

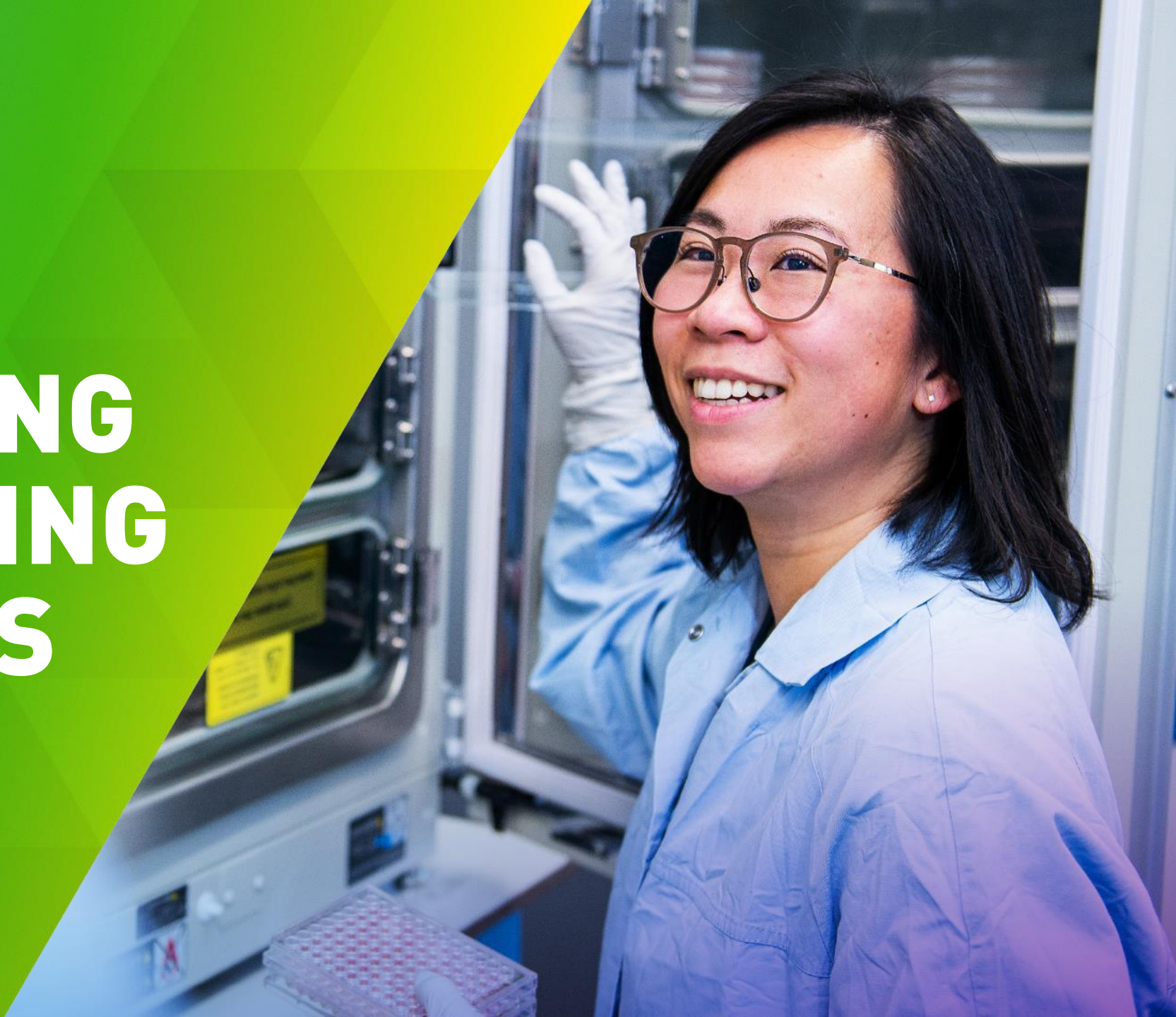


DEVELOPING RNA-EDITING MEDICINES

for patients in need

Nasdaq: PRQR

August 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.

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

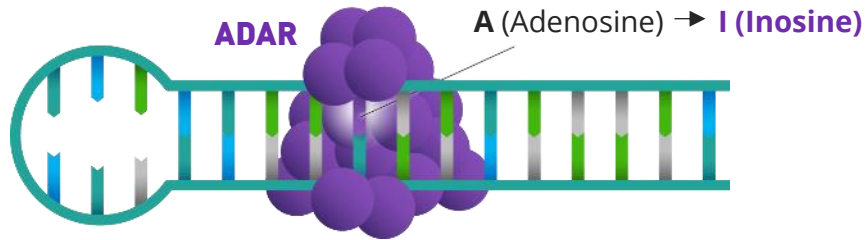


RUNWAY INTO MID 2027

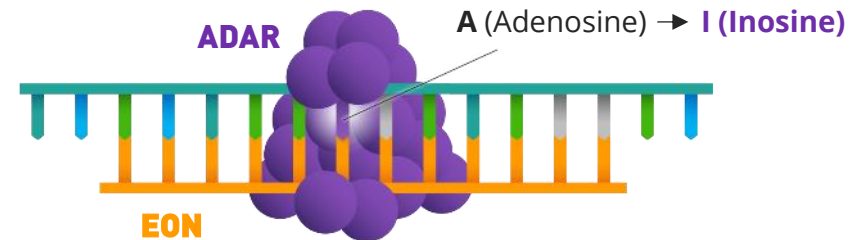
€ 119.8 million cash
and cash equivalents
as of end of Q2 2025,
providing runway
into mid-2027

Axiomer™ EONs enable A-to-I editing in RNA

Natural ADAR editing



Editing Oligonucleotide (EON)-directed editing

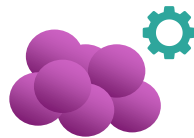


Correction



Mutations correction

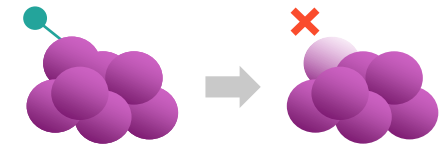
Protein modulation



Alter protein function or
include protective variants



Disrupt >400 different types
of PTMs



Change protein
interactions

ProQR development pipeline

	TARGET	DISCOVERY	NON-CLINICAL	CLINICAL	NEXT MILESTONE	ESTIMATED POPULATION
DEVELOPMENT PIPELINE						
AX-0810 for Cholestatic diseases	NTCP	<div><div></div></div>	<div><div></div></div>		Initial data Q4 2025 ¹	~100K patients ²
AX-2402 for Rett syndrome	MECP2 R270X	<div><div></div></div>			Candidate selection in 2025	~5K patients
AX-1412 for Cardiovascular disease	B4GALT1	<div><div></div></div>			Scientific update in mid 2025	~200M patients ³
AX-2911 for MASH	PNPLA3	<div><div></div></div>			Candidate selection in 2025	~8M patients
DISCOVERY PIPELINE						
AX-1005 for CVD	Undisclosed	<div><div></div></div>				~200M patients
AX-0601 for obesity and T2D	Undisclosed	<div><div></div></div>				~650M patients
AX-9115 for rare metabolic condition	Undisclosed	<div><div></div></div>				
AX-2403 for Rett syndrome	MECP2 R168X	<div><div></div></div>				~6K patients
AX-2404 for Rett syndrome	MECP2 R255X	<div><div></div></div>				~5K patients
AX-2405 for Rett syndrome	MECP2 R294X	<div><div></div></div>				~6K patients
AX-2406 for Rett syndrome	MECP2 R133H	<div><div></div></div>				
AX-3875 for rare metabolic & CNS disorder	Undisclosed	<div><div></div></div>				
AX-4070 for rare CNS disorder	Undisclosed	<div><div></div></div>				
PARTNERED PIPELINE						
10 targets (option to expand to 15)	Undisclosed	Progress undisclosed				<i>Lilly</i>

¹CTA regulatory clearance for AX-0810 is pending. ²Approximately 100K people affected with Primary Sclerosing Cholangitis and Biliary Atresia in US and EU5. ³Approximately 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

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 transporter which is responsible for majority of bile acid re-uptake in liver cells.



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

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 liver¹⁻³



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 acids⁴⁻⁵



IN CLINIC

Clinical PoC with bulevirtide in Ph3 Hepatitis D trial, for which liver improvement occur in patients, even without virologic response⁶⁻⁸



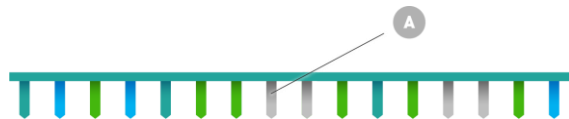
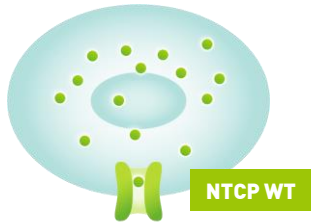
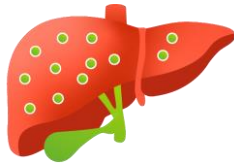
Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. NTCP channel is a known transporter for bile acids and hepatitis virus from bloodstream to the liver.

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

Human genetics validates NTCP modulation as strategy for cholestatic disease

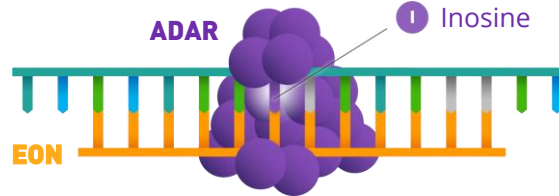
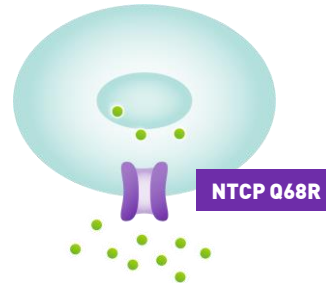
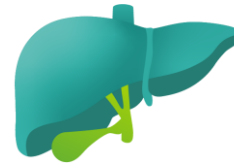
Liver with cholestatic disease

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

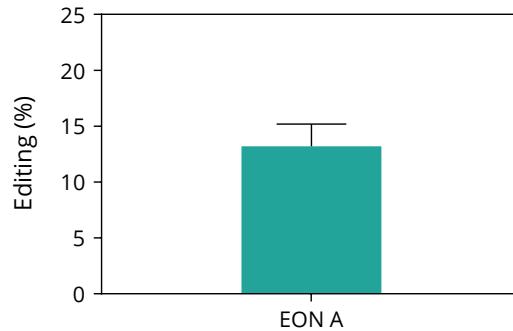
BA, Biliary atresia; PSC, Primary Sclerosing Cholangitis

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

Editing efficiency

NTCP RNA Editing in Humanized Mice

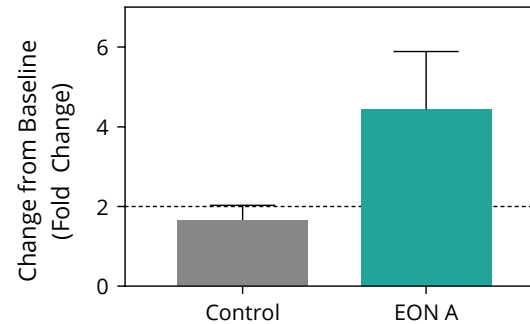
(N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25, ddPCR)



Plasma total bile acids

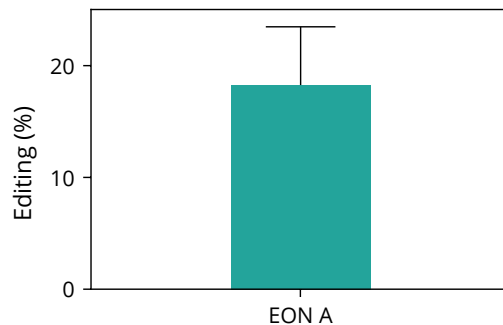
Plasma TBA in Humanized Mice

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



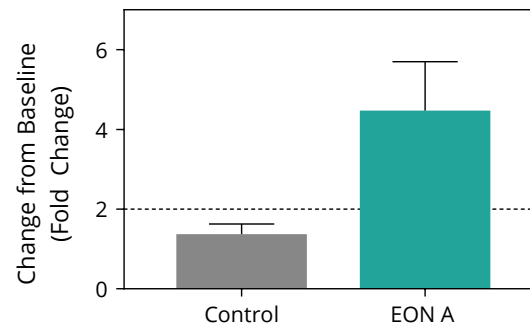
NTCP RNA Editing in NHP

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



Plasma TBA in NHP

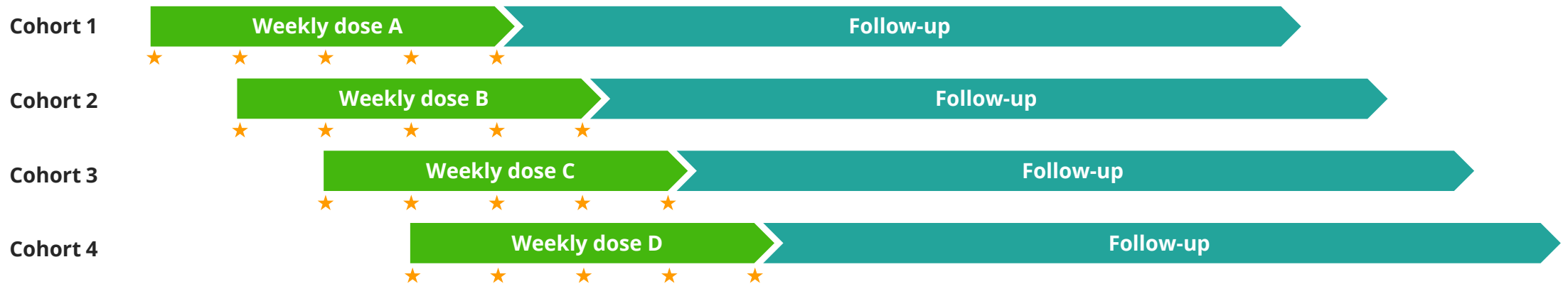
(N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D39)



- 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

First in human trial of AX-0810 to establish target engagement, TPP=Q3M

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 healthy volunteers, 4 weeks dosing phase followed by 12 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 submitted in Q2 2025

Top-line data in Q4 2025

AX-2402 RNA editing therapy targeting MECP2 for Rett Syndrome



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.



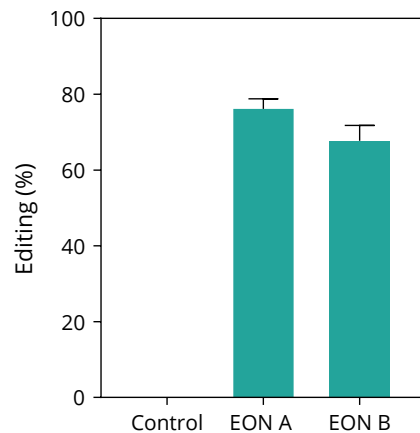
Rett Syndrome Research Trust partnership includes \$9.2 M in funding; collaboration established in January 2024, expanded in December 2024



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

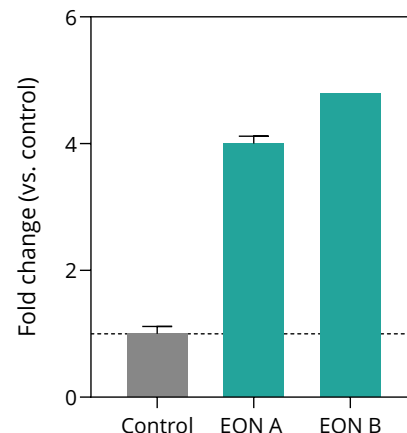
Editing increases mRNA levels and restores protein expression; Broad editing distribution in CNS

R270X MECP2 editing



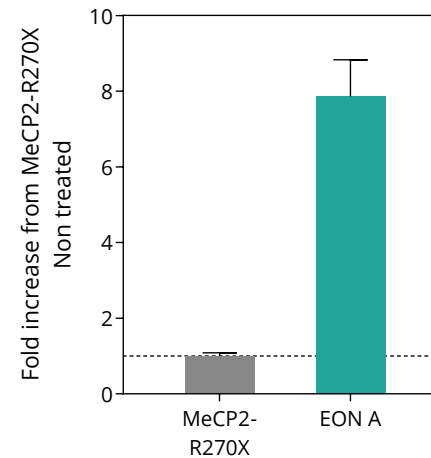
Up to 80 % editing of R270X MECP2 in patient fibroblasts

MECP2 RNA levels



Increased MECP2 RNA levels due to PTC recoding and NMD inhibition

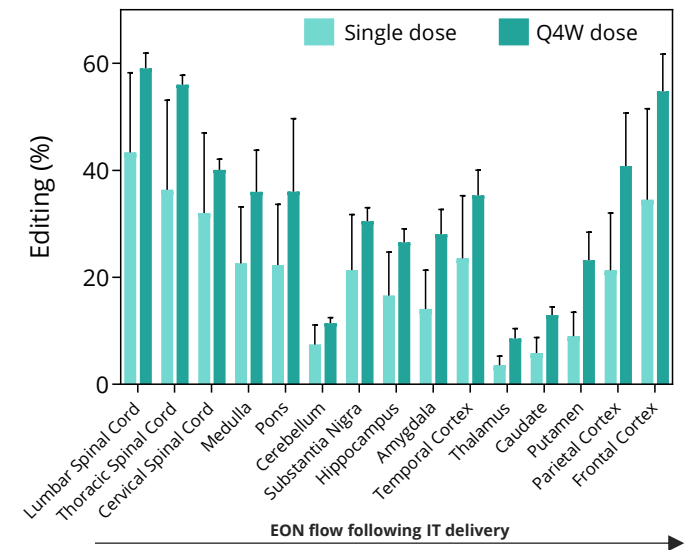
R270W MECP2 protein levels



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

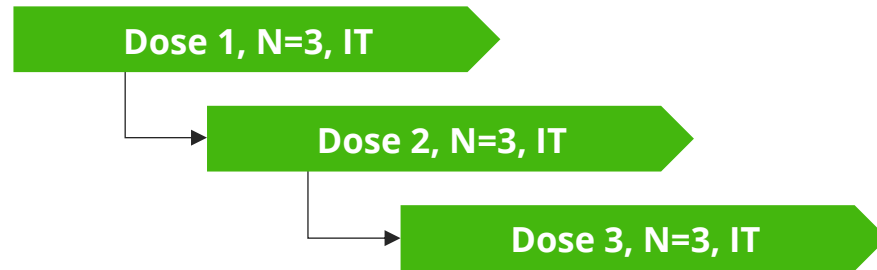


Stable and prolonged editing efficiency in both superficial and deep brain regions

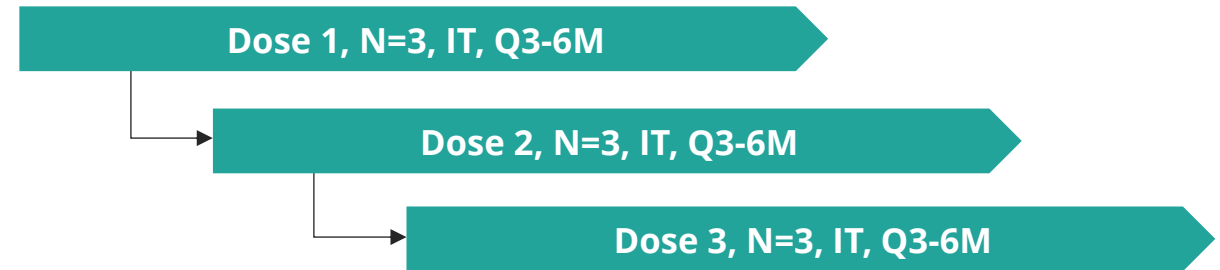
EON, Editing oligonucleotide; NT, Non-treated; TF, transfection, Conditions panel on the left and middle: 100 nM EON, transfection, 48h, N=2, mean±SEM. Conditions panel on the right: MeCP2-R270X-NanoLuc activity; 100 nM EON, transfection, 48h, N=8, mean±SEM.

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 \$9.2 M funding provided by Rett syndrome Research Trust
- **Clinical candidate selection in 2025**
- **Top-line data expected in 2026**

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.

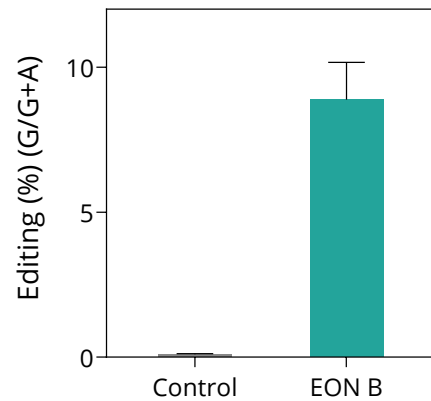


¹Montasser ME, et al. Science. 2021 Dec 3;374(6572):1221-1227

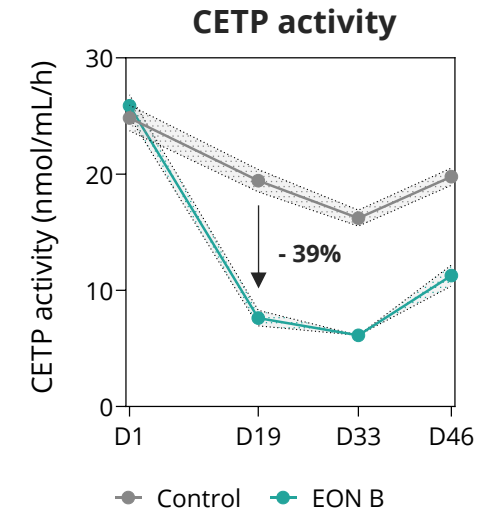
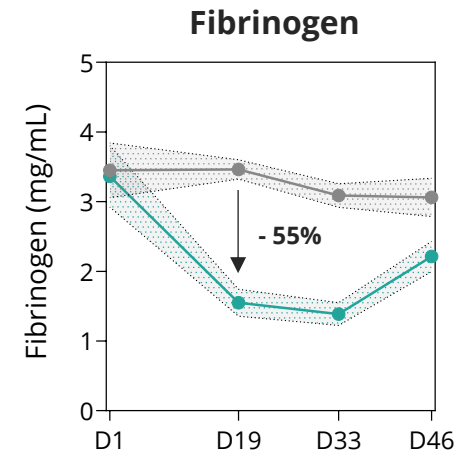
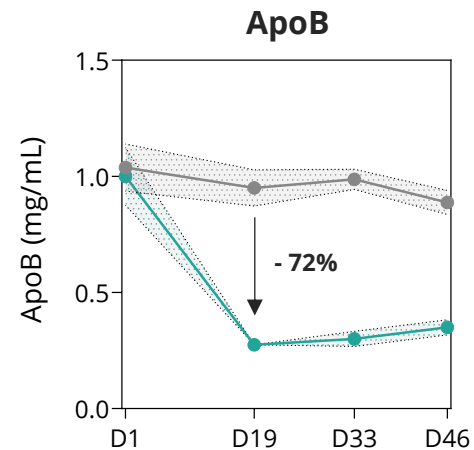
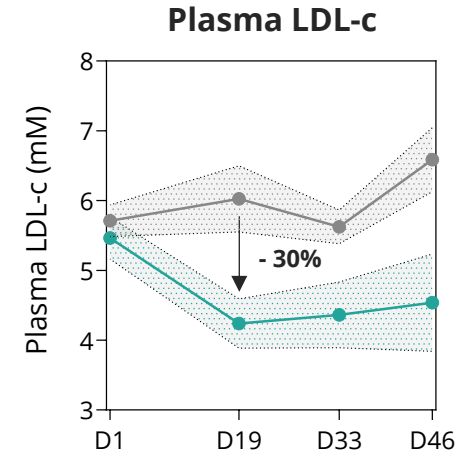
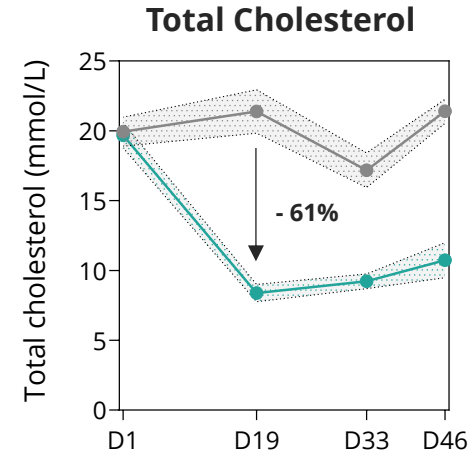
EON-mediated editing of B4GALT1 leads to meaningful effect on key biomarkers in E3L.CETP Mice

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



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, CETP, 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 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** available¹



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.



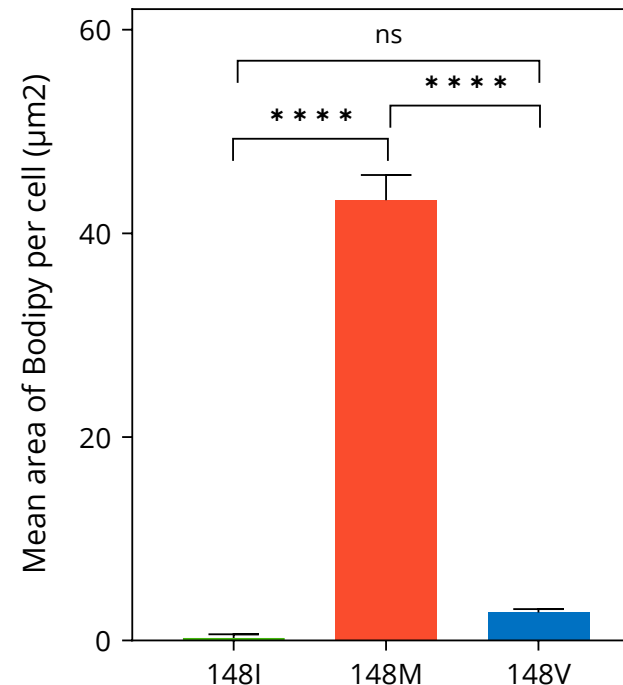
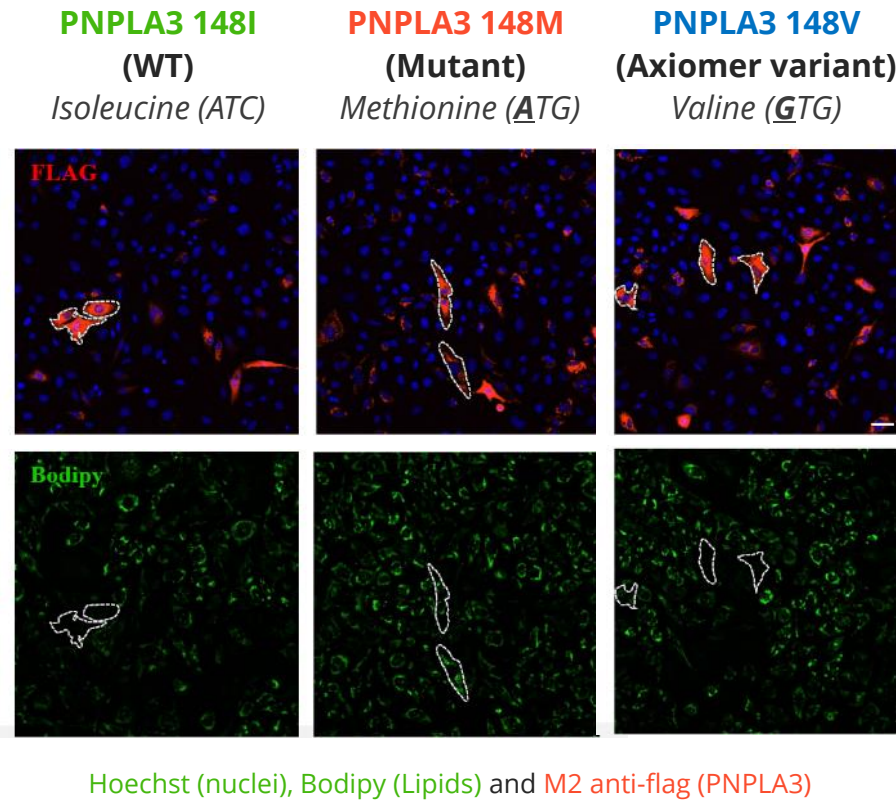
Axiomer EONs have the potential to change the Methionine into a Valine bringing the **PNPLA3 protein back to a WT-like functional conformation**.



¹Sandireddy R, et al. Front Cell Dev Biol. 2024 Jul 16;12:1433857; ²Romeo S, et al. Nat Genet. 2008 Dec;40(12):1461-5; ³Salari 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



- 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, 250µM linoleic acids, 24h, cell lipase activity by IF One-way ANOVA, ****, P<0.0001; Mean, SEM.

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

Catalyst overview

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

AX-0810 for Cholestatic diseases

- ✓ 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

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

- € 119.8 million cash and cash equivalents as of end of Q2 2025
- Cash runway to mid-2027, excluding potential for additional BD-related upside

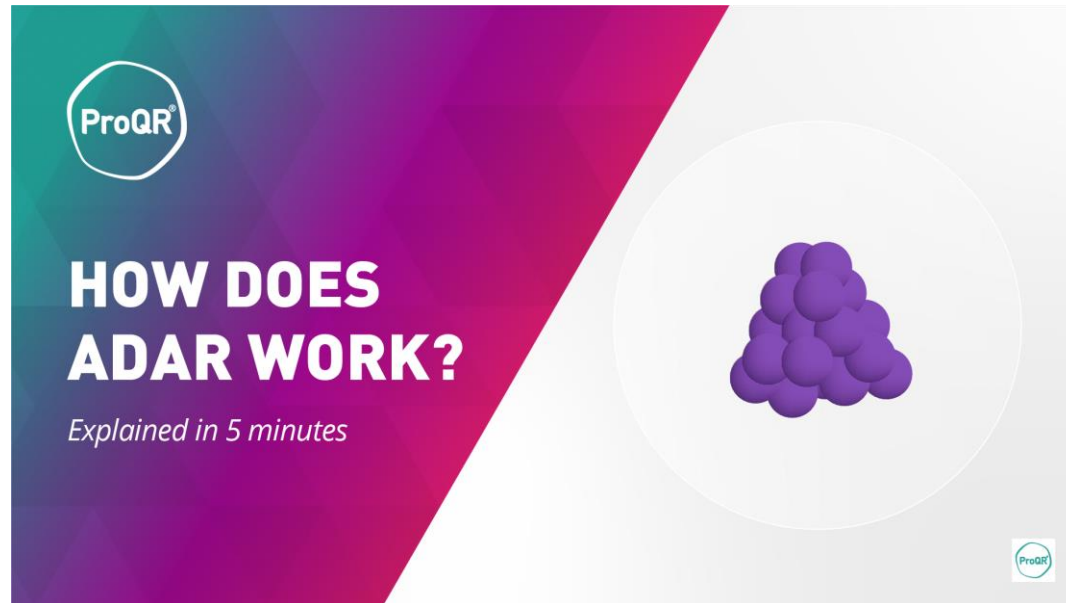


**IT'S IN
OUR RNA**



Resource slides

Video



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



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Board advisor



Peter A. Beal, PhD

ProQR Chief ADAR Scientist

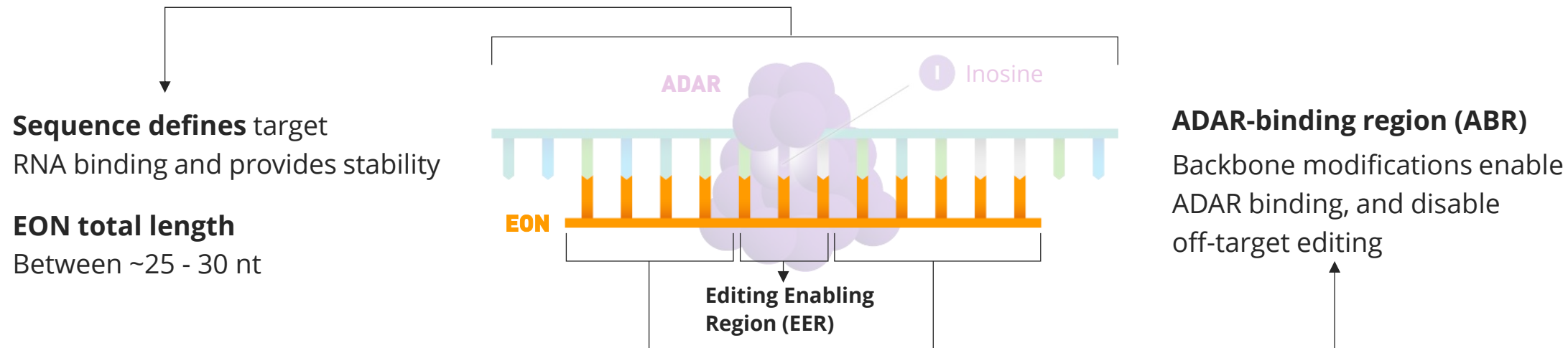


Phillip D. Zamore, PhD

Scientific Advisory Board



Driving the development of optimized EONs for therapeutic use



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 27 published patent families, comprising 37 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)	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
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
26 (0062)	07SEP2023	MC4R	Published	Target
27 (0066)	16NOV2023	GALK1	Published	Target

ProQR Axiomer™ IP

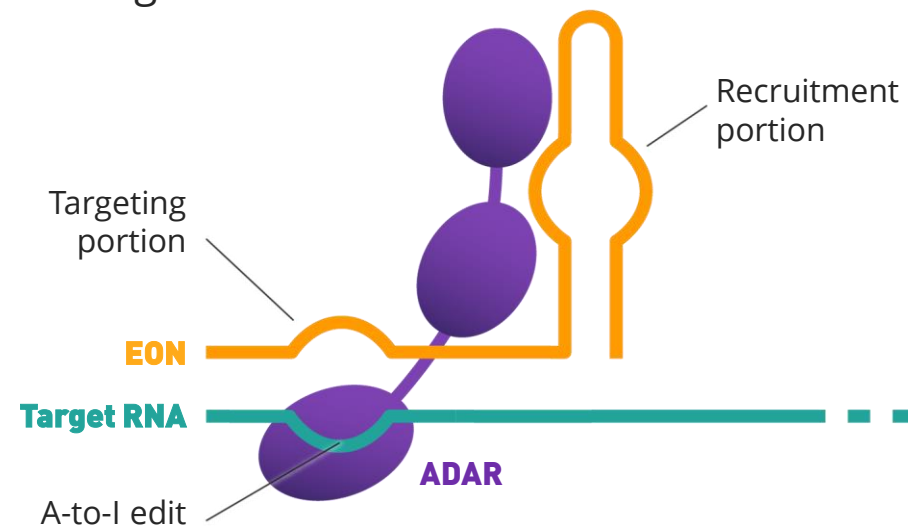
Broad coverage

- 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

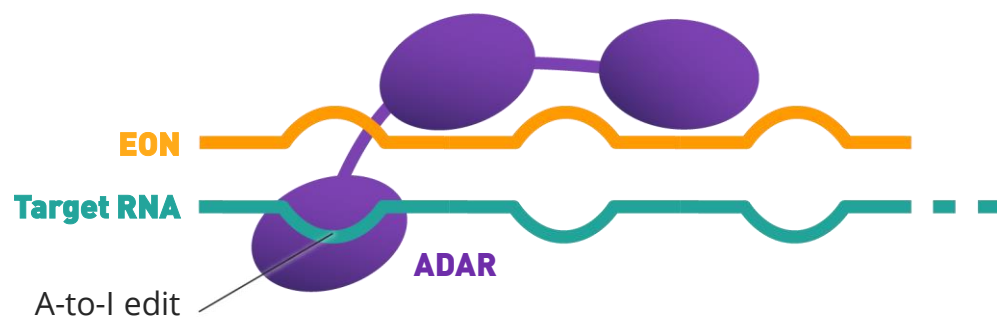
Claim 17 (US 11,781,134):

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 hADAR1 or hADAR2 enzyme naturally present in the cell**;
- allowing the hADAR1 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.



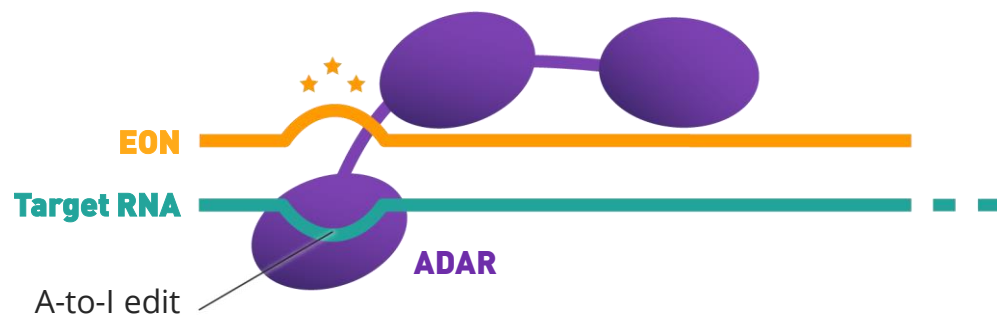
US 10,988,763	Granted
US 11,649,454	Granted
US 12,018,257	Granted

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.



**IT'S IN
OUR RNA**