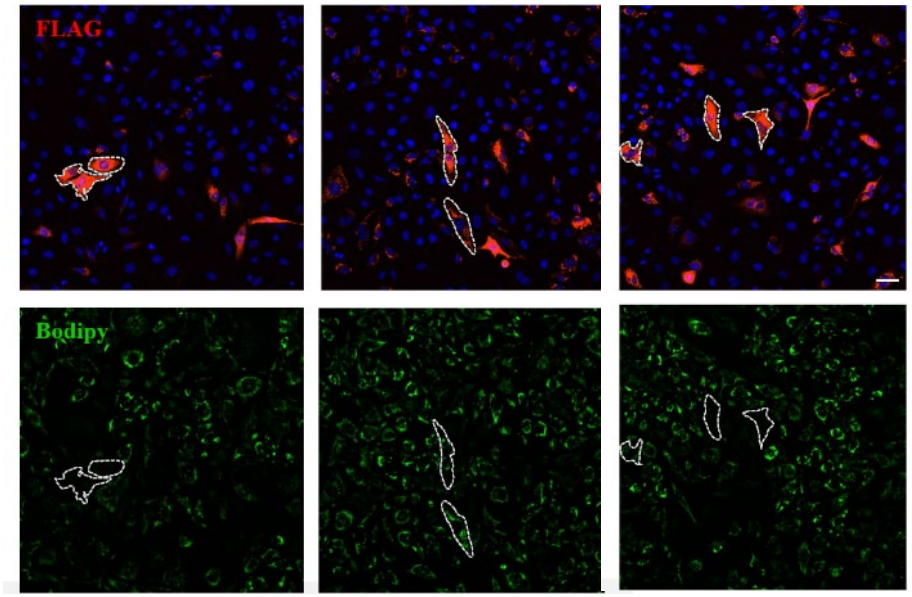
Axiomer™ creates a PNPLA3 protein with WT-like functionality

148I and 148V reports equivalence in lipid droplet sizes

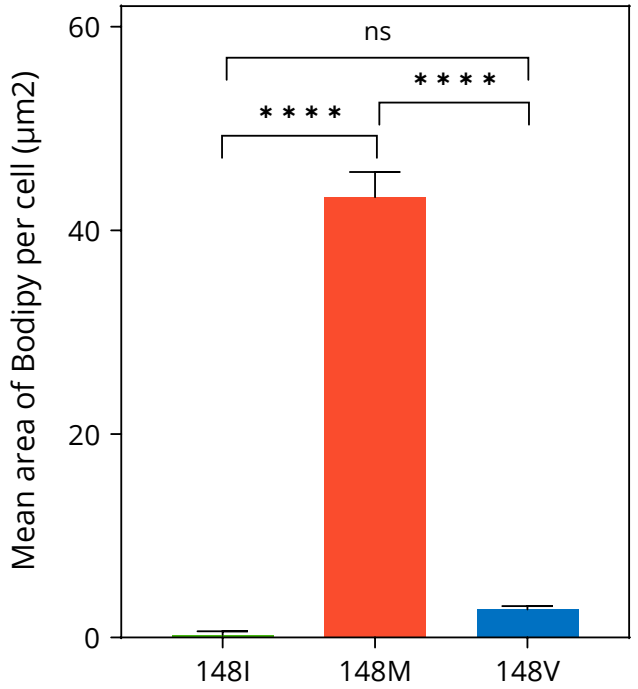
PNPLA3 148I
(WT)
Isoleucine (ATC)

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

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



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

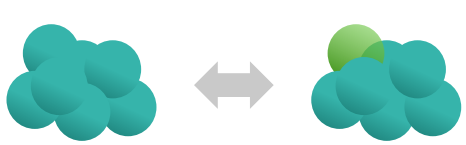


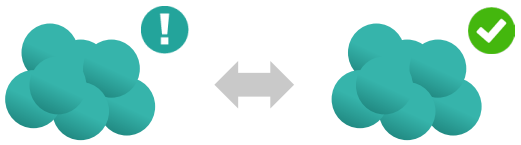
- The wild-type 148I shows smaller lipid droplets, reflecting normal lipid metabolism
- The 148M variant induces significantly larger lipid droplets, consistent with its pathogenic role in lipid metabolism disorders
- The corrected variant 148V results in wild-type like droplet sizes, suggesting a corrective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

Pipeline leverages the promise of RNA editing

Demonstrating applications to modulate, correct and protect





MODULATE	CORRECT		PROTECT
AX-0810 *NTCP for cholestatic diseases*	**AX-2402** *MECP2 program for Rett syndrome R270X*	**AX-2911** *PNPLA3 program for MASH*	**AX-1412** *B4GALT1 program for cardiovascular diseases*
Preliminary safety and PK data towards end of 2025; Target engagement in H1 2026	*Multiple additional Rett programs*		

Lilly **Partnered pipeline** *10 undisclosed targets (option to expand to 15)*

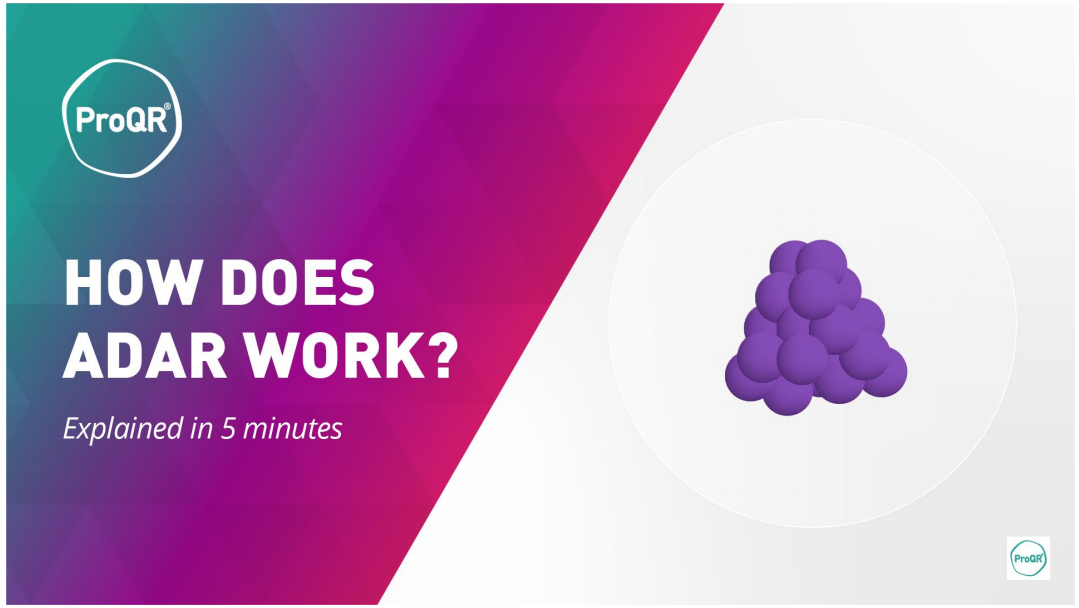
B4GALT1, Beta-1,4-galactosyltransferase 1; MECP2, Methyl CpG binding protein 2; NTCP, sodium taurocholate co-transporting polypeptide; PNPLA3, Patatin-like phospholipase domain-containing 3.

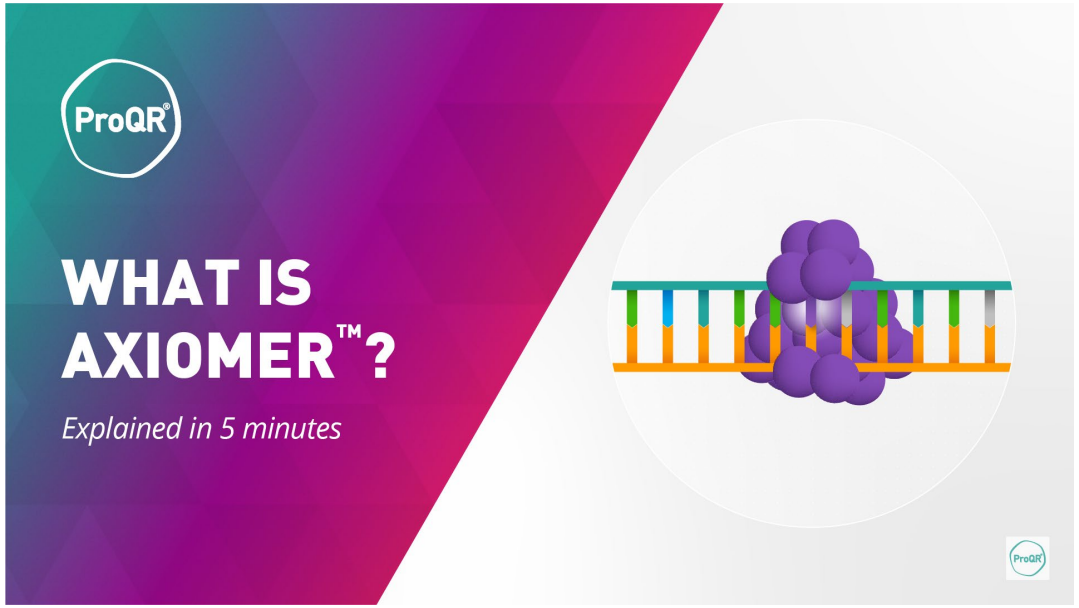
ProQR®

IT'S IN OUR RNA

Resource slides

Video


ProQR
HOW DOES ADAR WORK?
Explained in 5 minutes

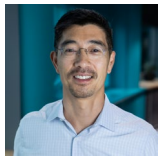

ProQR
WHAT IS AXIOMER™?
Explained in 5 minutes

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

ProQR development pipeline

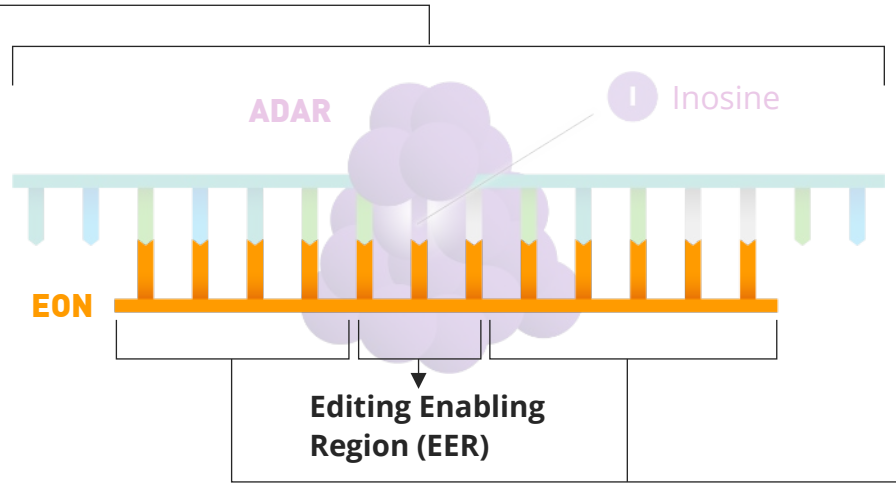
	TARGET	DISCOVERY	NON-CLINICAL	CLINICAL	NEXT MILESTONE	ESTIMATED POPULATION
DEVELOPMENT PIPELINE						
AX-0810 *for Cholestatic diseases*	NTCP				Initial safety and PK data[1]	~100K patients[2]
AX-2402 *for Rett syndrome*	MECP2 R270X				Candidate selection	~5K patients
AX-1412 *for Cardiovascular disease*	B4GALT1				Scientific update GalNAc	~200M patients[3]
AX-2911 *for MASH*	PNPLA3				Candidate selection	~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]CTA authorization announced October 2020. [2]Approximately 100K people affected with Primary Sclerosing Cholangitis and Biliary Atresia in US and EU5. [3]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

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

Axiomer™ RNA editing journey

From invention to the clinic

ProQR invents oligo mediated RNA Editing recruiting endogenous ADAR

2014

2014-2018+

ProQR secures broad key patent positions on ADAR-mediated RNA editing

2015-2021

ProQR optimizes the ADAR platform in stealth

2021

ProQR and Eli Lilly enter into first 5 target partnership worth $1.25B

ProQR pivots to solely focus on ADAR editing

2022

ProQR and Eli Lilly expand partnership to 10 targets worth ~$3.9B

2023

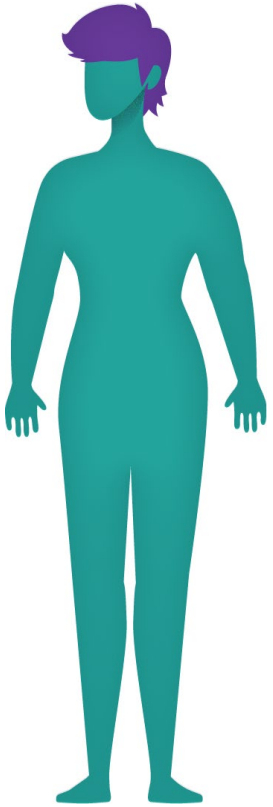
ProQR demonstrates >50% RNA editing in CNS and liver in NHP and announces pipeline

ProQR starts a FIH Clinical Trial targeting NTCP

2025

2024

- *ProQR first in the field to report a disease relevant biomarker effect using Axiomer in NHP.*
- *Initial indication of good safety profile.*
- *Initial clinical validation of ADAR editing.*

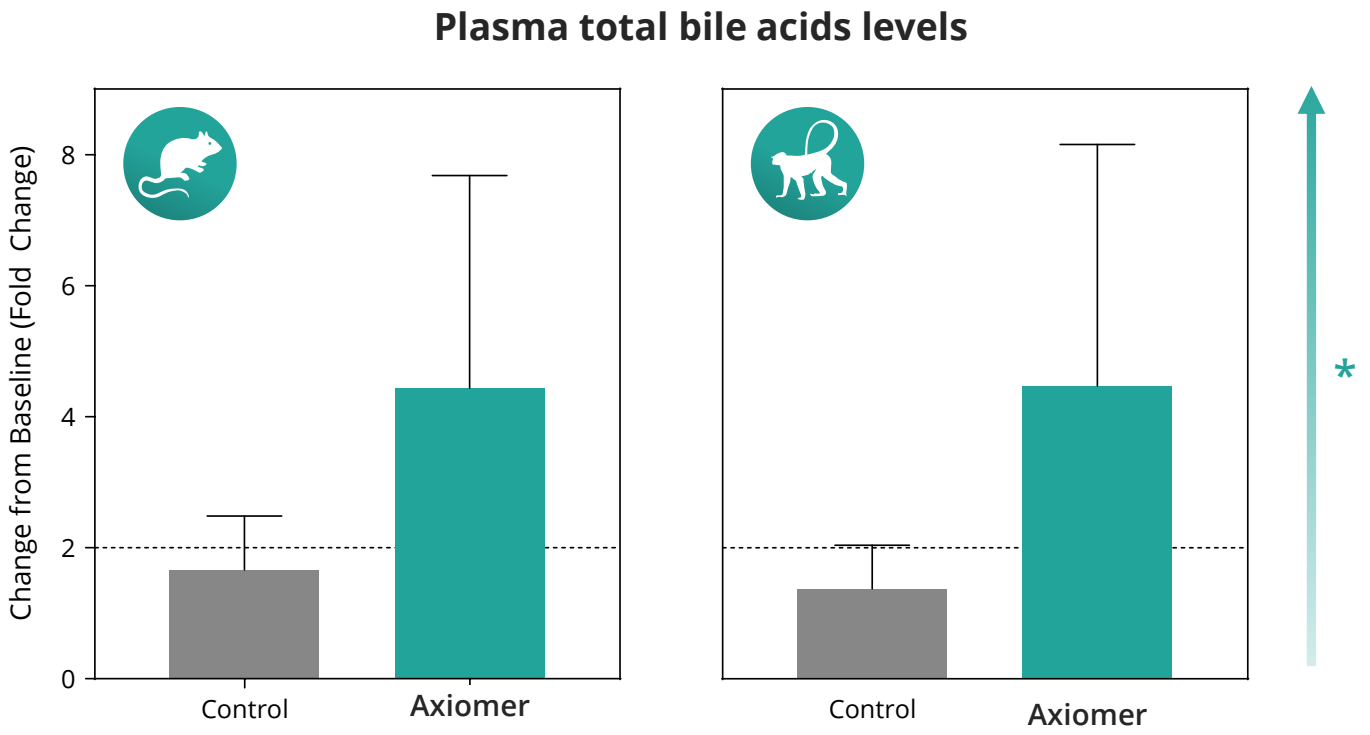


ADARs: Adenosine deaminases acting on RNA, EONs: Editing oligonucleotides

Assessing total bile acids (TBA) levels

Demonstrating AX-0810 EON effect on liver bile uptake function

- NTCP transporter is responsible for **>90% of total bile acid (TBA) reuptake** from the bloodstream into the liver
- NTCP modulation of bile acids reuptake function by AX-0810 is expected to result in an **increase in plasma TBA**
- A 2-fold change is expected to be meaningful in the patient population



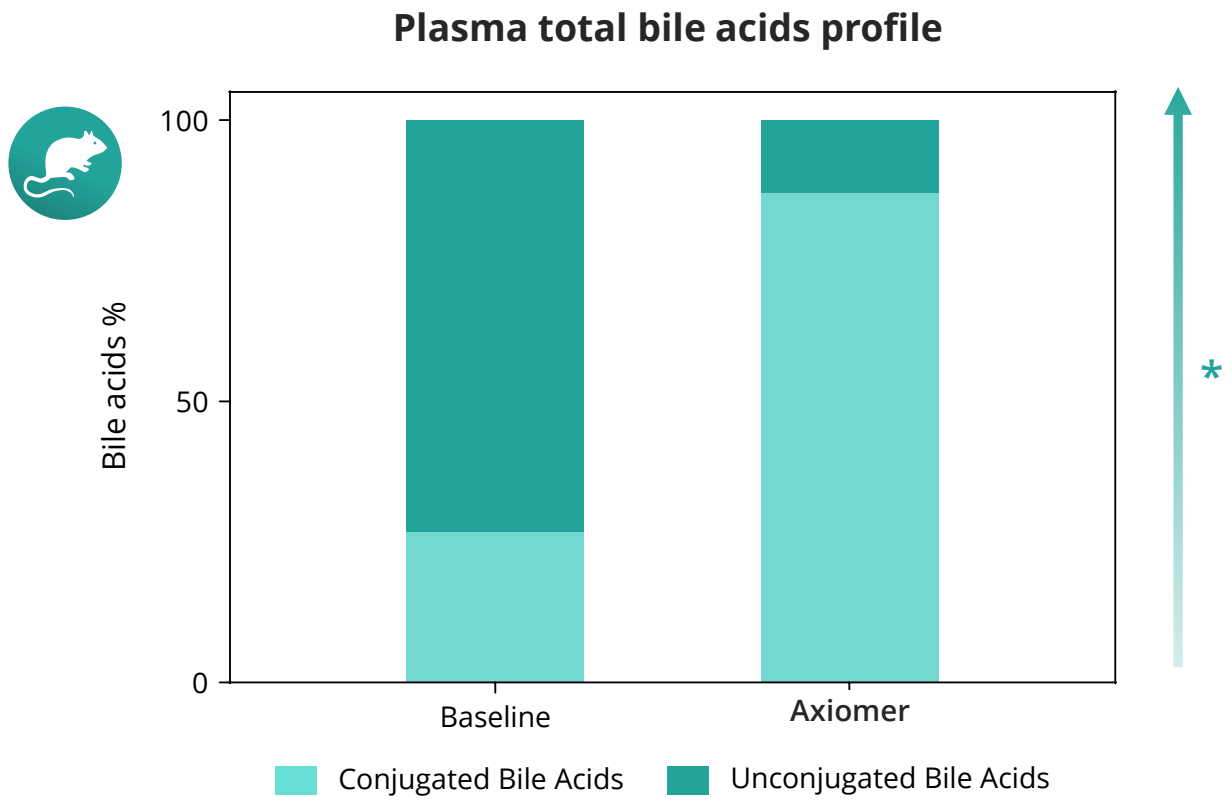
** Expected direction of change in TBA levels*

NTCP, sodium taurocholate co-transporting polypeptide; TBA, Total Bile Acid; UDCA, Tauroursodeoxycholic acid. Panel on the left: Mice, N=4, 20mg/kg EON, 6 doses, GalNac conjugation, SC, D25; panel on the right: NHP, N=1, 1-4mg/kg EON, 4 doses, LNP formulation IV, up to D39

Confirming AX-0810 specificity for NTCP

By assessing changes in bile acids profile

- NTCP is the **main transporter of conjugated bile acids** from the portal vein into hepatocytes
- NTCP modulation of bile acids reuptake function by AX-0810 is expected to result in:
  - An **increase in conjugated bile acids in the plasma**
  - No-to-limited changes in unconjugated bile acids levels in plasma

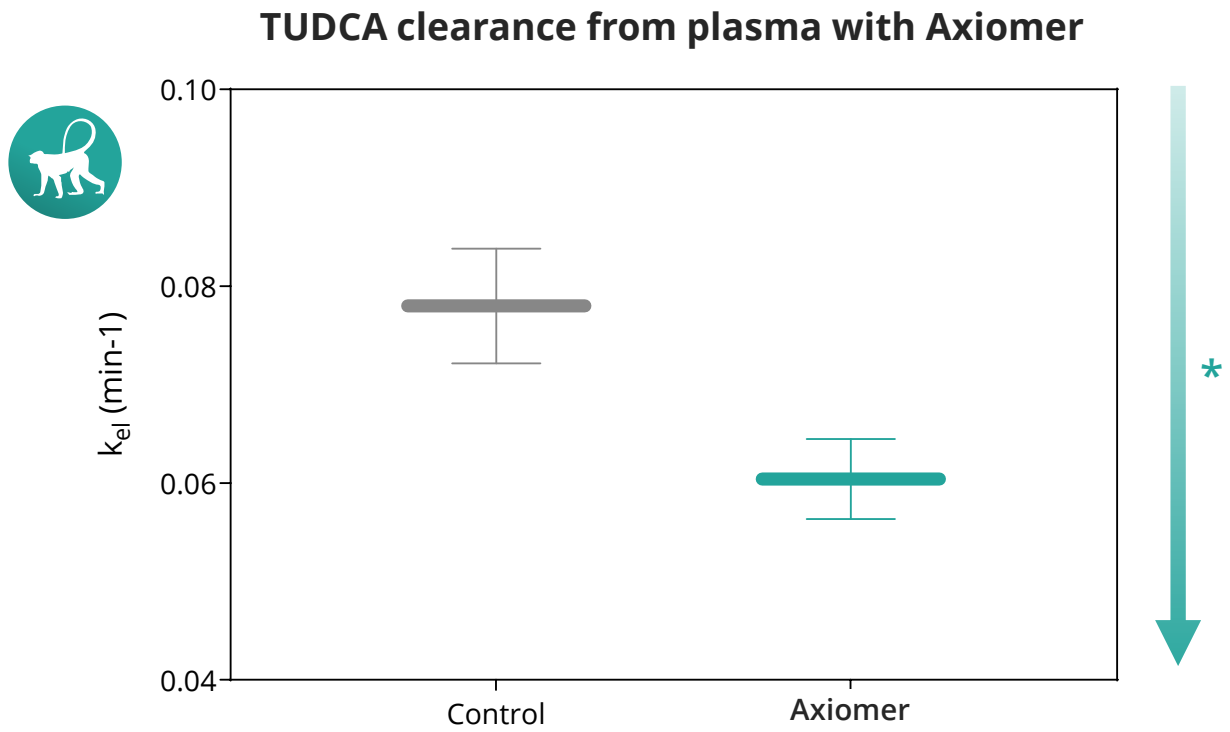


***** *Expected direction of change in plasma conjugated bile acids*

NTCP, sodium taurocholate co-transporting polypeptide. Experiment conditions: Mice, N=4, 20mg/kg EON, 6 doses, GalNac conjugation, SC, D25

Safely and transiently mimic disease conditions with a TUDCA challenge

- A mechanistic challenge with TUDCA is expected to:
  - Give indication on NTCP bile acids uptake **activity** and Axiomer **specificity** on NTCP transporter
  - Provide **discriminatory effect between doses** to inform future dosing regimen selection
- An increase in TUDCA plasma levels is expected to further confirms AX-0810 efficiency and selectivity



* *Expected direction of change in TUDCA clearance*

NTCP, sodium taurocholate co-transporting polypeptide; TUDCA, Tauroursodeoxycholic acid. Experiment conditions: NHP, exploratory study, n=5-7, 10mg/kg EON, 4 doses, SC, D51.

Leading IP supporting ADAR-mediated RNA editing platform technology

- Axiomer™ IP strategy commenced in 2014 with first patent application filings
- Currently 32 published patent families, comprising 39 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 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 NZ US US US US	Platform IP
3 (0014)	01SEP2016	Chemically modified short EONs	Granted AU CN EP IL IN 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)	Granted AU US	Platform IP
6 (0025)	28JAN2019	Editing of PTC in exon 61 USH2A	Granted US	Target
7 (0026)	11FEB2019	Phosphonacetate linkages / UNA modifications	Published	Platform IP
8 (0029)	03APR2019	MP linkages	Granted JP	Platform IP
9 (0031)	24APR2019	Editing inhibition	Published	Platform IP
10 (0032)	13JUN2019	Benner's base (dZ)	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

Overview of Axiomer™ related patents

Docket	Priority	Feature	Status	Remarks
17 (0052)	24NOV2022	HFE	Published	Target
18 (0053)	09DEC2022	B4GALT1	Published	Target
19 (0054)	01DEC2022	ALDH2	Published	Target
20 (0055)	20JAN2023	AG1856 saponin	Published	Platform IP – with FU Berlin (A Weng)
21 (0057)	20FEB2023	ANGPTL3	Published	Target
22 (0058)	24MAR2023	KCC2	Published	Target – with Eli Lilly
23 (0059)	24MAR2023	PNms linkages	Published	Platform IP
24 (0060)	27MAR2023	NTCP	Published	Target
25 (0061)	16JUN2023	RELN	Published	Target
26 (0062)	07SEP2023	MC4R	Published	Target
27 (0066)	16NOV2023	GALK1	Published	Target
28 (0067)	20DEC2023	HTT	Published	Target
29 (0070)	18JAN2024	IDUA	Published	Target – with Eli Lilly
30 (0071)	02APR2024	NTCP	Published	Target
31 (0072)	25APR2024	PNPLA3	Published	Target
32 (0073)	11APR2024	PIAS1	Published	Target

ProQR Axiomer™ IP

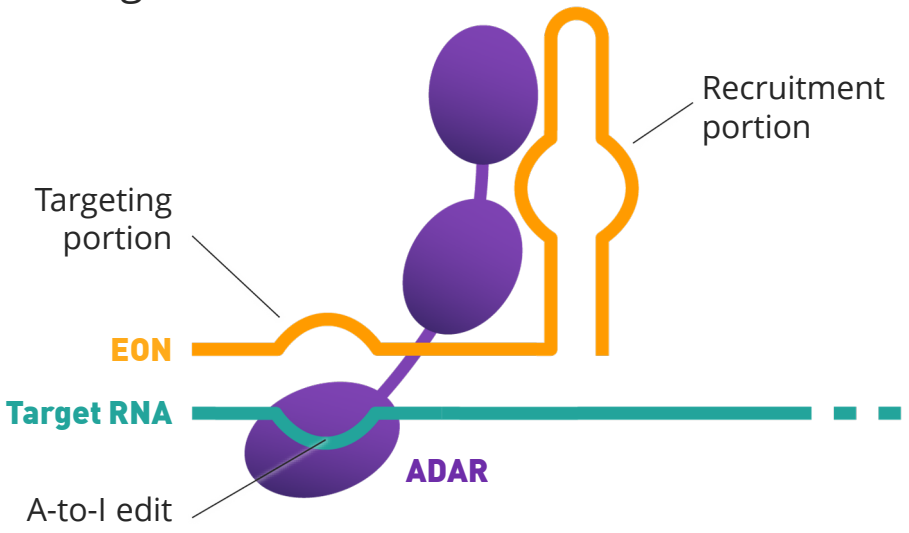
Broad coverage

- 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



US 10,676,737	Granted
US 11,781,134	Granted

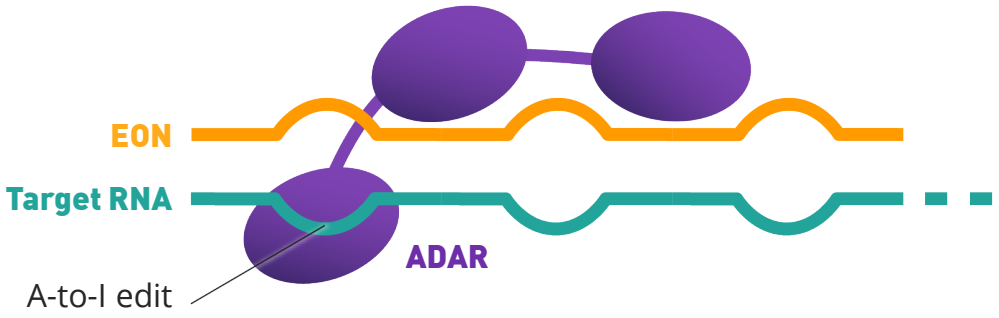
Claim 17 (US 11,781,134):

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.



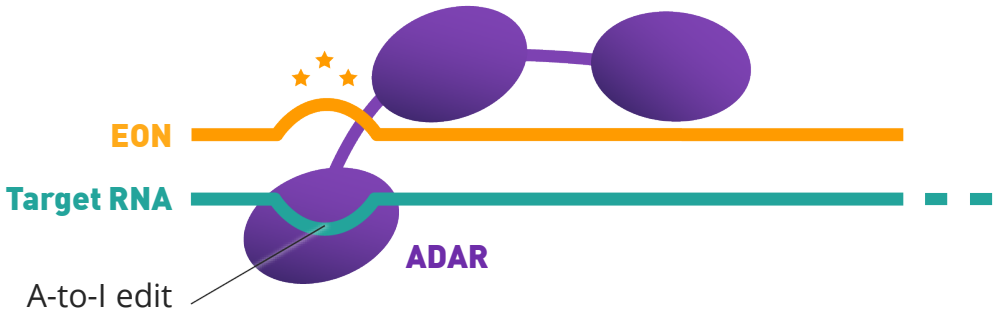
US 10,988,763	Granted
US 11,649,454	Granted
US 12,018,257	Granted

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.

ProQR®

IT'S IN OUR RNA