ProQR®

# DEVELOPING RNA-EDITING MEDICINES

*for patients in need*

Nasdaq: PRQR

Date: May 2024

# 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 Therapeutics

*Short overview*

## Focus on Axiomer™

Exclusively focused on the development of proprietary Axiomer™ RNA editing platform across multiple therapeutic areas; initial focus on liver and CNS diseases

## Novel mechanism of action, leading patent estate

Axiomer™ was discovered in ProQR labs in 2014 and uses well-proven modality of oligonucleotides to recruit a novel mechanism of action

## Validated across multiple genes

Preclinical data demonstrate Axiomer™ is broadly validated across multiple genes

## ADAR

Axiomer™ is ADAR-mediated RNA editing, recruiting endogenous adenosine deaminase acting on RNA (ADAR)

## Two pillars underlie strategy

ProQR developing wholly owned pipeline with initial targets in liver-originated diseases

- AX-0810 program preclinical proof of concept at ASGCT 2024
- AX-0810 for cholestatic diseases and AX-1412 for cardiovascular disease rapidly advancing to the clinic late 2024/early 2025

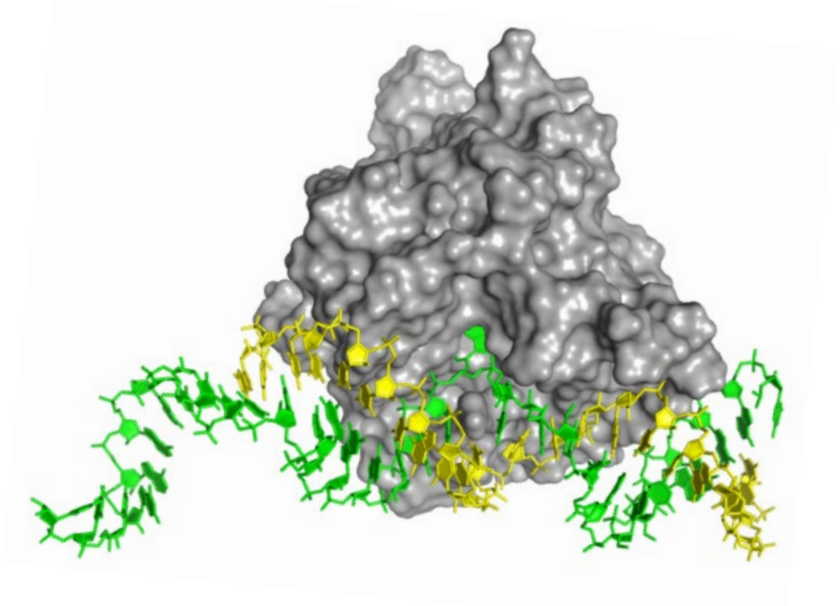
Selectively enter into partnerships: initial partnership with Lilly in September 2021, expansion announced December 2022

## Cash-runway into mid-2026

Cash position of €102.7 M as of end of Q1 2024 provides runway to mid 2026, beyond multiple clinical data readouts

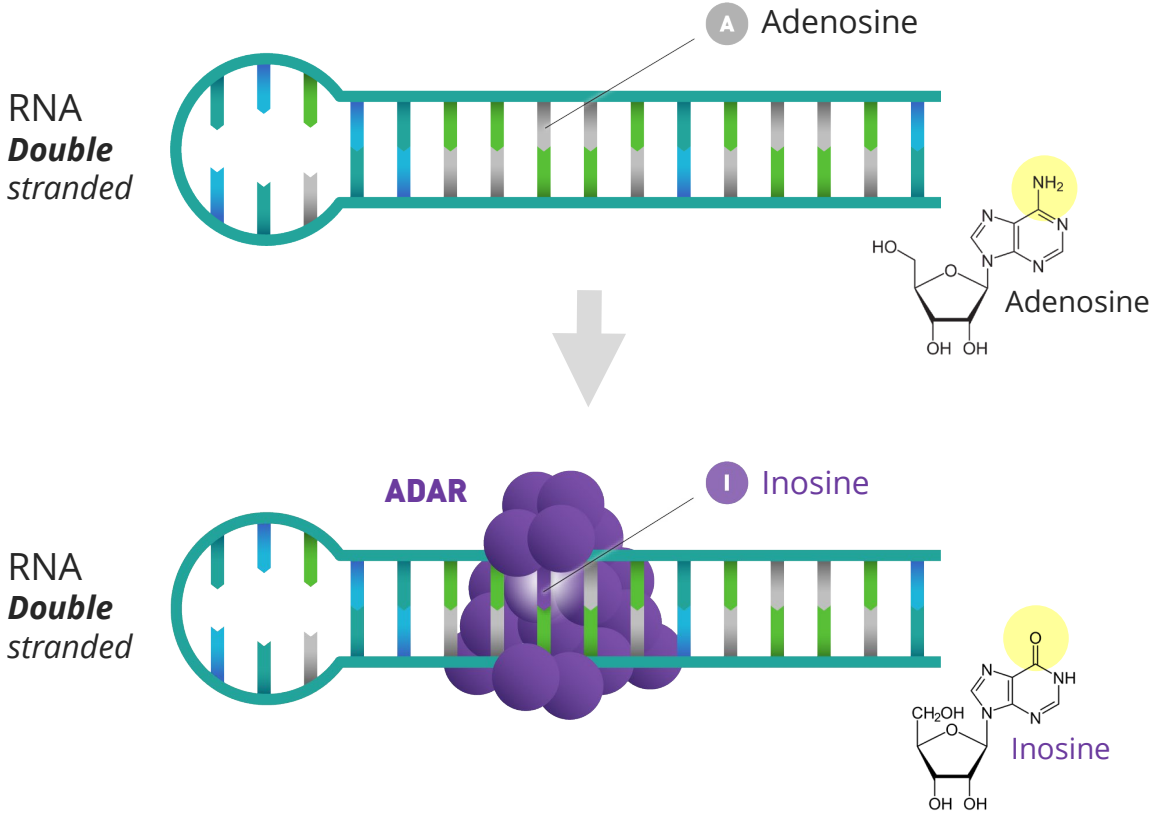
# What is ADAR editing?

**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)**

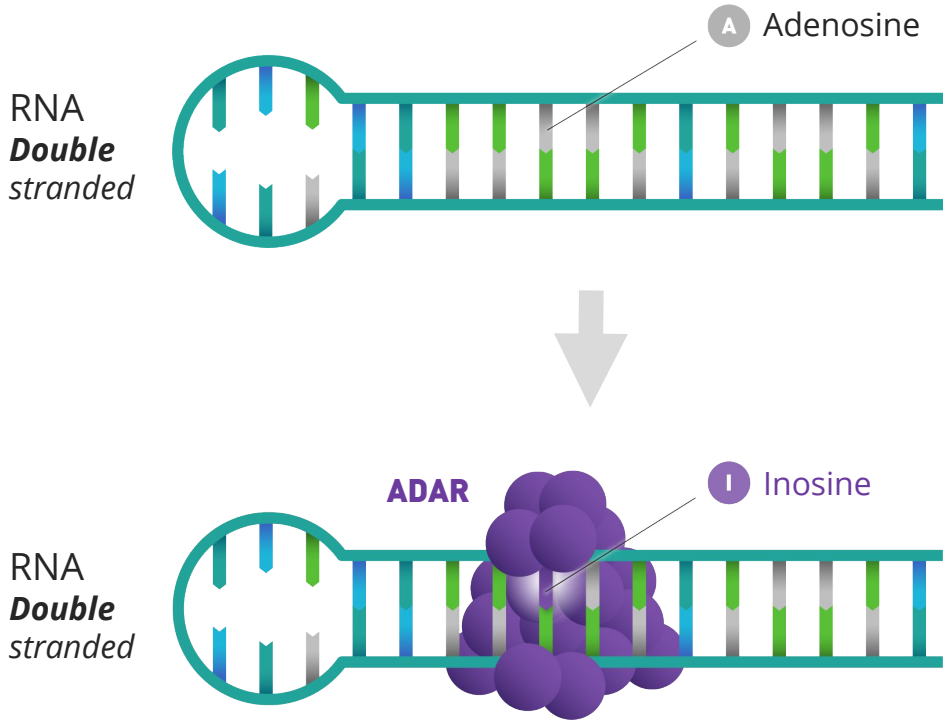
**Natural ADAR editing** *(A-to-I)*



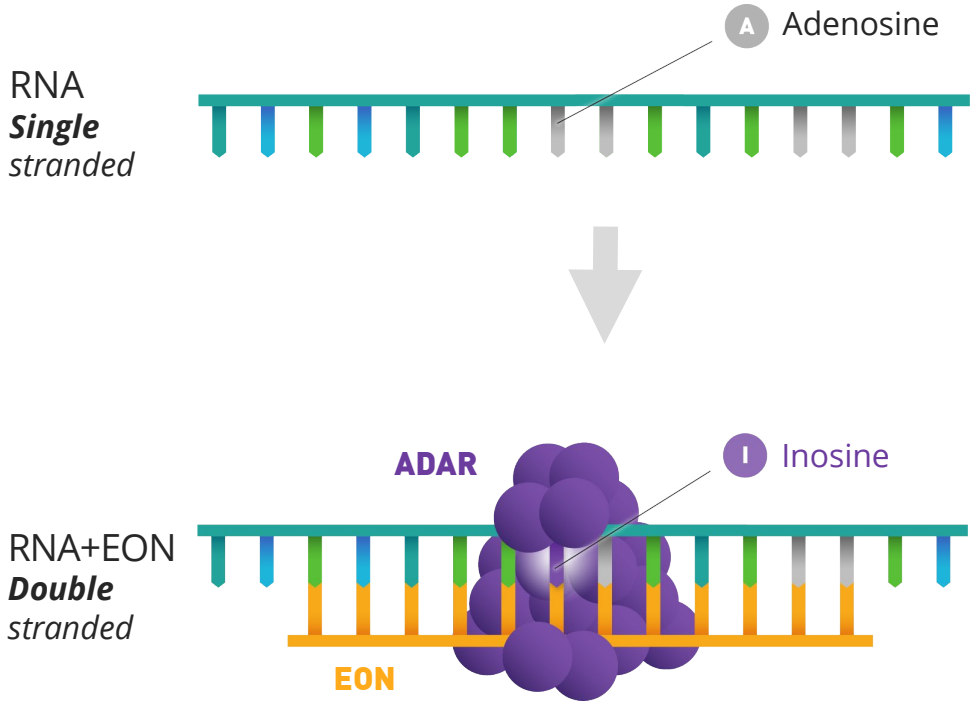
# Axiomer™ EONs unlock cellular machinery potential to treat diseases

*By attracting ADARs and allowing highly specific editing*

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




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

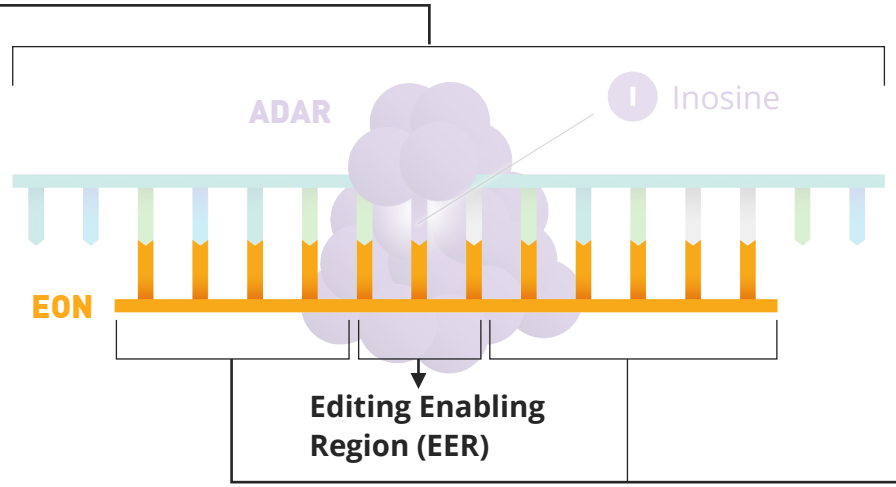



ADARs: Adenosine deaminases acting on RNA.

# 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

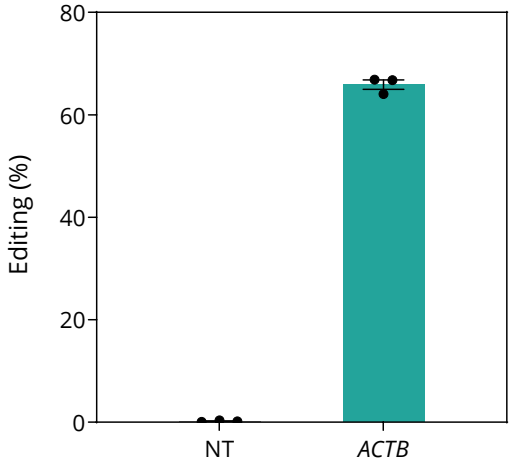
ADAR: Adenosine deaminase acting on RNA, EON: Editing oligonucleotide, Nt: nucleotides

# High intrinsic editing capability of Axiomer™ in the liver across models

## Cell models

**Up to 70% Editing of *ACTB* in primary human hepatocytes**

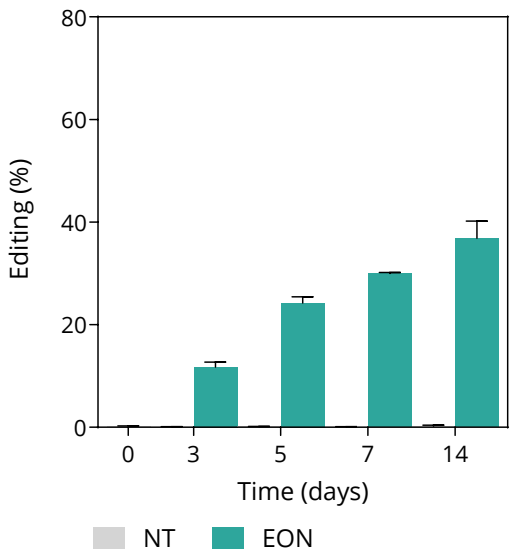
*Gymnosis, 5µM, single dose, n=1 with triplicates, 72 hours, dPCR, mean, SD*




## Organoids

**Up to 40% Editing of *ACTB* in human LMTs**

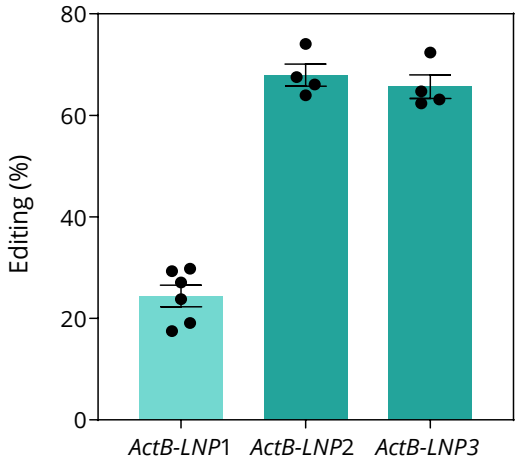
*Gymnosis, 1µM, constant dose, 3 pools of 24 LMTs per condition, 14 days, dPCR, mean, SD*




## Mice *in vivo*

**Up to 70% editing of ActB in liver**

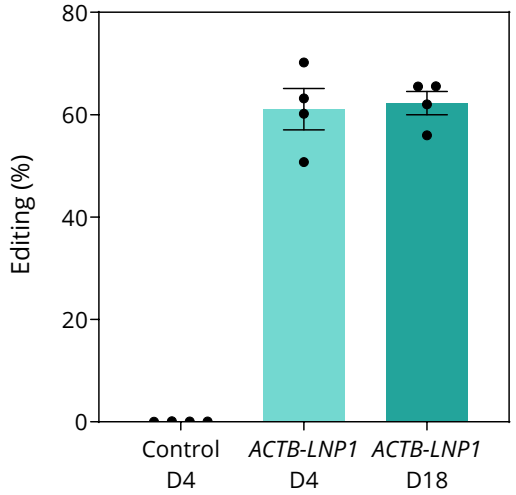
*IV, 3mg/kg or 4mg/kg, N=4-6, LNP formulations, D7 data, dPCR, AVG±SEM*




## NHP *in vivo*

**Up to 70% editing of *ACTB* in NHP**

*IV, 2mg/kg, 3 doses at D1, D8 and D15, LNP formulation, n=4, D4 and D18 data, dPCR, mean±SEM*



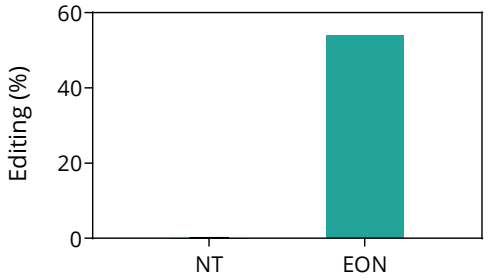

*PHH: Primary Human Hepatocyte; LMT: Liver Micro Tissue; NHP: Non-human primate*

# Axiomer™ potential beyond liver

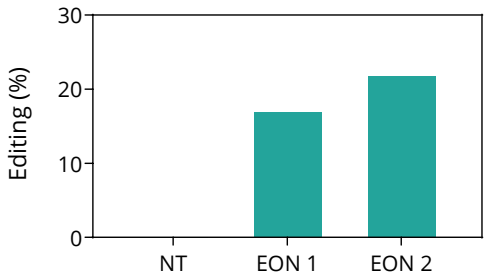
*Strong editing in the nervous system across models*

## Cell models

**More than 50% RNA editing of *ACTB* in human iPSC derived neurons**

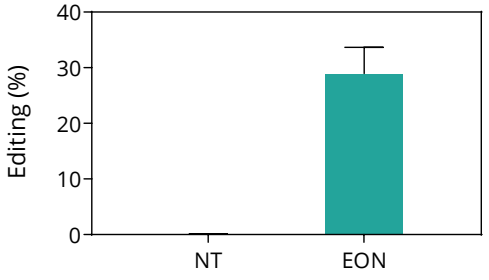



**More than 20% RNA editing of APP in human iPSC derived neurons**

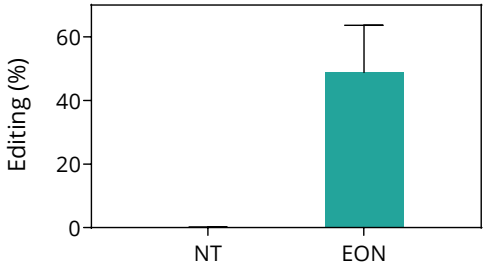



## Organoids

**Up to 35% RNA editing of *ACTB* in cerebral organoids**

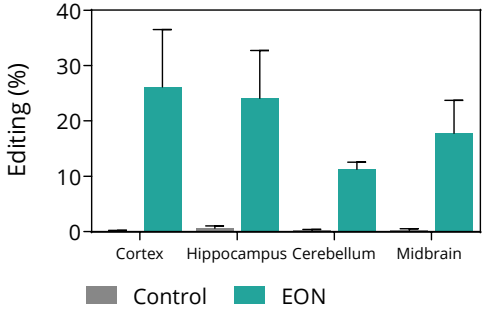



**Up to 65% RNA editing of *APP* in cerebral organoids**

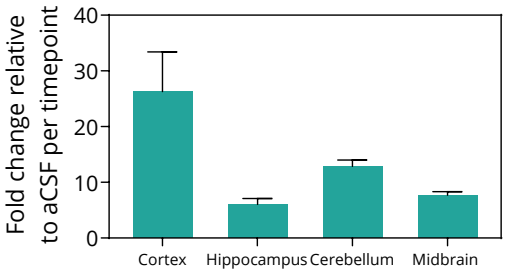



## Mice *in vivo*

**Up to 40% RNA editing in mice brain***

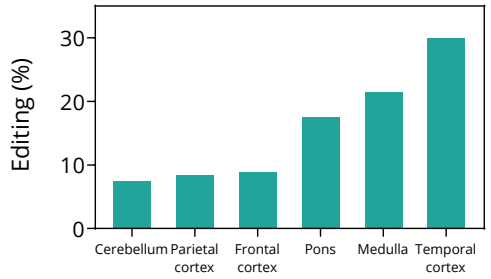



**26-fold change in protein function in mice brain***

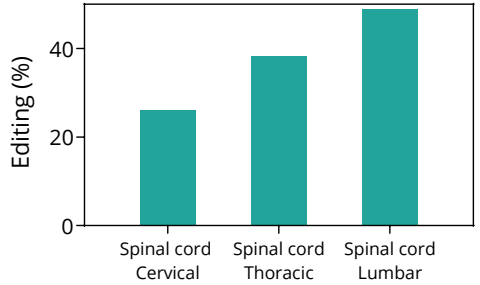



## NHP *in vivo*

**Up to 30% RNA editing in NHP brain***




**Approx. 50% RNA editing in NHP spinal cord***




*Undisclosed target. Conditions of the *ACTB* iPSC derived neurons experiment: gymnosis, 2.5µM, single dose, n=1, 2 weeks, dPCR and conditions of the *APP* iPSC derived neurons experiment: gymnosis, 10µM, single dose, washout, n=1, 2 weeks, dPCR. Conditions of the *ACTB* cerebral organoids of 130 days: gymnosis, 10µM, single dose, washout, n=7, 6 days, ddPCR, mean, SD and *APP* cerebral organoids of 150 days: gymnosis, 5µM, single dose, washout, n=5, 2 weeks, ddPCR, mean, SD. Conditions of the mice *in vivo* experiment: intracerebroventricular (ICV), 250µg, single dose, N=6, 4 weeks, editing: ddPCR and protein function: western blot, mean, SD and SEM. Conditions of the non-human primate (NHP) *in vivo* experiment: intrathecal (IT), 12mg, single dose, n=3**, 7 days. ** Data of 2 NHPs not analyzable due to human error during injection procedure.

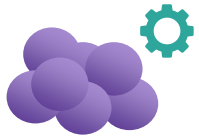
# Axiomer™ creating a new class of medicines with broad therapeutic potential

## Correction

**Mutations correction**

Thousands of G-to-A mutations, many of them described in literature

## Protein modulation

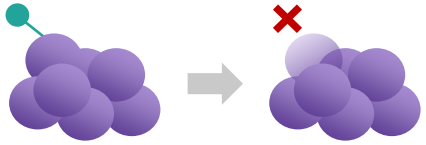


**Alter protein function or include protective variants**

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

## BROAD THERAPEUTIC POTENTIAL

- Common diseases
- Rare diseases
- Target a wide variety of organs
- Treat so-far undruggable targets

PTMs: Post-translational modifications.

# Pipeline

# ProQR development pipeline

| | TARGET | DISCOVERY | NON-CLINICAL | CLINICAL | GUIDANCE | ESTIMATED POPULATION |
|---|---|---|---|---|---|---|
| **PROQR PROGRAMS** | | | | | | |
| CHOLESTATIC DISEASES | **AX-0810** *for* **NTCP** | | | | Entry into clinical trials in late 2024 / early 2025 | ~ 100K[1] |
| CARDIOVASCULAR DISEASES | **AX-1412** *for* **B4GALT1** | | | | Entry into clinical trials in late 2024 / early 2025 | ~ 200M[2] |
| | **AX-1005** *for CVD* | | | | | |
| RARE NEURODEVELOPMENT DISORDER | **AX-2402** *for Rett syndrome* | | | | | ~ 20K |
| METABOLIC DISEASES | **AX-2911** *for NASH* | | | | | ~ 16M |
| | **AX-0601** *for obesity and T2D* | | | | | ~ 650M |
| | **AX-9115** *for rare metabolic condition* | | | | | ~ 20K |
| OTHERS | *Multiple targets in discovery pipeline* | | | | | |
| **PARTNERED PROGRAMS** | | | | | | |
| Lilly | *Initial **5** undisclosed targets* | *Progress undisclosed* | | | | |
| | *Next **5** undisclosed targets* | *Progress undisclosed* | | | | |
| | *Up to **5** potential additional targets* | | | | | |

[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: Boonstra K, Beuers U, Ponsioen CY. J Hepatol. 2012 May;56(5):1181-1188; Karlsen TH, et al. J Hepatol. 2017 Dec;67(6):1298-1323; Dyson JK, et al. Lancet. 2018 Jun 23;391(10139):2547-2559; Sundaram SS, et al. Liver Transpl. 2017 Jan;23(1):96-109. Raghu VK, et al. Liver Transpl. 2021 May;27(5):711-718; NORD, 2019. Tsao CW, et al. Circulation. 2022;145(8):e153–e639. World Health Organization, World Gastroenterology Organization

# AX-0810 for cholestatic diseases

## RNA-editing therapy

*for Primary Sclerosing Cholangitis and Congenital Biliary Atresia*

Cholestatic diseases have high unmet medical need. Patients accumulate bile acid 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 require liver transplantation.

- **Biliary Atresia** is projected to affect ~24,000 pediatric individuals in US, EU and JP.
- **Primary Sclerosing Cholangitis** is projected to affect more than 80,000 individuals in EU, US and JP.

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.

# AX-0810 a novel therapeutic strategy to reduces bile acids re-uptake into liver

**AX-0810 is a novel and "on target" approach reducing bile acid re-uptake into the hepatocytes**

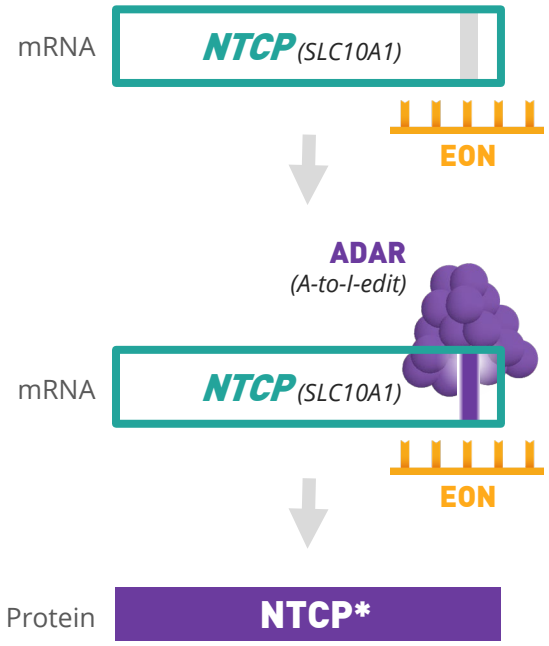
- Transient and controlled approach leading to a modulated NTCP function

**AX-0810 can reduce bile acid toxic load in the liver**

- To alleviate associated pathology and symptoms in PSC and BA
- To prevent or delay the development of cirrhosis, organ failure and need for transplant

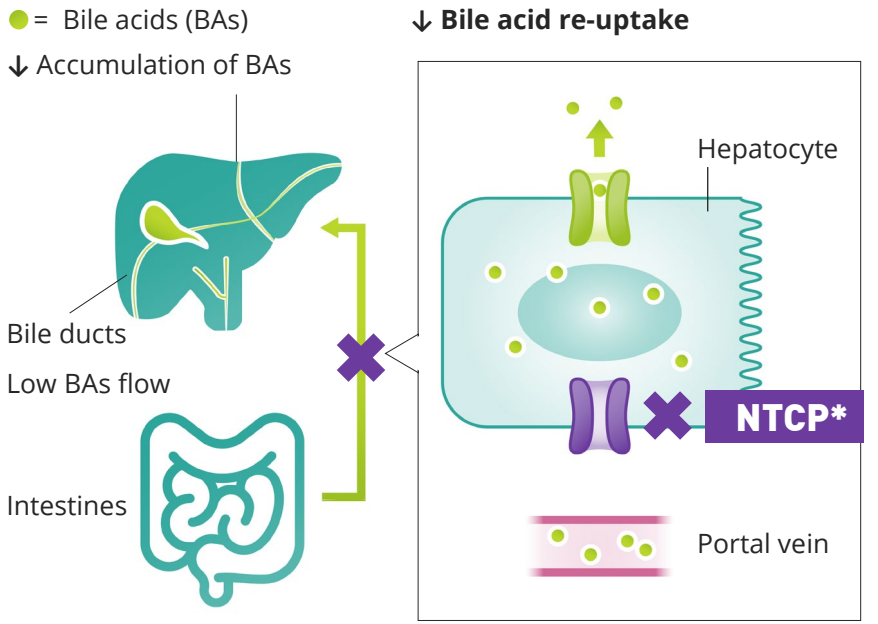
## AX-0810 therapy

*for cholestatic diseases*




*Bile acids re-uptake modulated function

## Reduced BAs levels in the hepatocytes



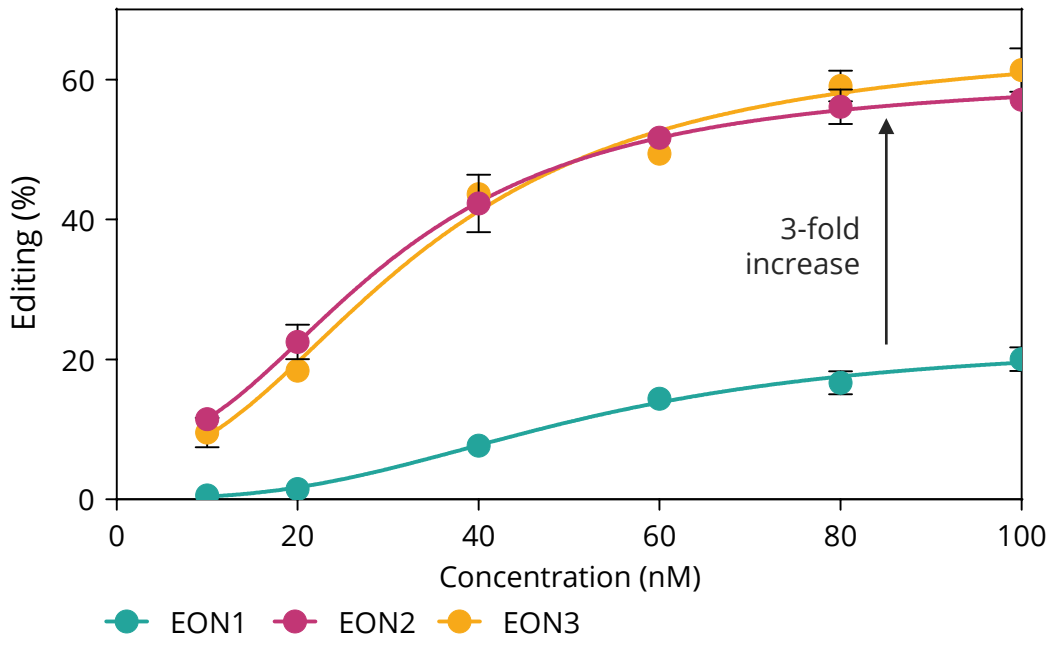

* Bile acids re-uptake modulated function

BAs: Bile acids, NTCP: Na-taurocholate cotransporting polypeptide, PSC: Primary Sclerosing Cholangitis. *SLC10A1* is the gene that encodes for NTCP protein.

# Proof of concept with Axiomer EONs targeting NTCP in liver of NHPs

## EONs targeting NTCP RNA optimization in PHH

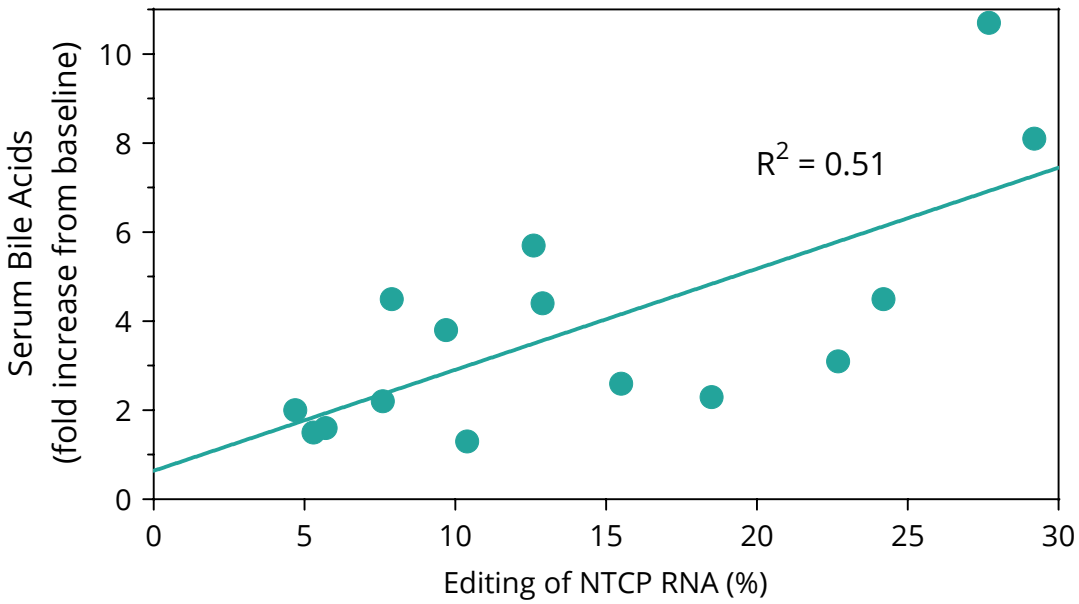
*Transfection, n=3, 72 hours, dPCR, mean±SEM*




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

## Correlation between change in serum BAs and editing of NTCP RNA in NHPs *in vivo*

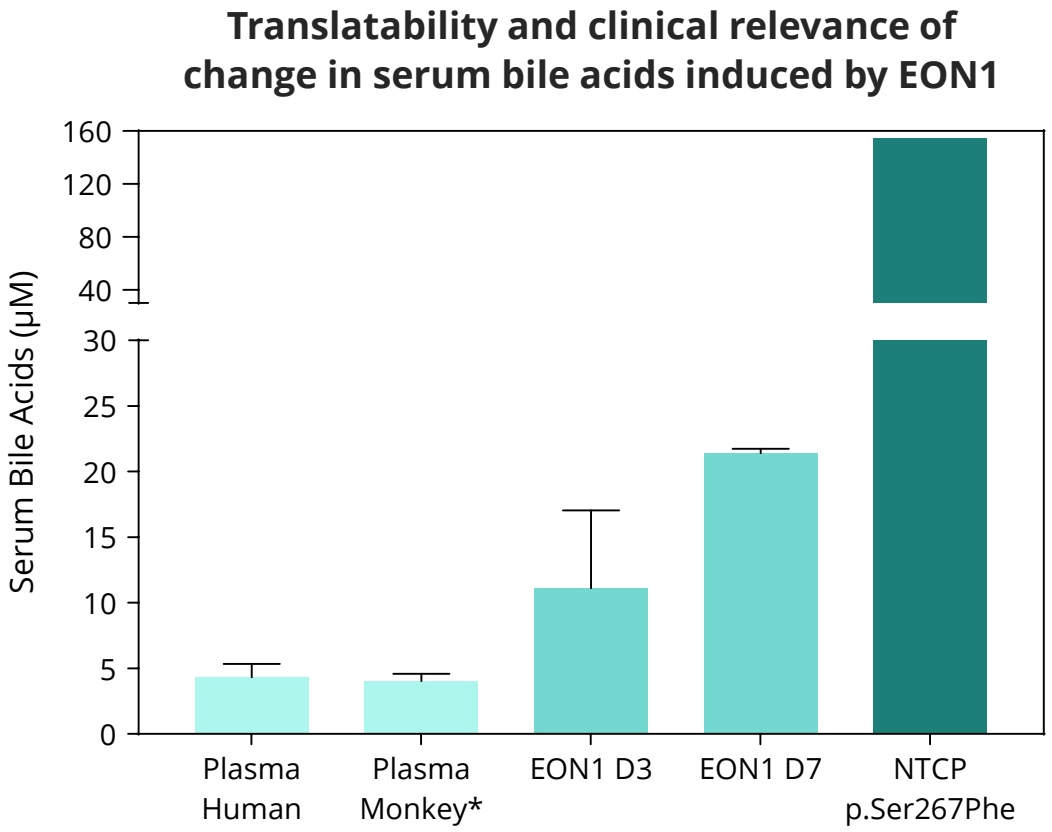
*n=6, EON1, IV, LNP formulation, 72 hours*




NTCP target engagement with Axiomer EONs leads to the desired changes and high correlation between serum bile acids and EON1 editing level in NHPs *in vivo* (linear regression $R^2$ = 0.51)

BAs: Bile acids, EON1: early generation editing oligonucleotides targeting SCL10A1 (NTCP) mRNA, 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

# Translatability and clinical relevance of serum bile acids changes in liver fibrosis




- **Translatability and derisking of FIH in healthy volunteers**
  Translatability between NHP and human confirmed with human sequence homology and equivalent level of serum bile acids
- **Potential for clinically meaningful improvement**
  Expected that a change in 2-fold of serum bile acids could lead to clinically meaningful improvement in disease progression in patients suffering from chronic liver disease
- **No harmful effects from elevated total bile acids**
  High total bile acids levels are not harmful, as evidenced by natural variants in some individuals (NTCP p.Ser267Phe) who exhibit much higher levels of sBA without clinical symptoms.

*Cynomolgus monkey and Rhesus macaques.

# Well-defined development path for AX-0810

| PRECLINICAL STAGE | EARLY CLINICAL | LATE CLINICAL |
|---|---|---|
| *Preclinical models available with strong translatability into the clinic* | *Early insight on safety and target engagement using validated biomarkers* | *Clinical programs with disease specific endpoints for regulatory approval* |
| **Translational models available**<br>• Organoids models<br>• Animal models<br><br>**Proof of mechanism measures in animal models**<br>• Serum levels of ALP and γ-GT<br>• Total bile acids in serum and liver<br>• Hepatic inflammation and fibrosis | **Program with Phase 1 on healthy volunteers**<br><br>**Validated biomarkers in cholestatic diseases**<br>• Bile acids in serum, urine and feces<br>• Liver enzymes<br>• Serum cholesterol<br><br>**Disease specific biomarkers in preparation for next trials**<br>• ALP for PSC<br>• Bilirubin for BA | **Primary Sclerosing Cholangitis**<br>Co-primary endpoint for regulatory approval:<br>• Reduction in ALP and<br>• Histological liver evaluation<br><br>**Biliary atresia**<br>• Time to liver transplantation<br>• Mean change in total serum bilirubin levels, liver enzymes, bile acid levels, blood platelets and serum albumin |

γ-GT: γ-glutamyl transferase; ALP, Alkaline phosphatase; BA, biliary atresia; BDL, Bile duct ligation; LMT, Liver microtissues; NTCP, Na-taurocholate cotransporting polypeptide; PSC, Primary Sclerosing Cholangitis

# AX-0810 early evidence generation approach on safety and target engagement

*Phase 1 on healthy volunteers for cholestatic diseases*

**Objectives**

- Assess safety, tolerability, PK and PD of AX-0810 without interference by concomitant pathological conditions
- Establish target engagement by biomarkers

**Trial design**

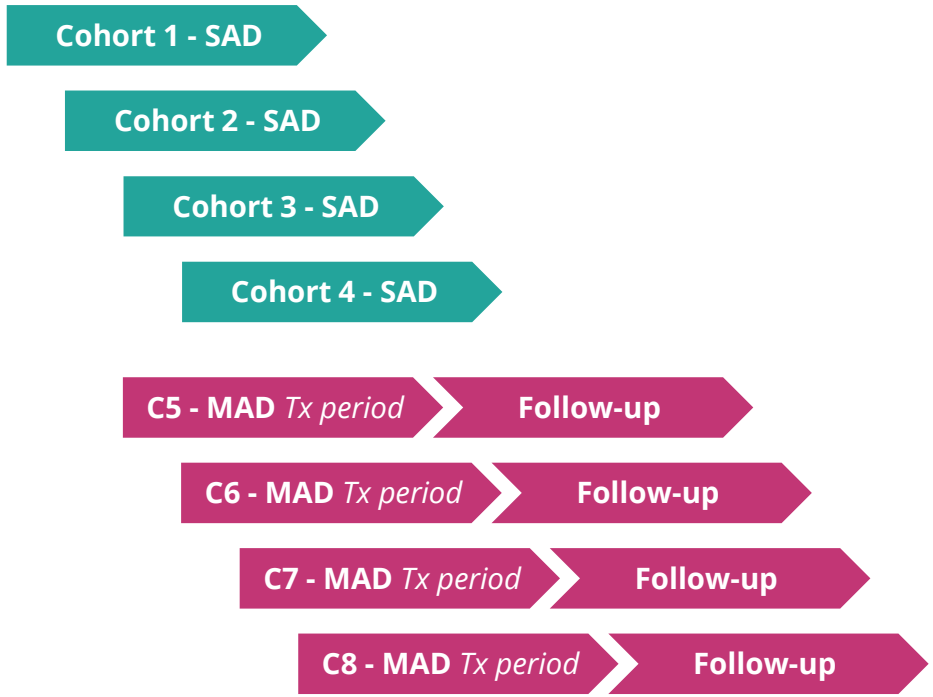
- Single and multiple dose ascending trial
- Single trial site: timely recruitment and data generation

**Endpoints will include**

- Safety, tolerability, PK and PD of AX-0810
- Change in bile acids in serum, urine and feces, liver enzymes and serum cholesterol
- Change in disease specific biomarkers: ALP and bilirubin
- Measure RNA editing in circulating exosomes in plasma

**Entry into clinical trials in late 2024 / early 2025**

**Preliminary study design**




ALP, Alkaline phosphatase; MAD, multiple ascending dose; PD, Pharmacodynamic; PK, Pharmacokinetics; SAD, single ascending dose.

# AX-1412 for cardiovascular diseases

## RNA-editing therapy

*for cardiovascular disease (CVD)*

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

**With projected increased number of patients**
By 2035, >130 million adults in the US are projected to have some form of CVD with a total costs of $1.1 trillion.

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

AX-1412 introduces a protective variant that reduces multiple independent risk factors for CVDs as was found in human genetics research.

# AX-1412 brings a novel approach to reduce residual risk for a potential cardiovascular event

*RNA editing to a loss of function variant of B4GALT1 can have pleiotropic effect targeting two CVD risk factors*

***B4GALT1* p.N352S protective allele**

- Leads to hypo-galactosylation of apolipoprotein B100, fibrinogen

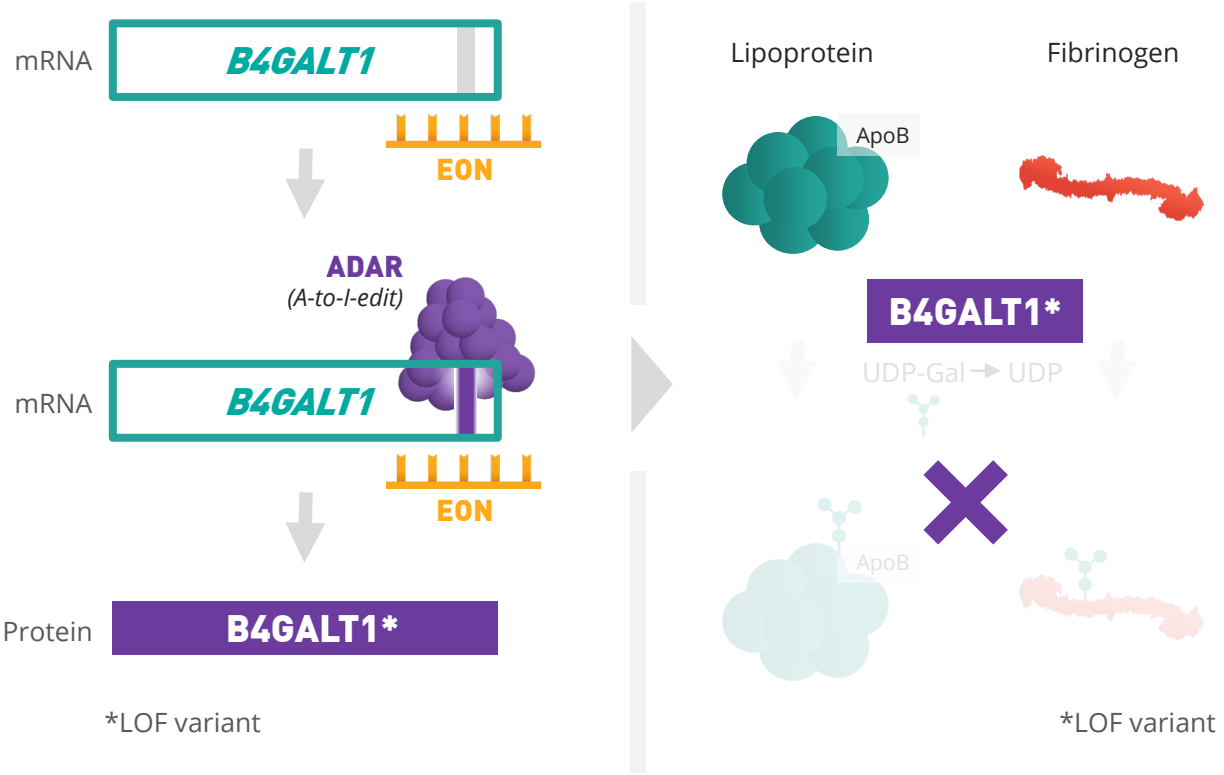
**AX-1412 is a novel and unique approach to address CVD**

- Pleiotropic effects for cardiovascular protection
- Not suitable for knockdown technologies, as leads to semi-lethality and severe development abnormalities in mouse studies

**AX-1412 can lower LDL-C and fibrinogen levels to reduce residual risk in cardiovascular diseases**

- Prevent or delay the development of cardiovascular events

**AX-1412 therapy for cardiovascular diseases**




ADAR: adenosine deaminase acting on RNA, ApoB: Apolipoprotein B, CVDs: cardiovascular diseases, LDL-C: Low-density lipoprotein cholesterol. Reference: Montasser ME. et al., 2021 Science 374(6572):1221-1227.

# Well-defined development path for AX-1412

| PRECLINICAL STAGE | EARLY CLINICAL | LATE CLINICAL |
|---|---|---|
| *Preclinical models available with strong translatability into the clinic* | *Early insight on safety and target engagement using validated biomarkers* | *Clinical programs with disease specific endpoints for regulatory approval* |
| **Organoids models for CVD**<br>• Blood-derived myeloid cells and THP-1 cells<br>• Cell-laden microtissue spheroids<br>**Animal models**<br>• The Apoe−/− mouse model<br>**Proof of mechanism measures in animal models**<br>• Serum lipid levels<br>• Atherosclerotic lesion area<br>• C-reactive protein (CRP) and Interleukin 6 (IL-6)<br>• Endothelial function | **Programs with Phase 1 on healthy individuals**<br>• Reduce potential signal-to-noise ratio as CVD patients have many comorbidities<br>**General CVD biomarkers**<br>• non-HDL-C<br>• Triglycerides<br>• Apoliprotein B<br>**Target specific biomarkers**<br>• LDL-C<br>• Fibrinogen | **Primary endpoints**<br>1. All-cause mortality and fatal CVD events or<br>2. Composite endpoints (incl. fatal and non-fatal CVD events)<br>**Secondary endpoints**<br>• Could consider using biomarkers as surrogate endpoints to reasonably predict treatment effects on outcome |

Apoe: Apolipoprotein E, CVD: cardiovascular diseases, HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol, THP-1: human monocytic cell line

# AX-2402 for Rett Syndrome

## Axiomer™ technology

*targeting the transcription factor MECP2 and potential to correct nonsense variants*

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.

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

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.

Krishnaraj R, Ho G, Christodoulou J. 2017. RettBASE: Rett syndrome database update. Hum Mutat 2017;00:1-10.

# Axiomer™ RNA Editing Research Collaboration with Rett Syndrome Research Trust

- RSRT awarded ProQR approximately $1M as a research grant for the initial phase of the project
  - EON design and optimization,
  - Evaluation in *in vivo* models for editing efficacy and MECP2 protein recovery
- Acting with a sense of urgency focusing on severe phenotype
- Following the initial discovery work, intent for expanded co-funding to enable continued development for the next phases
- Potential for further development for additional variants of relevance involved in Rett Syndrome

# Value creation strategy

*ProQR will develop its own pipeline and selectively enter into partnerships*

## ProQR Pipeline

- Build **in-house pipeline** based on Axiomer™ RNA editing technology platform
- Initial focus on **liver originated diseases**

## Partnerships

- Largely unencumbered platform, ProQR may **selectively enter partnerships**
- **Lilly partnership** with expansion announced December 2022 – total potential value of ~$3.9B

# 2024 and beyond outlook

*Building momentum toward development*

## Pipeline

**AX-0810 targeting NTCP for cholestatic diseases**

- 2024 – announce clinical development candidate translational data, and clinical development plans
- Late 2024/early 2025 – advance to clinic

**AX-1412 targeting B4GALT1 for cardiovascular disease**

- 2024 – report preclinical proof of concept data; announce clinical development candidate; report translational data; announce clinical trial design
- Late 2024/early 2024 – advance to clinic

**New pipeline program announcement(s)**
Potential in 2024 and beyond

## Partnerships

**Eli Lilly**

- Potential additional data updates
- Potential additional milestone income from existing partnership
- Potential option to exercise for expansion of deal to 15 targets, which would result in a $50 million opt-in payment to ProQR

**Rett Syndrome Research Trust**

- Partnership announced January 2024

**Potential new**

- Potential to electively form new partnerships, which could include multi-target discovery alliances, or product alliances on specific programs

## IP

**Leading patent estate**
Continued expansion of leading IP portfolio supporting that applying endogenous ADAR by administering antisense oligonucleotides for RNA editing is proprietary to ProQR

## Cash

**Strong cash runway**
Cash position of €102.7 M as of end of Q1 2024 provides runway to mid 2026, beyond multiple clinical data readouts

# Well positioned

*to advance Axiomer™*

## Science

- Deep understanding of basic science – ADAR, oligos
- Optimization of editing oligonucleotides (EONs) for therapeutic development

## Axiomer™ has broad applicability

- Large number of potential therapeutic applications
- In vivo POC established in nervous system, liver

## Advancing toward the clinic

- Extensive translational and developmental expertise with oligo modality
- AX-0810 and AX-1412 initial pipeline targets

## Leading IP position

- Axiomer™ is protected by >10 published patent families
- Continuously investing in expanding IP estate

## Strategic partnership

- Lilly collaboration
- Rett Syndrome Research Trust
- Selectively form additional partnerships
- Optionality and multiple value creating opportunities

## Experienced leadership

- Deep RNA, corporate finance, and business development expertise across Management Team, Supervisory Board, and Scientific Advisory Board

## Strong balance sheet

- Q1 2024 cash €102.7 M
- Cash runway to mid-2026, excluding potential for additional BD-related upside

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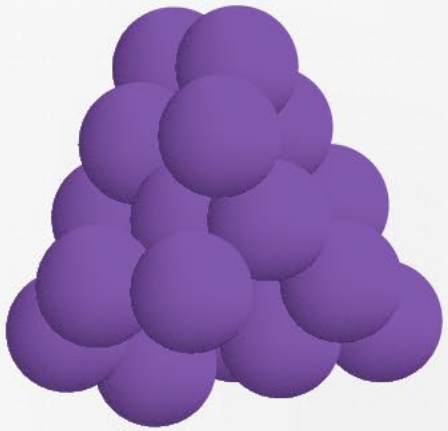
# IT'S IN OUR RNA

# Resource slides

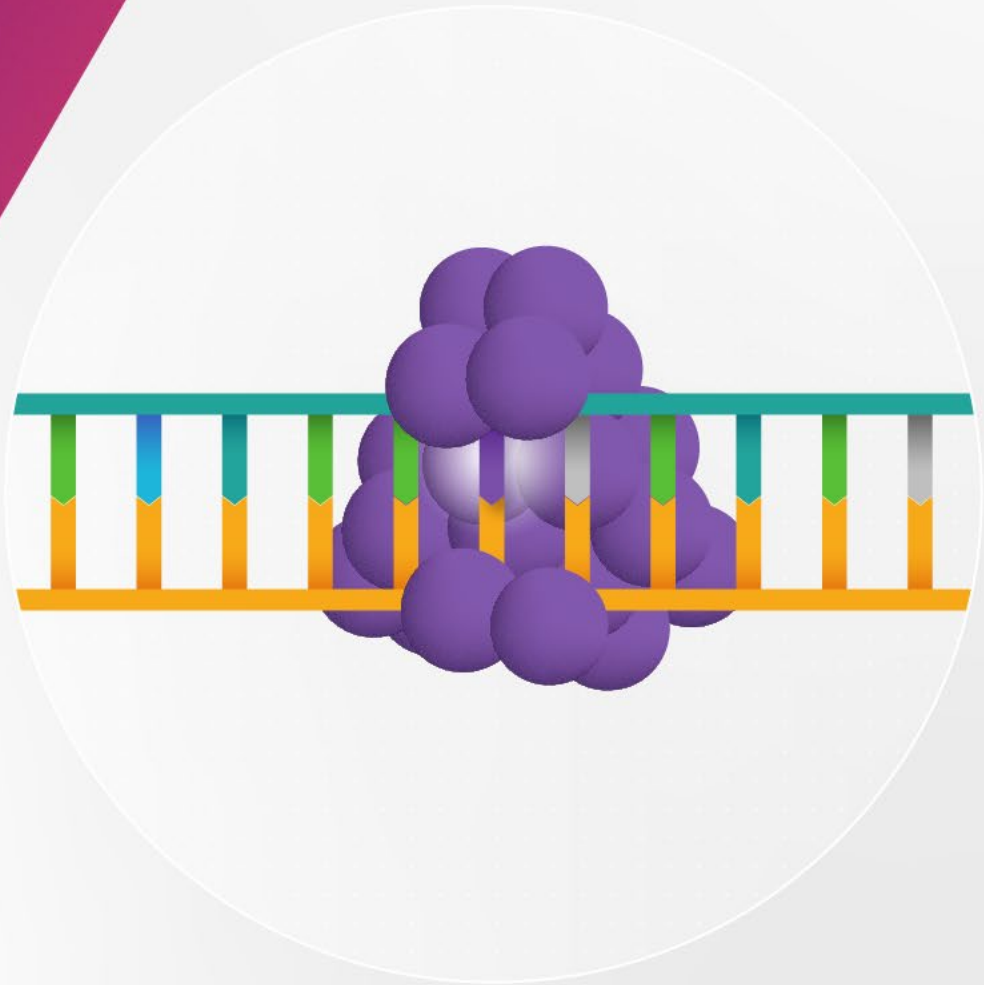
# HOW DOES ADAR WORK?

*Explained in 5 minutes*



# WHAT IS AXIOMER™?

*Explained in 5 minutes*



# ProQR Leadership Team

## Management Team

**Daniel de Boer**
*Chief Executive Officer*

**Gerard Platenburg**
*Chief Scientific Officer*

**René Beukema**
*Chief Corporate Development Officer*

**Jurriaan Dekkers**
*Chief Financial Officer*

**Sheila Sponselee**
*VP, Head of People and Operations*

## Supervisory Board

**Dinko Valerio**
*Chairman*

**James Shannon**, MD

**Alison Lawton**

**Bart Filius**

**Theresa Heggie**

**Begoña Carreño**

**John Maraganore**, PhD
*Strategic Advisor*

## In Memoriam

**Henri Termeer**
*Honorary former board member*

## Scientific Advisory Board

**James Shannon**, MD
*Chair*

**Phillip D. Zamore**, PhD

**Martin Maier**, PhD

**Peter A. Beal**, PhD

**Yi-Tao Yu**, PhD

# Leading IP supporting ADAR-mediated RNA editing platform technology

- Axiomer™ IP strategy commenced in 2014 with first patent application filings
- Currently 13 published patent families, comprising 29 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

# Overview of Axiomer™ related patents

| Docket | Priority | Feature | Status |
|---|---|---|---|
| **1 (0004)** | **17DEC2014** | **Targeted RNA Editing using endogenous ADARs** | Granted BR CA CN EP IL IN JP NZ US US ZA |
| **2 (0013)** | **22JUN2016** | **Short EONs with wobble and/or mismatch base pairs** | Granted AU IL JP KR US US US |
| **3 (0014)** | **01SEP2016** | **Chemically modified short EONs** | Granted AU CN EP JP KR NZ US US ZA |
| 4 (0016) | 19JAN2017 | EONs + protecting SONs (heteroduplex formation) | Granted US |
| 5 (0023) | 18MAY2018 | PS linkages / chiral linkages (*e.g.,* PS, PN) | Published |
| 6 (0026) | 11FEB2019 | Phosphonacetate linkages / UNA modifications | Published |
| 7 (0029) | 03APR2019 | MP linkages | Published |
| 8 (0031) | 24APR2019 | Editing inhibition | Published |
| 9 (0032) | 13JUN2019 | Benner's base (dZ) | Published Granted ZA |
| 10 (0039) | 23JUL2020 | Split EONs | Published |
| 11 (0045) | 14FEB2022 | PCSK9 editing | Published |
| 12 (0046) | 15JUL2022 | 5'-GA-3' editing | Published |
| 13 (0048) | 15JUL2022 | diF modification | Published |

In addition to the above, numerous patent applications are pending but have not yet been published.
ProQR expands its Axiomer™ IP portfolio continuously.

# ProQR Axiomer™ IP

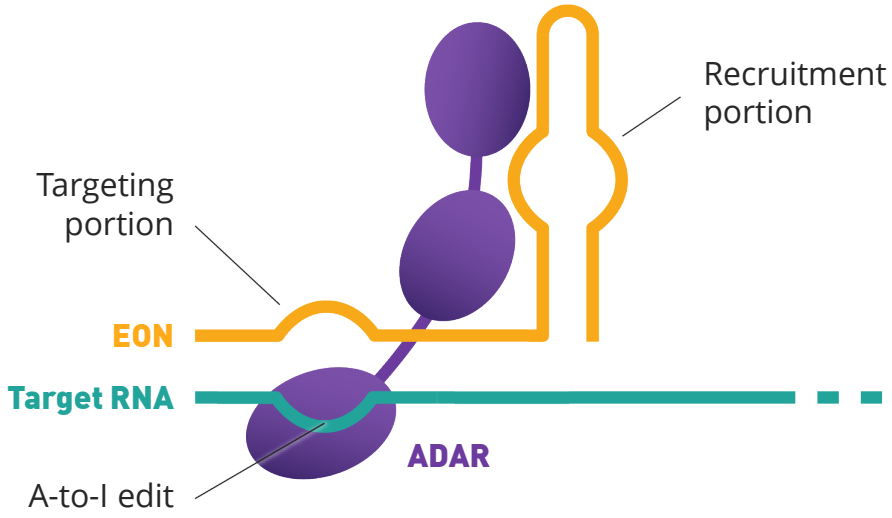
*Broad coverage*

- 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
  - 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



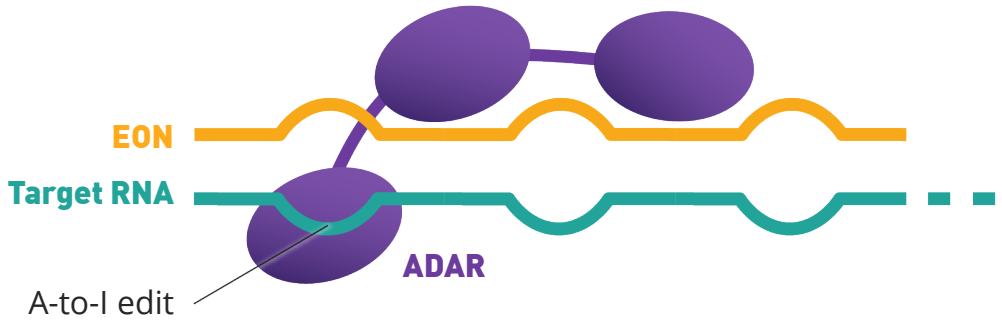

**EP 3 234 134 B1 - Granted; appeal pending**
**US 10,676,737 - Granted**
**US 11,781,134 - Granted**

Claim 17. 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.



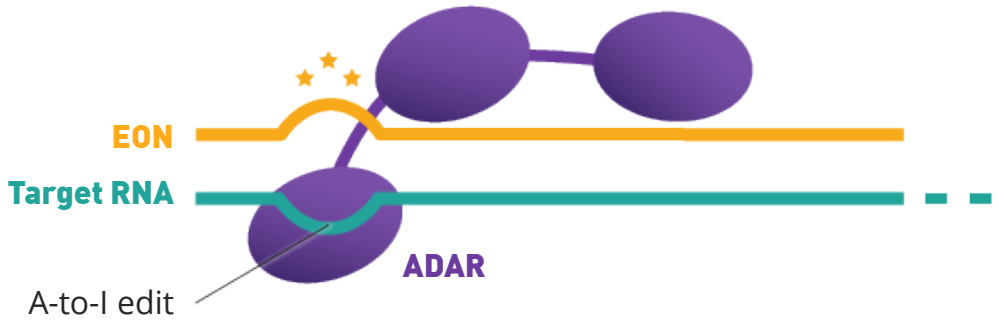

**US 10,941,402 - Granted**
**US 11,851,656 - Granted**
**US 18/296,912 - Allowed**

Target-specific claims

- An AON capable of forming a double stranded complex with a target RNA in a cell, wherein: the target RNA encodes CFTR, CEP290**, alpha1- antitrypsin (A1AT)**, LRRK2, or BDNF, 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.




**US 10,941,402 - Granted**
**US 11,851,656 - Granted**
**EP 3 507 366 B1 - Granted; opposition pending**

An antisense oligonucleotide (AON) capable of forming a double stranded complex with a target RNA sequence in a cell, preferably a human cell, for the deamination of a target adenosine in the target RNA sequence by an ADAR enzyme present in the cell, said AON comprising **a Central Triplet** of 3 sequential nucleotides, wherein the nucleotide directly opposite the target adenosine is the middle nucleotide of the Central Triplet, wherein 1, 2 or 3 nucleotides in said 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.

# ProQR Axiomer™ IP

*Summary*

- 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**'

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