ProQR®

AXIOMER™ ADAR-MEDIATED RNA EDITING PLATFORM

Translating RNA editing science into targeted liver and CNS applications

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TIDES Asia | Feb 24-26, 2026

Disclosures

- I am an employee of ProQR Therapeutics

ProQR development pipeline

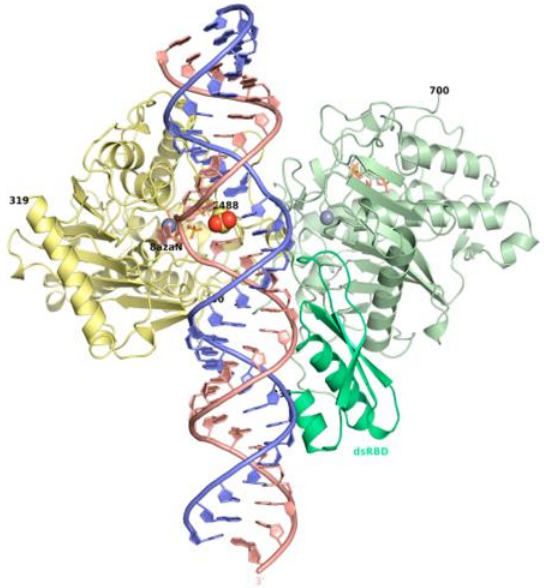
	TARGET	AXIOMER APPLICATION	DISCOVERY	NON-CLINICAL	CLINICAL	MILESTONES	ESTIMATED POPULATION
DEVELOPMENT PIPELINE							
AX-0810 *for Cholestatic diseases*	NTCP	*Modulate*				Target engagement data 1H 2026	~100K[1] patients
AX-2402 *for Rett syndrome*	MECP2 R270X	*Correct*				✓ Candidate selected	~5K patients
AX-2911 *for MASH*	PNPLA3	*Correct*				✓ Candidate selected	~8M patients
AX-1412 *for Cardiovascular disease*	B4GALT1	*Protect*					~200M[2] patients
DISCOVERY PIPELINE							
Multiple programs in liver and CNS							
PARTNERED PIPELINE							
10 targets (option to expand to 15)	Undisclosed		*Progress undisclosed*				Lilly

[1]Approximately 100K people affected with Primary Sclerosing Cholangitis and Biliary Atresia in US and EU5. [2]Approximately 200 million people suffer from too high a level of cholesterol in US and EU5; SLC10A1 is the gene that encodes for NTCP protein; CVD: Cardiovascular Diseases, NASH: Nonalcoholic steatohepatitis, | 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

Axiomer™ EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

ADAR *(Adenosine Deaminase Acting on RNA)*

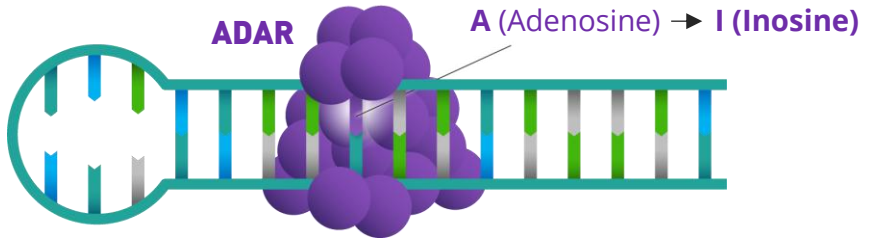


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing *(A-to-I)*

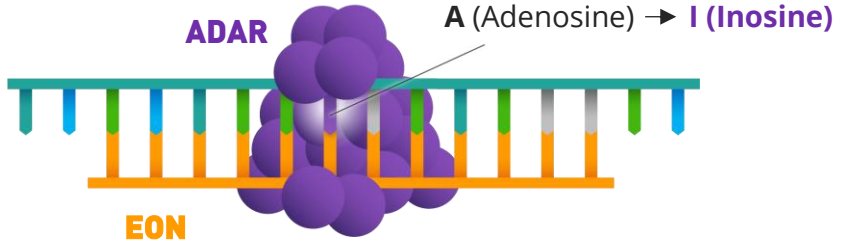
Natural ADAR editing *(A-to-I)*

RNA
Double stranded



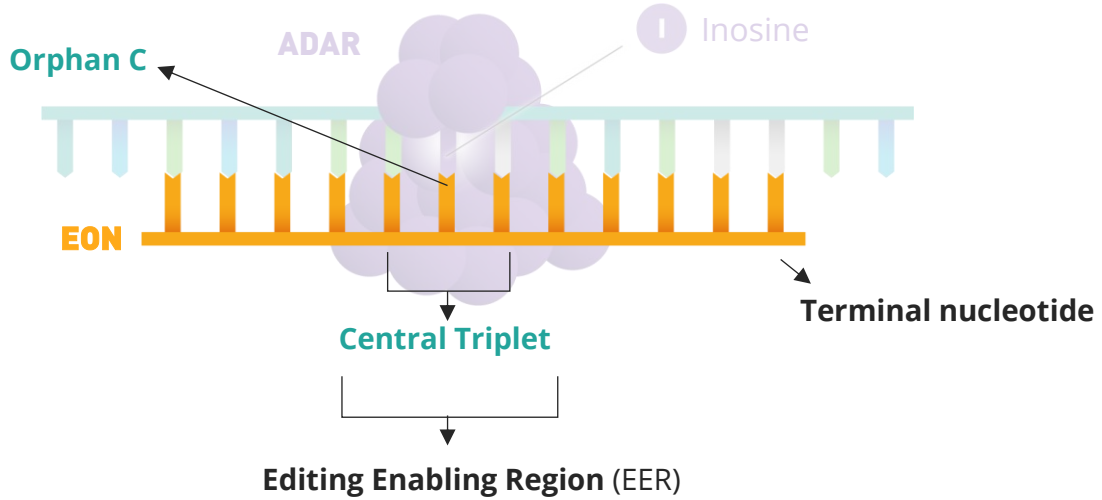
Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*

RNA+EON
Double stranded



Driving the evolution of therapeutic EONs

Locations of importance

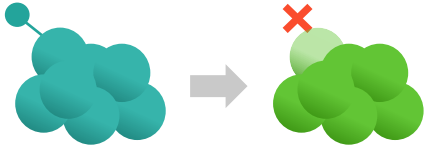


Optimized sequence and chemistry define functionality: EONs are not unlike other ASO types

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

Non-EON specific | EON specific

Creating a new class of medicines with broad therapeutic potential

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

Axiomer™ applications in liver

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.

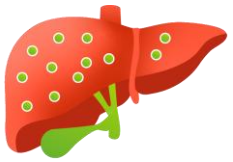
Learnings from human genetics and literature demonstrate that **modulation of the NTCP channel** responsible for majority of bile acids re-uptake in liver cells could lead to **hepato-protective effects**.

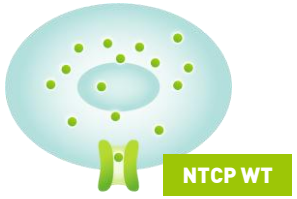
NTCP, sodium taurocholate co-transporting polypeptide. References: [1]Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; [2]Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999

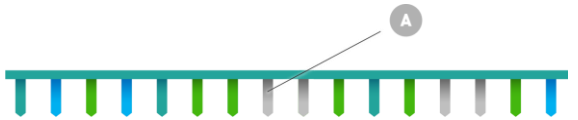
AX-0810: first-in-class RNA editing therapy targeting NTCP for cholestatic diseases

LIVER WITH CHOLESTATIC DISEASE

High concentration of bile acids in hepatocytes

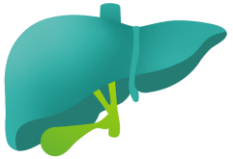


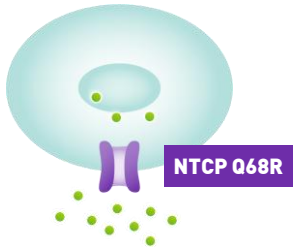


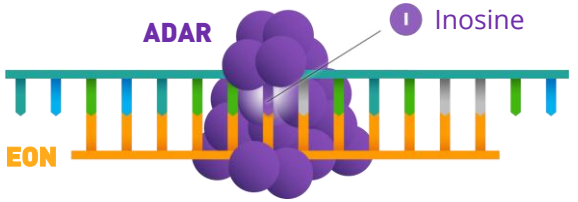


AX-0810 STRATEGY FOR DISEASED LIVER

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

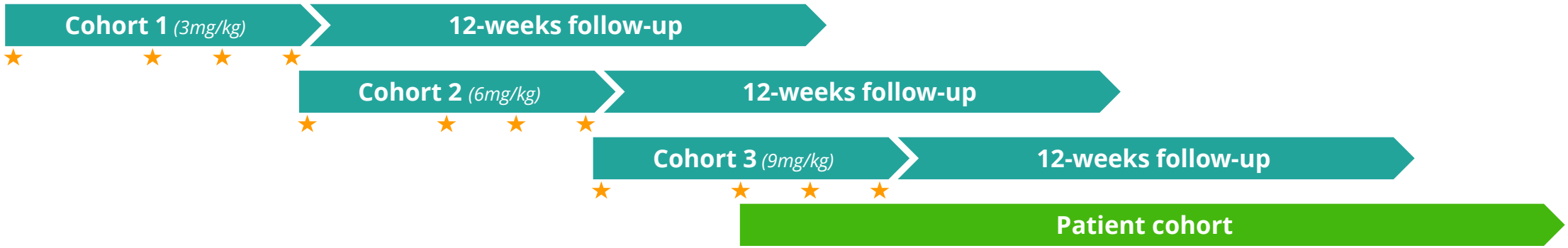
- Reduce inflammation and fibrosis from bile acids toxicity
- Alleviate symptoms in PSC and BA
- Prevent or delay cirrhosis, organ failure, and transplant

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.

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

- Initial AX-0810 data demonstrated no safety signals and pharmacokinetics consistent with non-clinical models
- Phase 1 enrollment and dosing in healthy volunteers ongoing

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).

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

MASH is **highly prevalent and increasing worldwide**. MASH individuals have a **high unmet medical** need due to disease progression into cirrhosis, HCC, and liver-related mortality with **limited therapeutic options** available.[1] Emerging evidence shows that NAFLD patients with the I148M variant are **less responsive** to GLP-1 agonists[2].

PNPLA3 (patatin-like phospholipase domain-containing 3) **I148M** is the **strongest known genetic risk** factor of steatosis, MASH and fibrosis, being present in **~39–47% of MASLD patients**[3].

Homozygous carriers are approx. **8 million individuals** in US+EU and show **+73% higher liver fat**[4], **3.5× higher risk of NASH/MASH**[4], faster fibrosis progression and increased liver-related **mortality and HCC**[5].

Axiomer EONs recode the PNPLA3 I148M variant (Met→Val), restoring WT-like protein function. AX-2911 is designed to **correct the primary genetic driver of MASH**, unlike current therapies that target downstream metabolic or inflammatory pathways.

[1]Sandireddy R, et al. Front Cell Dev Biol. 2024 Jul 16;12:1433857; [2] Chen, Yunzhi et al, 2020; [3]Tsedendorj Yumchinsuren et al., 2025; [4]Sookoian Silvia et al., 2011; [5]Souza Matheus et al., 2024

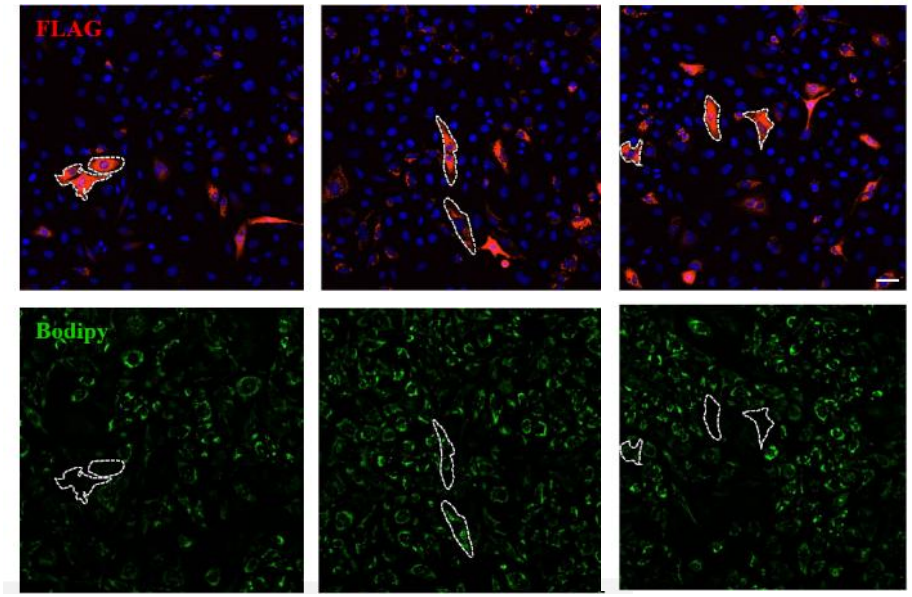
AX-2911 to restore WT-like PNPLA3 function

148I and 148V show comparable lipid droplet sizes

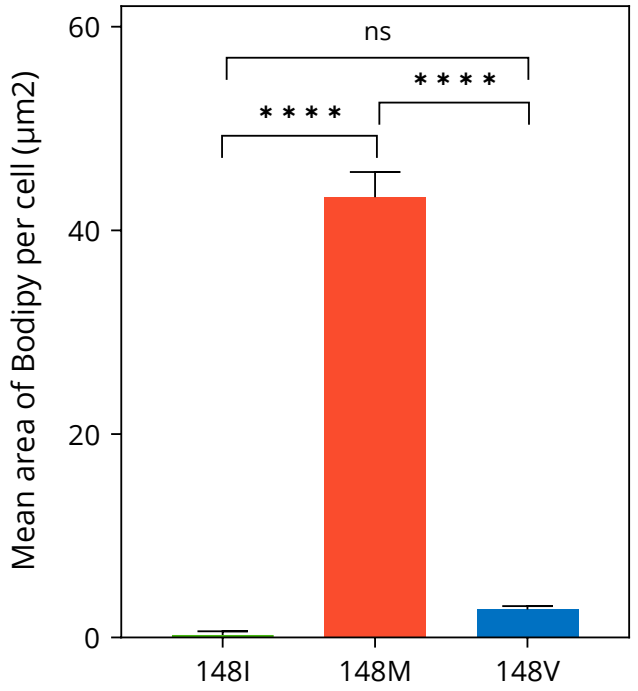
PNPLA3 148I
(WT)
Isoleucine (ATC)

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

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



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



- WT 148I PNPLA3 shows smaller lipid droplets, reflecting normal lipid metabolism.
- 148M PNPLA3 shows 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 similar effect on lipid accumulation to 148I.

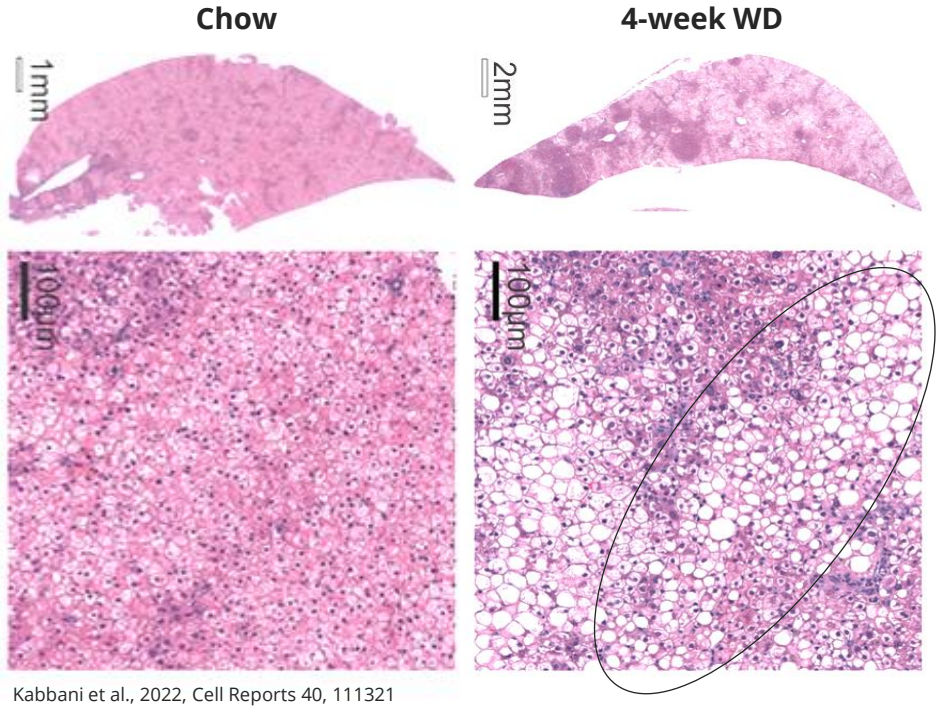
Treatment conditions: HeLa cells, plasmid, transfection, 250uM linoleic acids, 24h, cell lipase activity by IF One-way ANOVA, ****, P<0.0001; Mean, SEM.

Humanized PNPLA3 I148M model captures the primary genetic driver of MASH

Yecuris FRG PNPLA3 I148M model leverages the established Western Diet used in MASH drug development, enhanced by the key human genetic risk factor

Liver steatosis generation in Yecuris

FRG PNPLA3 I148M humanized mice on Western Diet for 4 weeks



Kabbani et al., 2022, Cell Reports 40, 111321

Standard MASH models

- Driven by diet or chemical injury
- Do not capture the primary human genetic driver (PNPLA3 I148M)

Yecuris FRG PNPLA3 I148M model

- Engrafted with PNPLA3 I148M primary human hepatocytes
- Recapitulates the human lipid-handling defect
- Translational relevance
- Industry-standard Western Diet
- Rapid, robust steatosis (4 weeks)

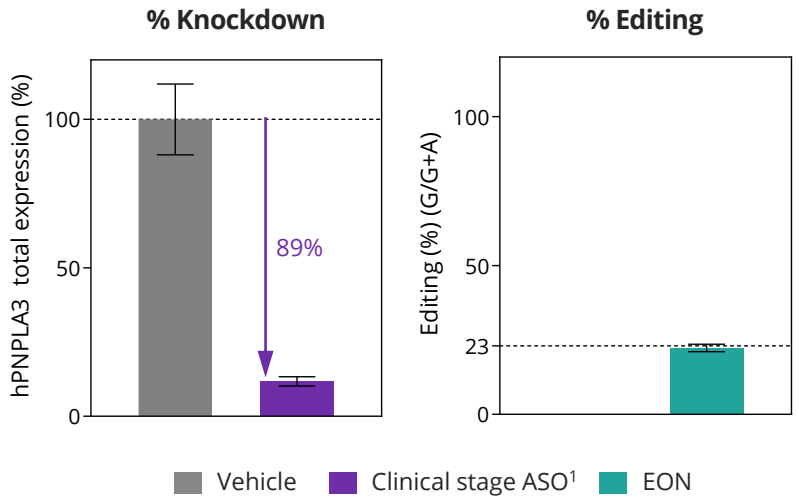
Editing has functional advantage over knockdown

AX-2911 substantially reduces liver fat vs clinical-stage ASO[1] (mouse steatosis model)

mRNA

hPNPLA3 I148M humanized mouse liver model

dPCR (Qiagen), AVG±SEM



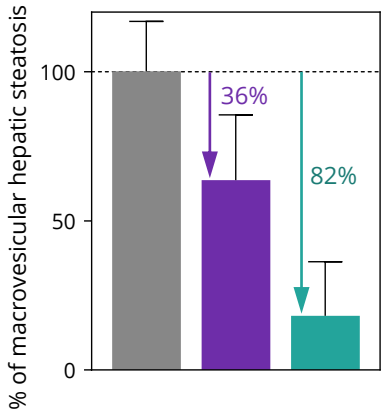
Clinical-stage ASO[1]: **~89%** mRNA reduction via knockdown of hPNPLA3

EON: **23%** editing of hPNPLA3 mRNA

LIVER FUNCTION *(steatosis)*

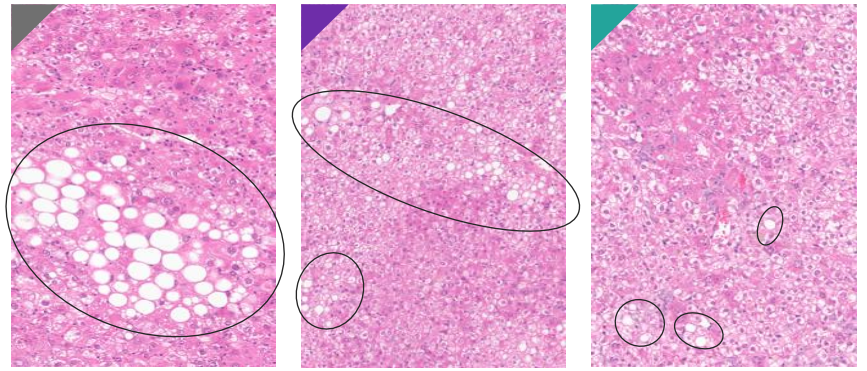
Macrovesicular steatotic incidence scoring (%)

AVG±SEM



Liver sections of steatosis mouse model treated with ASO or AX-2911

PNPLA3 I148M humanized FRG mouse, WD 4W+4W



Vehicle | Clinical stage ASO[1] | EON

EON: **82%** reduction of macrovesicular lipid droplets

Vehicle

Clinical-stage ASO[1] (Day 28)

EON (Day 28)

[1]Clinical candidate AZ AZD2693

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

Human Genetics Validation of B4GALT1: Nature's Proof of Concept

From rare carriers and genetic disease to controlled therapy: B4GALT1 biology validated in humans

RARE PROTECTIVE VARIANT B4GALT1 P.ASN352SER

↓ LDL-C (–14 mg/dL)
↓ Fibrinogen (–29 mg/dL)
↓ CAD risk (36%)

MOUSE 353SER/353SER KNOCK-IN MICE

↓ LDL-C (–38%)
↓ Fibrinogen (-20%)

CONGENITAL B4GALT1 LOSS-OF-FUNCTION (CDG)

↓ LDL-C (-47%)
↓ ApoB (–49%)
↓ CETP (-26%)

EON-E3L.CETP MICE EON TREATED TO FORM B4GALT1 PROTECTIVE VARIANT

↓ LDL-C (-30%)
↓ ApoB (–72%)
↓ CETP (-39%)

↓ Cholesterol (-61%)
↓ Fibrinogen (-55%)

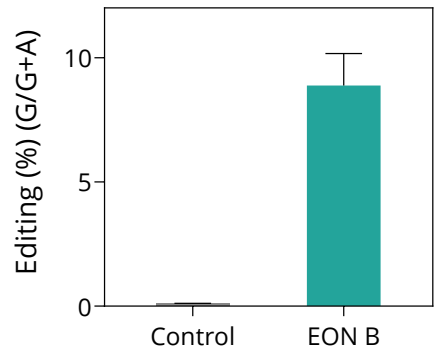
Therapeutic replication

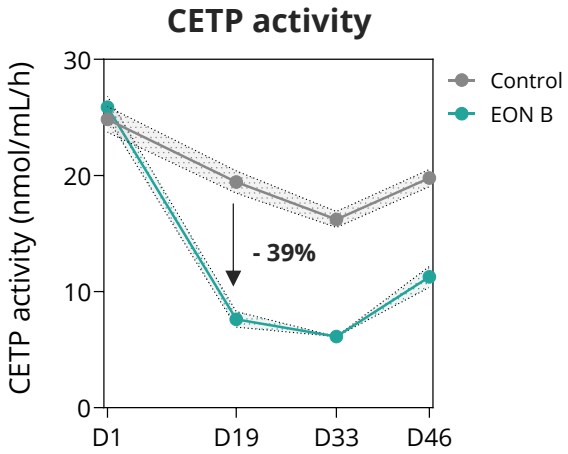
- Our RNA editing approach **replicates protective alleles** in a **controlled, non-pathogenic** way
- **Human genetics derisks development** by showing the biology is already validated in nature

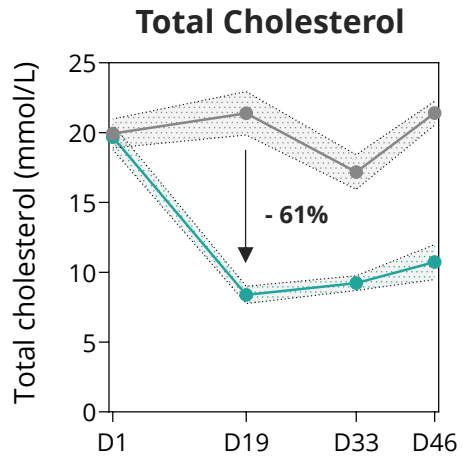
Montasser May E. et al., 2019

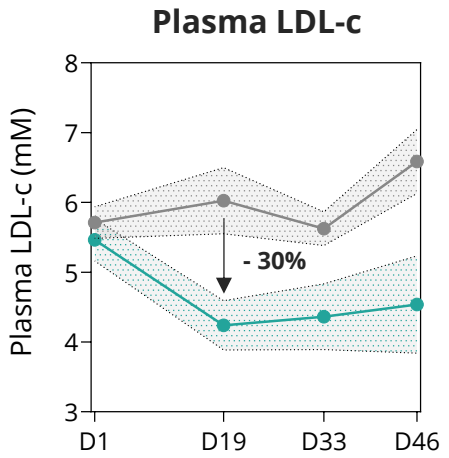
EON-mediated editing of B4GALT1 leads to meaningful effect on key biomakers in E3L.CETP Mice

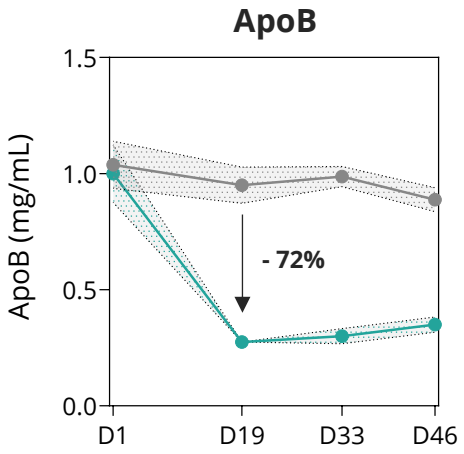
B4GALT1 editing and biomarkers in E3L.CETP mice *(N=10, 2mg/kg, LNP formulation, IV Q1W, D46, ddPCR)*

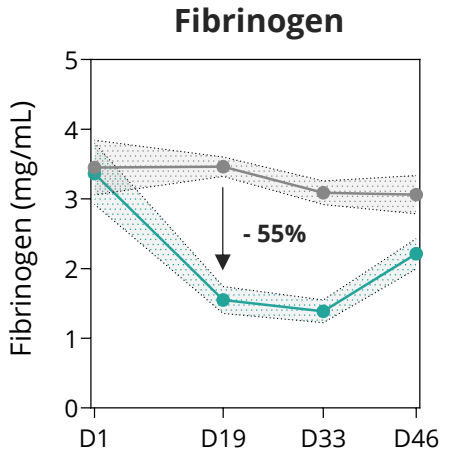












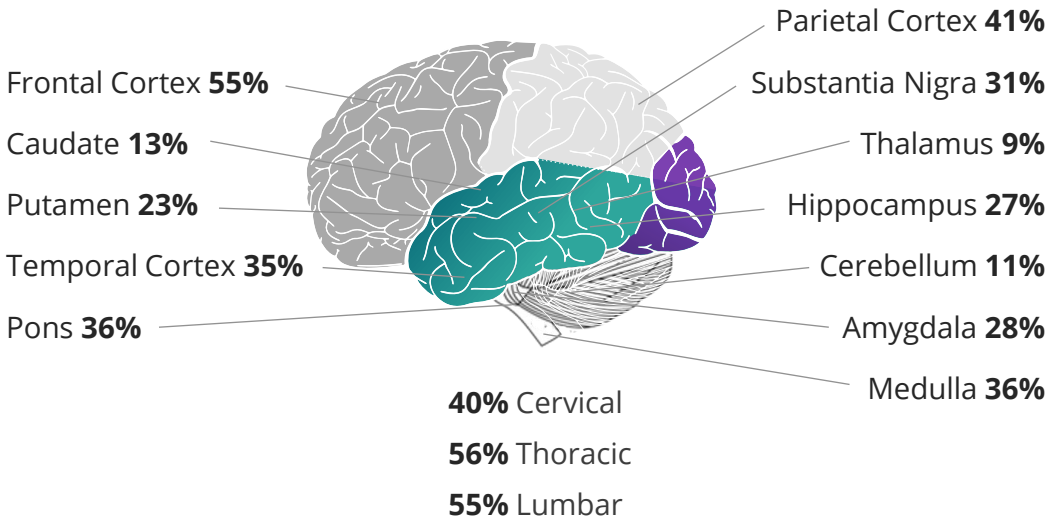
- Following EON treatment a **marked reduction** in total cholesterol, ApoB, and LDL-c by observed
- Already at Day 19 confirms our approach to address cardiovascular diseases

Axiomer™ applications in CNS

EON IT injection drives durable, widespread RNA editing across the CNS in NHP

RNA editing in NHP *in vivo*

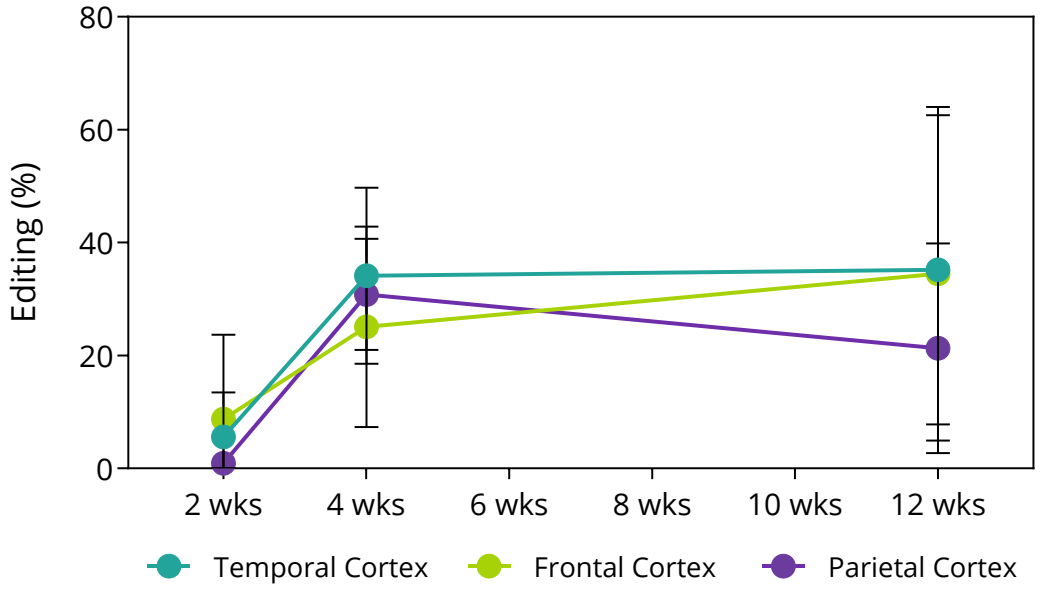
IT administration, ACTB, 10.6mg, Q4W, N=2-3, 12 weeks, ddPCR, mean±SEM



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

RNA editing of ACTB in NHP - Cortex

IT administration, 10.6mg EON, single dose, n=3, up to 12 weeks, ddPCR, mean, SD



Axiomer EONs lead to robust and sustained editing up to 12 weeks, following single dose

ACTB: Actin beta ; EON: Editing Oligonucleotide; IT: Intrathecal; NHP: Non-Human Primate; SC: Spinal Cord; SD: Standard Deviation

AX-2402 RNA editing therapy targeting *MECP2* for Rett Syndrome

Rett Syndrome is a **severe neuro-developmental** disorder caused by variants in the transcription factor Methyl CpG binding protein 2 (MeCP2) with high unmet need for a disease modifying therapy.

Nonsense variants lead to **severe phenotypes and affect ~1/3** of **patients** (**~20,000 individuals** in US/EU.[1,2])

Rett Syndrome is not a neuro-degenerative disorder. Restoring MeCP2 protein levels **reversed** symptoms in mice.[3]

AX-2402 aims to restore the **normal level of MeCP2 protein**, enabling disease modification

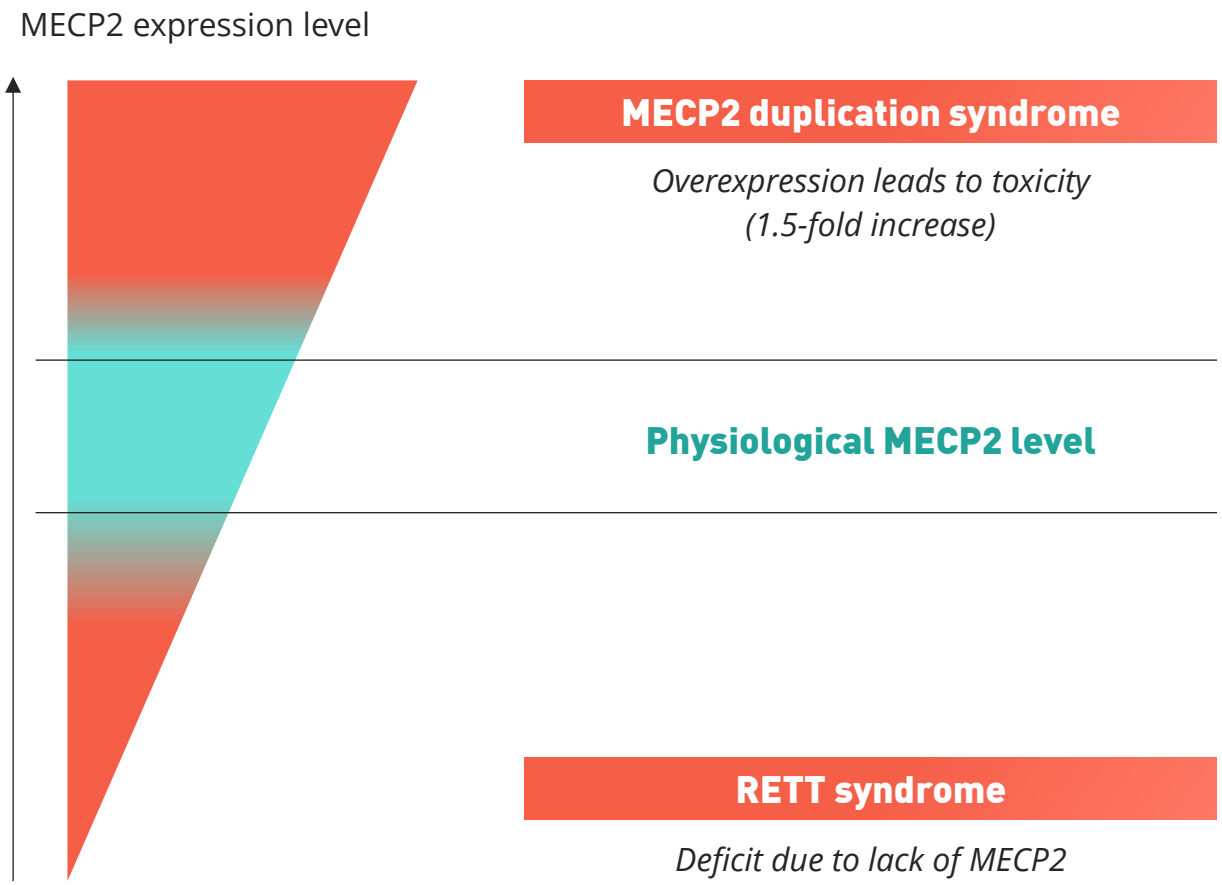
Development candidate selected; first-in-human trial planned **H1 2027**

$9.2M partnership with Rett Syndrome Research Trust

[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.

MECP2 expression level tightly regulated in neurons

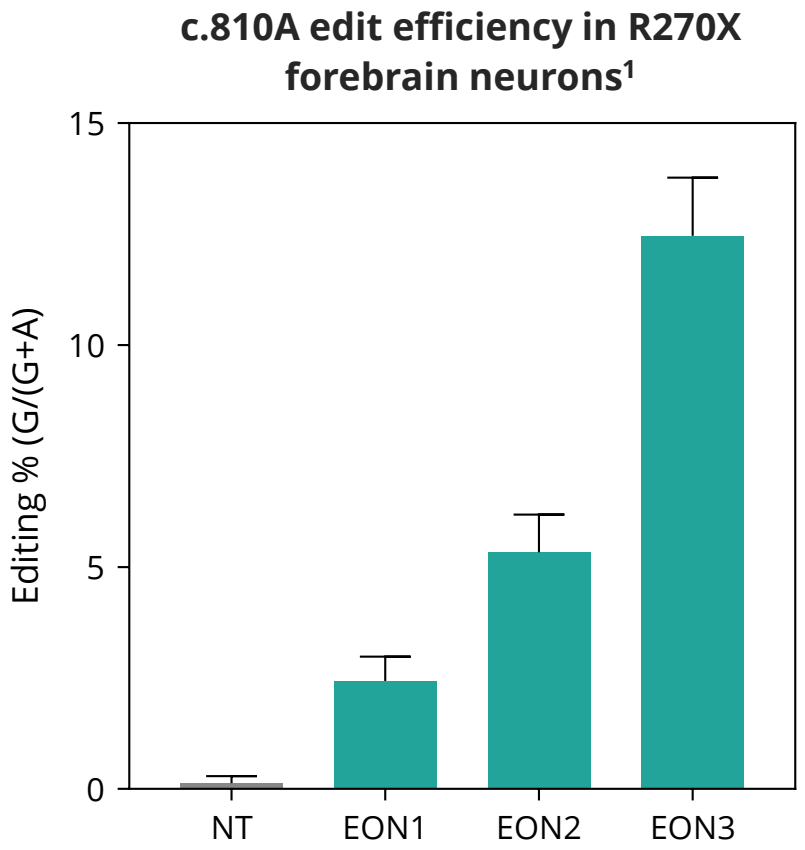
Axiomer is a well-suited approach to restore physiological levels of MECP2



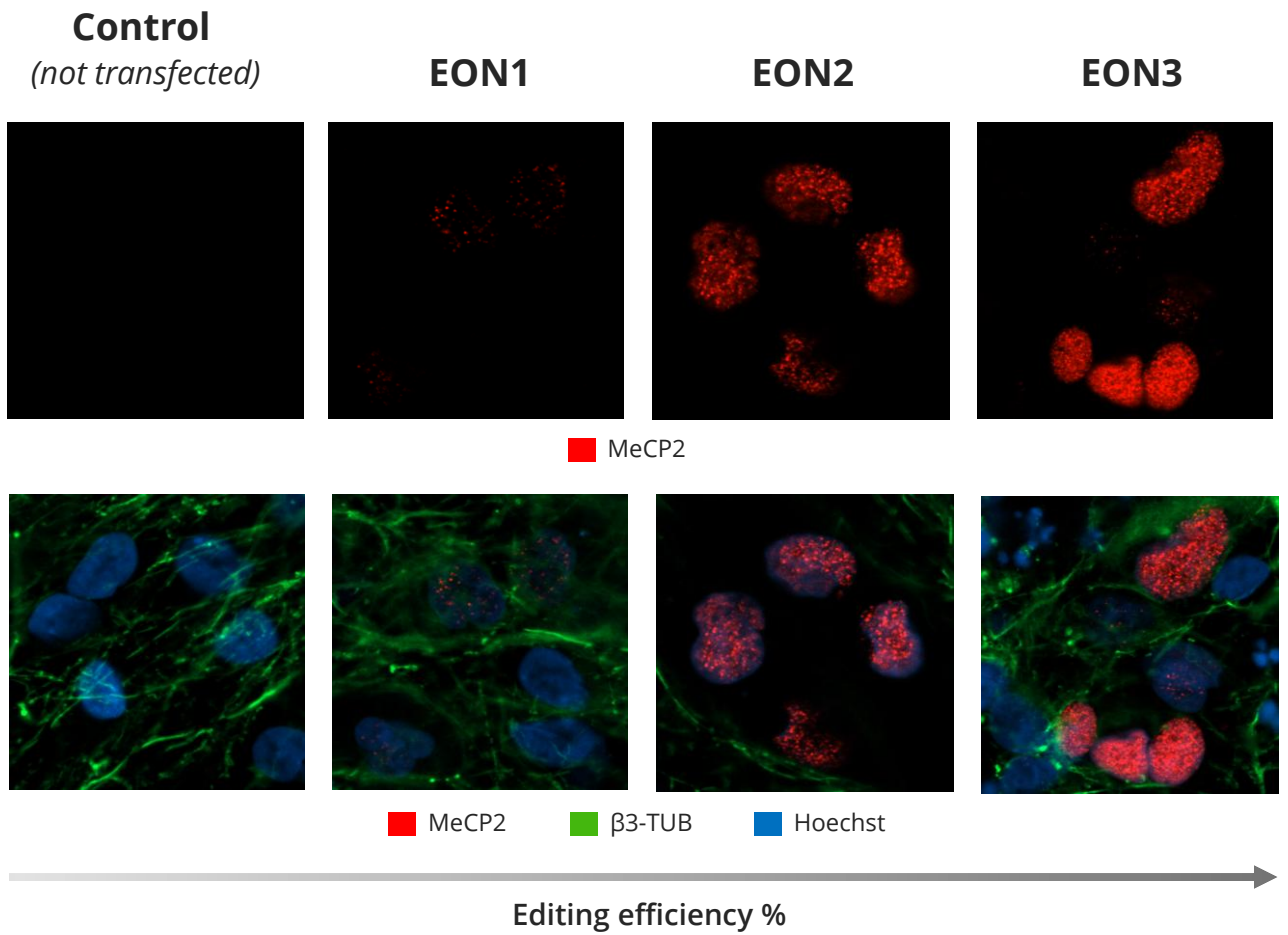
- Axiomer approach makes use of ADAR endogenous system to restore physiological levels of functional MECP2
- Axiomer avoid the risk of expressing unsafe levels of MECP2, potentially leading to MECP2 duplication syndrome

AX-2402 restores MeCP2 protein in Rett neurons

Higher RNA editing efficiency shows greater MeCP2 protein restoration in hiPSC-derived neurons of Rett Syndrome patients



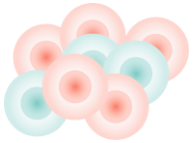
[1]*TF (RNAimax), 100nM, 11d, N=3, Avg +/-SD*



A severe Rett syndrome mouse model enables rapid assessment of disease modification

Model relevance

- Truncating MECP2 R270X loss-of-function mutation, representative of classic Rett syndrome
- Neonatal hemizygous male mice with early-onset, severe, and fully penetrant neurological phenotype
- Rapid and consistent disease progression, providing a robust system for proof-of-concept and dose-response evaluation

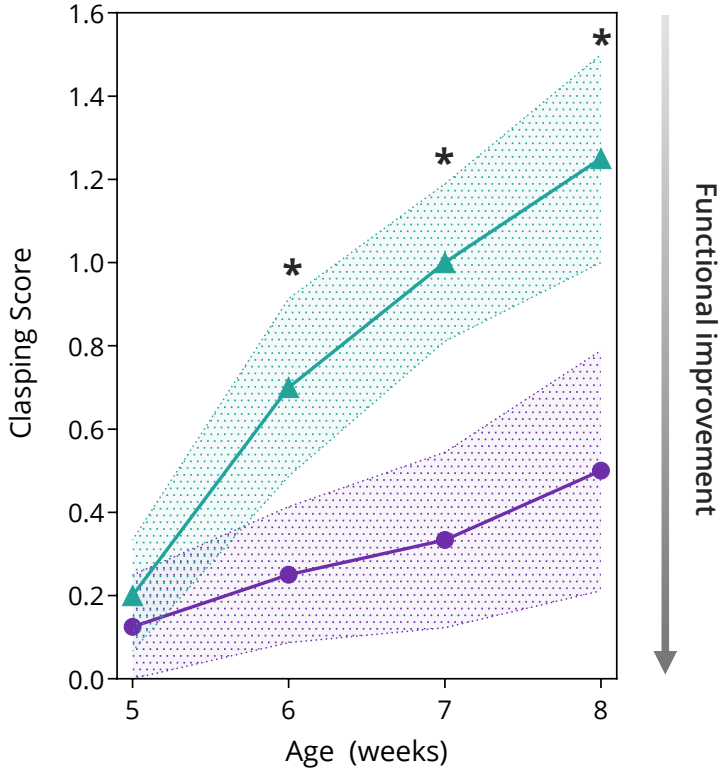
Mutant R270X strain			
Male/female	♂	♀	
Mutant gene			
Wild type gene	Not present		
Protein expression	 Truncated protein	 Truncated protein	 Wild type protein
Cells	 Severe mutant phenotype	 Moderate mutant phenotype	

Functional readout

- Primary functional readout: Bird score
- Composite measure of motor function, gait, hindlimb clasping, and breathing

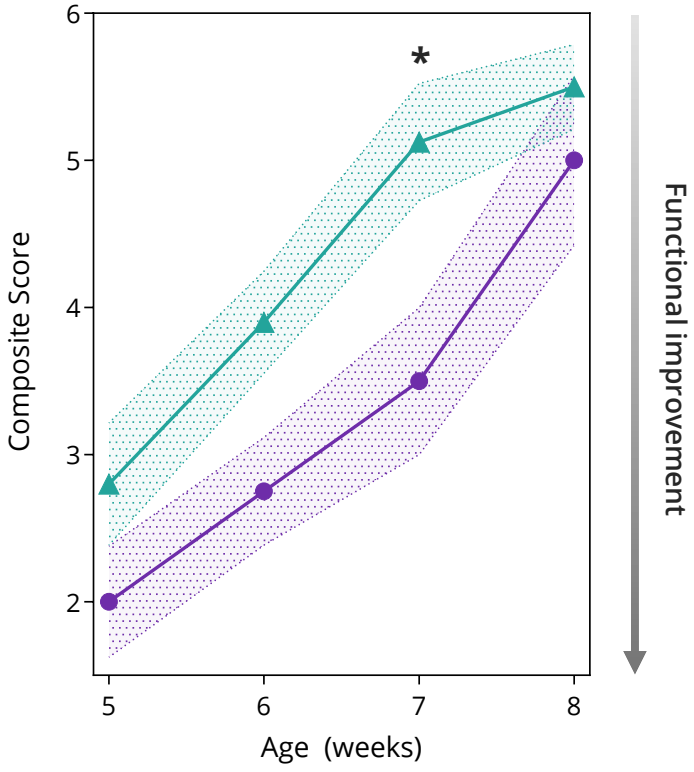
AX-2402 reverses disease in a severe Rett mouse model

Hindlimb clasping score
(Mean ± SEM)



AX-2402 improves motor deficits[2] sustained through 8 weeks post-dosing

Composite Bird score
(Mean ± SEM)



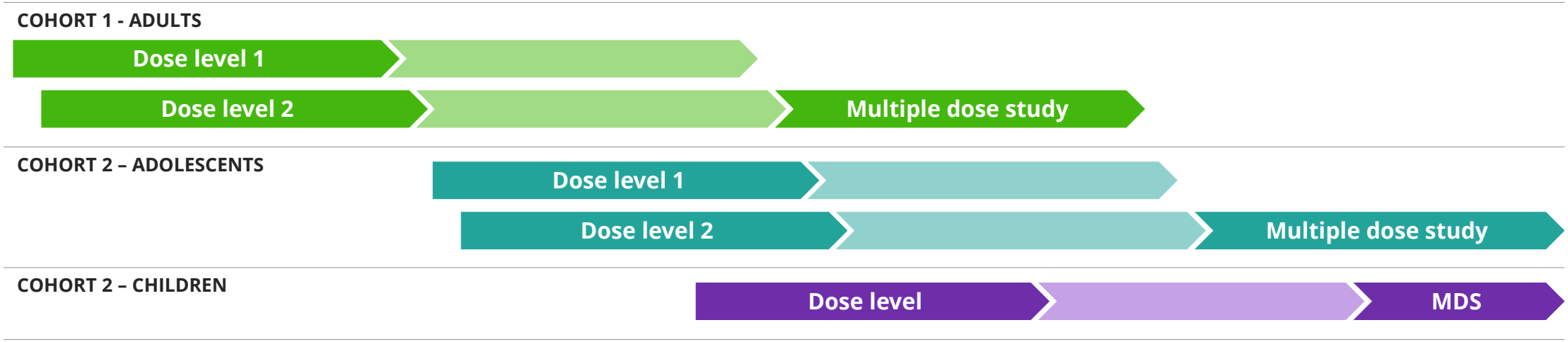
AX-2402 improves neurological disease severity[1] with effects sustained through 7 weeks post-dosing

Vehicle EON

[1]As measured by the Bird score, a composite neurological severity score in Rett models evaluating motor function, gait, clasping, breathing, and overall condition. [2]As measured by the hindlimb clasping score , a behavioral measure of neurological impairment in Rett mouse models, where reduced clasping reflects improved motor function. Graphs represent mixed-effects model (repeated measures) + Tukey's posthoc test (* p<0.05)

AX-2402 preliminary Phase 1/2 design

A First-in-Human, Phase 1/2 study to assess safety, tolerability, and pharmacokinetics of AX-2402 in female patients with Rett syndrome



- Primary objective: safety, tolerability
- Secondary: PK (CNS and circulation)
- Exploratory PD and clinical measures: Developmental milestones, EEG/EP, biosensor data, ECG, seizure frequency, RSBQ, CGI-I, Motor Behavior Assessment, CSF biomarkers of target engagement and neurobiological activity

- Financially supported by up to $9.2M funding provided by Rett Syndrome Research Trust
- Development candidate selection announced January 2026
- Advancing development activities for first-in-human trial to start in first half 2027

CNS=-central nervous system; EEG= electro-encephalogram; RSBQ= Rett Syndrome Behavioral Questionnaire; CGI-I= Clinical Global Impression of Improvement

Axiomer™ RNA editing science translating towards therapeutic application

DRIVING INNOVATION IN ADAR RNA EDITING FIELD

- Advancing predictive models to accelerate ADAR-mediated EON development
- Pioneering the optimization of EONs for best-in-class liver and CNS therapies

AXIOMER™ RNA EDITING TRANSLATING TOWARD CNS THERAPIES

- EON penetration and efficient editing into the CNS via the editing map in NHP *in vivo*
- Science translating towards clinical application in Rett syndrome

FIRST-IN-HUMAN TRIAL OF AX-0810 (NTCP) UNDERWAY IN HEALTHY VOLUNTEERS

- Evaluating safety, tolerability, PK and biomarker-based target engagement
- No safety signals after 4 wks; pharmacokinetics consistent with non-clinical data
- Target engagement data expected H1 2026

INITIATING PATIENT COHORT PLANNING

- Activities are underway to include a patient cohort following the healthy volunteer cohorts

Recent highlights in pipeline

Thank you!

Eli Lilly

Genetic Medicine Department

Monica Coenraads

and the team at RSRT

Prof. Peter Beal

and his group at UCD Davis

ProQR®

IT'S IN OUR RNA