# ADVANCING ADAR RNA EDITING TECHNOLOGY

*for Broad Applicability in Precision Medicines*

Gerard Platenburg, Co-founder and CSO at ProQR

TIDES USA - May 13, 2026, 9:00–9:30 AM ET

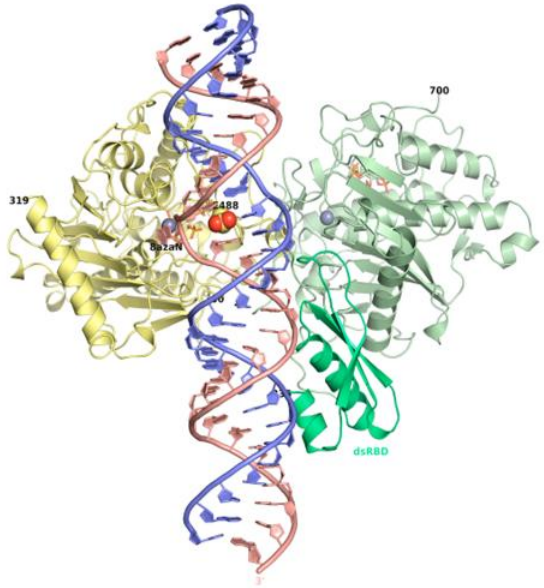
# Disclosures

- I am an employee of ProQR Therapeutics

# Axiomer™ EONs unlock cellular machinery potential to treat diseases

*By attracting ADARs and allowing highly specific editing*

## **ADAR** *(Adenosine Deaminase Acting on RNA)*

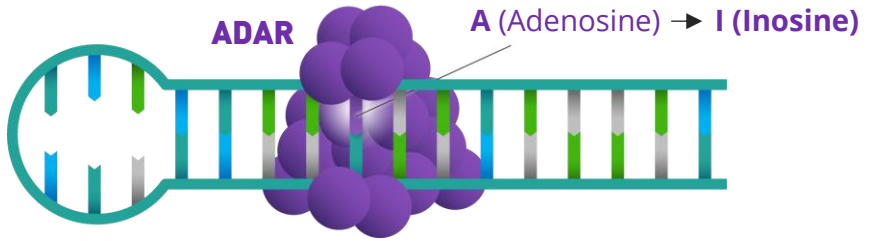



Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

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

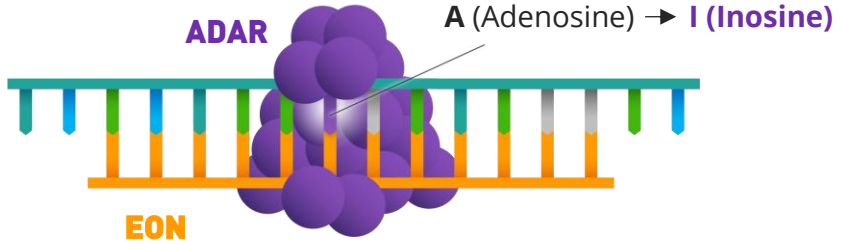
**Natural** ADAR editing *(A-to-I)*

RNA
*Double stranded*



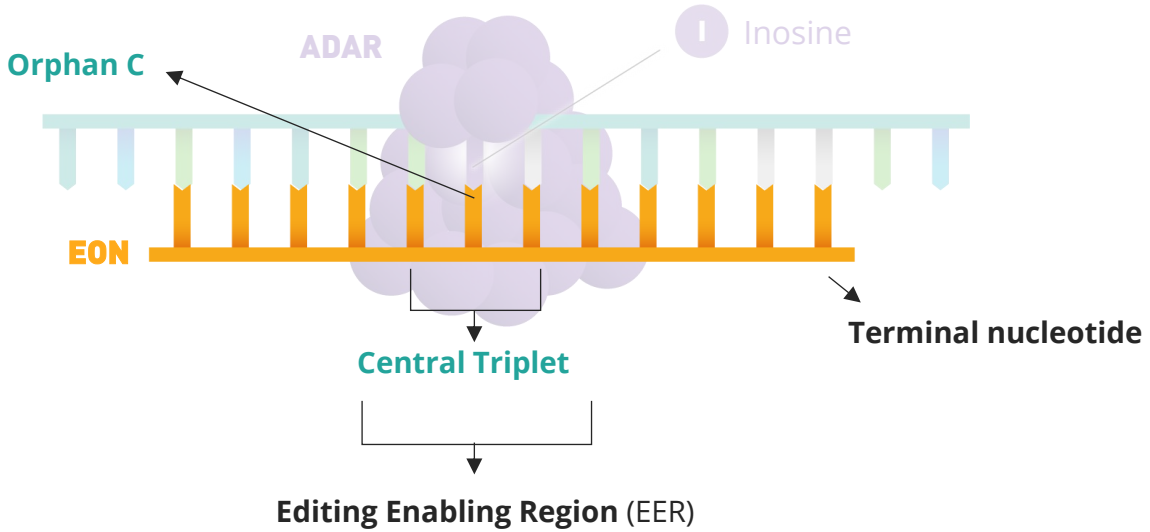

**Editing Oligonucleotide (EON)-directed** therapeutic editing *(A-to-I)*

RNA+EON
*Double stranded*



# Driving the evolution of therapeutic EONs

**Locations of importance**



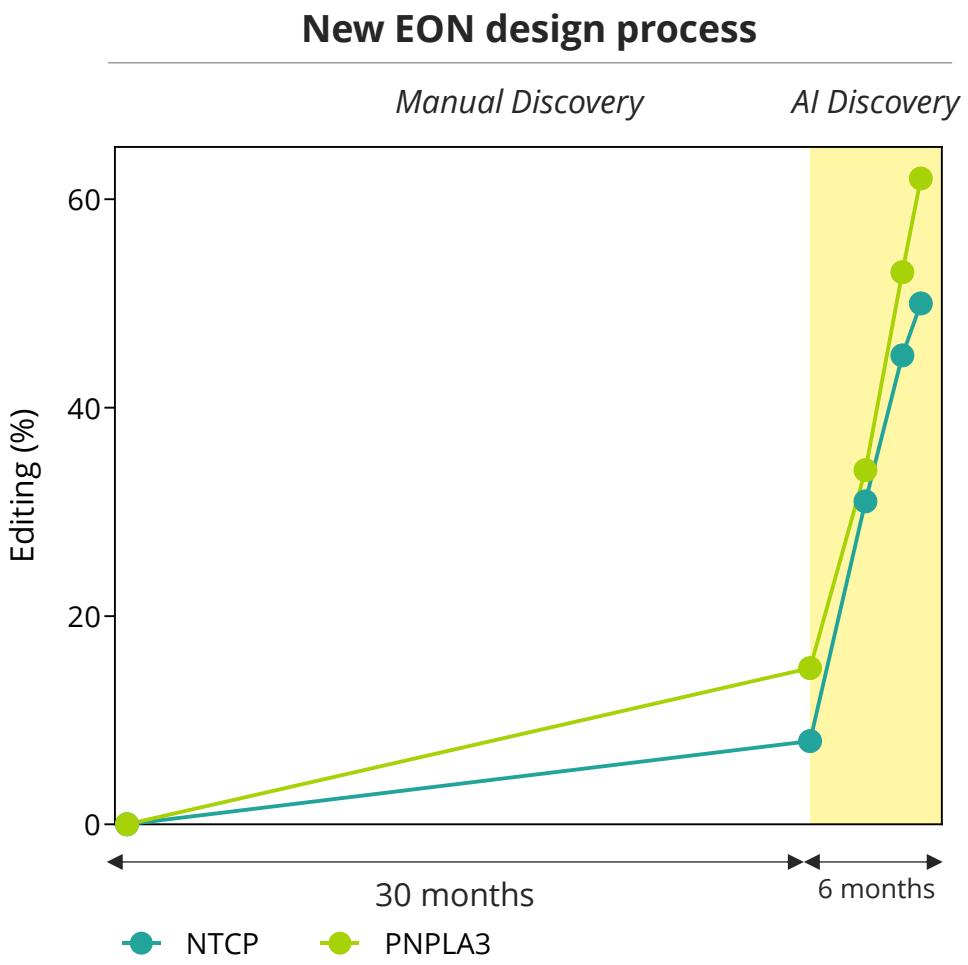

**Optimized sequence and chemistry define functionality**: EONs are not unlike other ASO types

- 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

# AI-guided EON design accelerates discovery

*~90% faster discovery and up to 6× improvement in EON performance*




*Trained on 12+ years of*

**PROPRIETARY AXIOMER DATA**

*Trained on experimentally-validated editing outcomes of numerous EONS and targets*

*AI enables discovery of*

**BETTER-PERFORMING EONs**

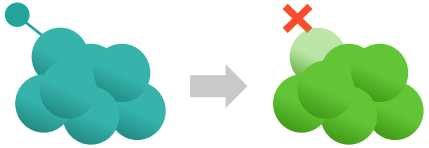
*Models trained on our in-house data generate EONs with higher editing efficiency and greater sequence diversity*

*Robotics-enabled HTS*

**ACCELERATES DESIGN-TEST CYCLES**

*Enabling rapid iteration per target and amplifying AI-driven learning through continuous model improvement*

# Creating a new class of medicines with broad therapeutic potential

| Correction | Protein modulation | | |
|---|---|---|---|
|  |  |  |  |
| **Mutations correction**<br>Thousands of G-to-A mutations, many of them described in literature | **Alter protein function or include protective variants**<br>Modified proteins achieving loss- or gain-of-functions that help addressing or preventing diseases | **Disrupt >400 different types of PTMs**<br>Regulate protein activity, change localization, folding, preventing immune escape or slowing down degradation | **Change protein interactions**<br>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 |

# 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 patients |
| **AX-0811** *for Cholestatic diseases* | NTCP | *Modulate* | | | | Target engagement data in 2026 | |
| **AX-0422** *for Hurler Syndrome* | IDUA | *Correct* | | | | CTA filing early 2027; Clinical biomarkers in H1 2027 | ~500-1000 patients |
| **AX-2911** *for MASH* | PNPLA3 | *Correct* | | | | FIH H1 2027 | ~8M patients |
| **AX-2402** *for Rett syndrome* | MECP2 R270X | *Correct* | | | | | RETT SYNDROME RESEARCH TRUST ~5K |
| **PARTNERED PIPELINE** | | | | | | | |
| 10 undisclosed targets (option to expand to 15) | | | *Progress undisclosed* | | | | Lilly |

# AX-0810 RNA editing therapy

*to address Cholestatic Disease*

## CHOLESTATIC DISEASE

- Biliary Atresia affects pediatrics early in life (~20,000 patients WW)
- Primary Sclerosing Cholangitis affects adults (~80,000 US+EU)
- No approved therapies and may require liver transplantation[1,2]

## BILE ACID TOXICITY

- Bile acid accumulation drives liver injury, leading to fibrosis and liver failure

## NTCP MODULATION

- Human genetics supports NTCP modulation as hepato-protective mechanism to reduce bile acid reuptake and protect liver


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

# NTCP modulation approach broadly validated

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

## HUMAN GENETICS

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

## *IN VITRO*

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

## *IN VIVO*

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

## IN CLINIC

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

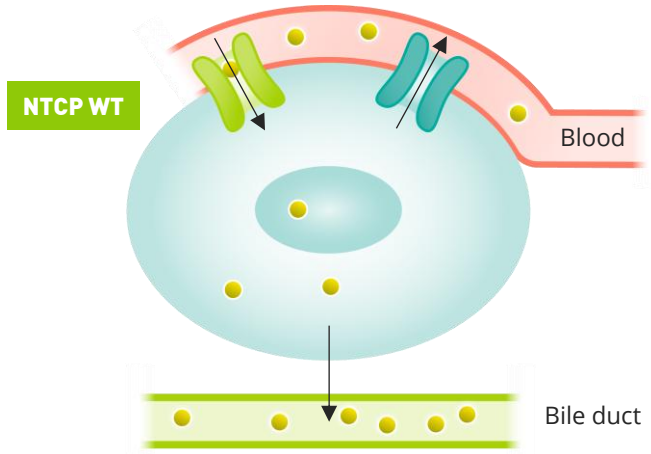

Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. NTCP channel is a known transporter for bile acids and hepatitis virus from bloodstream to the liver.

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

# AX-0810 reduces bile acid accumulation in hepatocytes by modulating NTCP activity

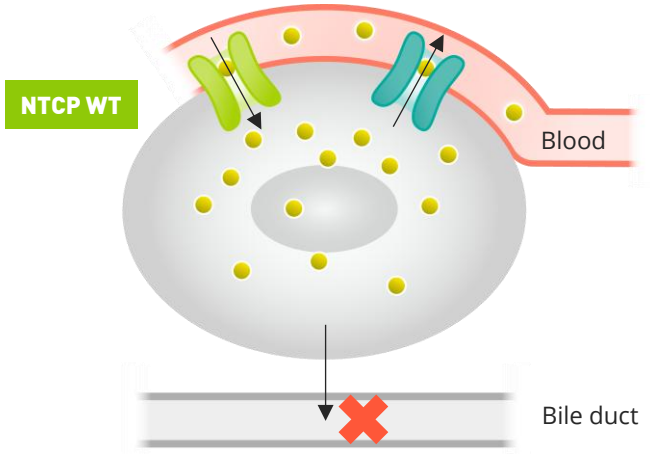
## HEALTHY LIVER

*Normal bile acids homeostasis in hepatocytes*



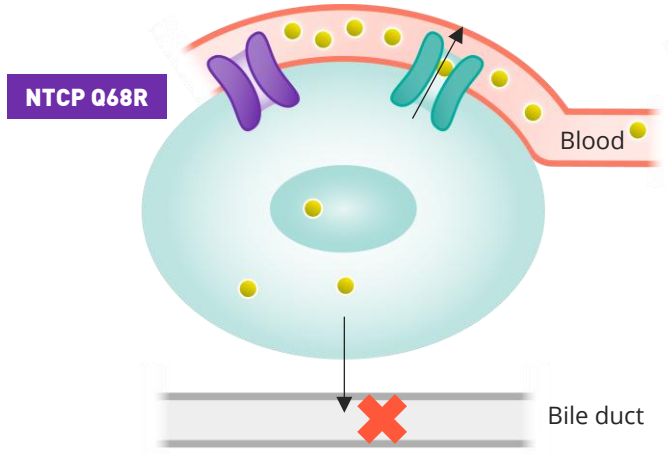

## LIVER WITH CHOLESTATIC DISEASE

*High concentration of bile acids in hepatocytes*




## AX-0810 STRATEGY FOR DISEASED LIVER

*AX-0810 restore bile acids homeostasis in the hepatocytes*

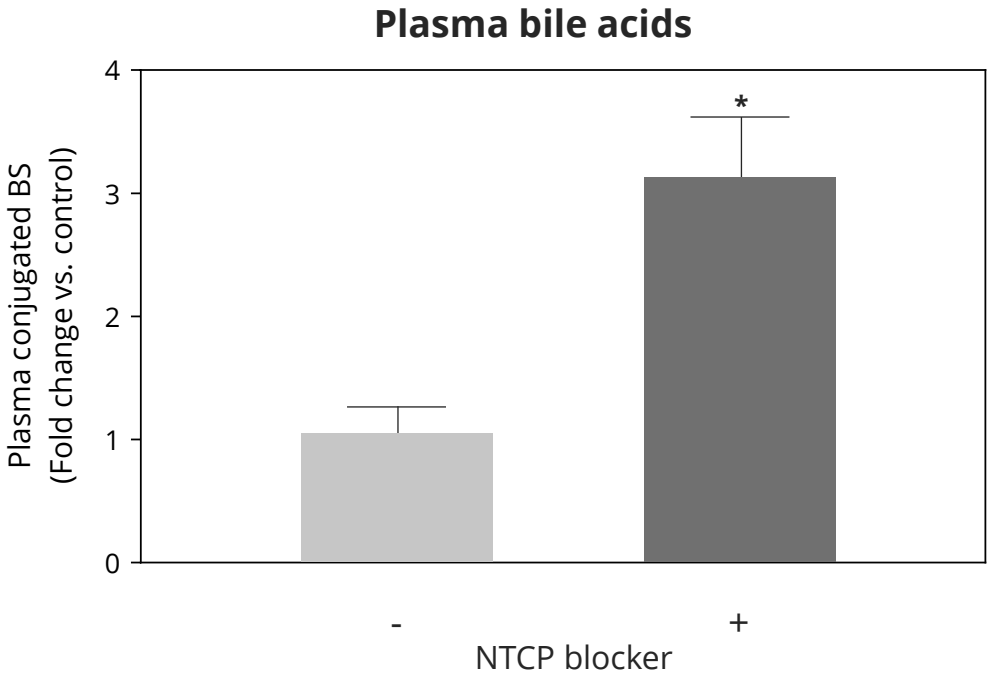


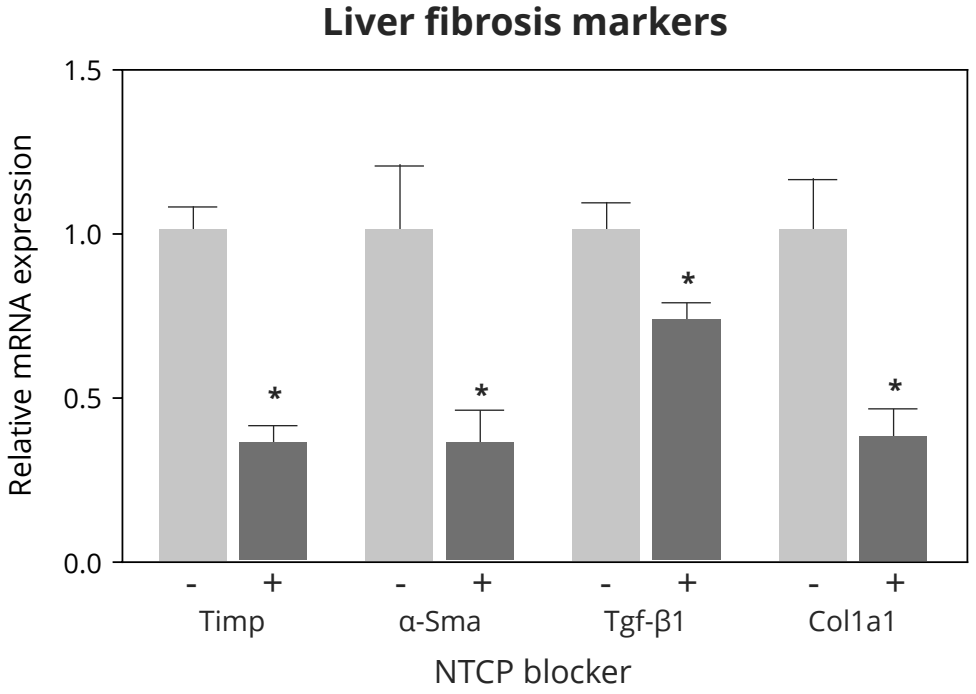

↓ *hepatocyte toxicity*

↓ *inflammation/ fibrosis*

Halilbasic E, et al. J Hepatol. 2013 Jan;58(1):155-68; Nyholm I, et al. J Hepatol. 2025 Aug;83(2):440-452.

# NTCP modulation reduces fibrosis markers and elevates circulating bile acids




NTCP channel blocking **increases plasma bile acids concentrations,** up to 3-fold in cholestatic disease mouse model

**Pro-fibrotic markers show reduced expression** after NTCP channel blocking

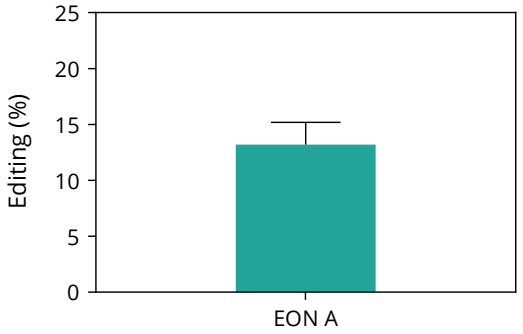
*Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069.*

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

## EDITING EFFICIENCY

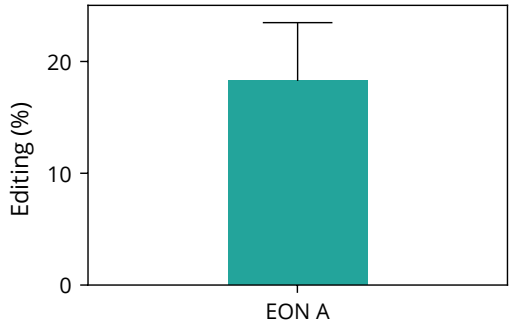
### NTCP RNA Editing in Humanized Mice

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




### NTCP RNA Editing in NHP

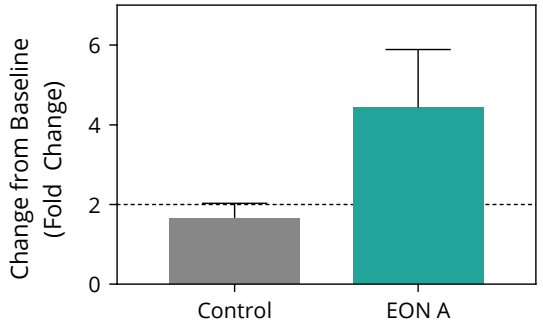
*(N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D46, ddPCR)*




## PLASMA TOTAL BILE ACIDS

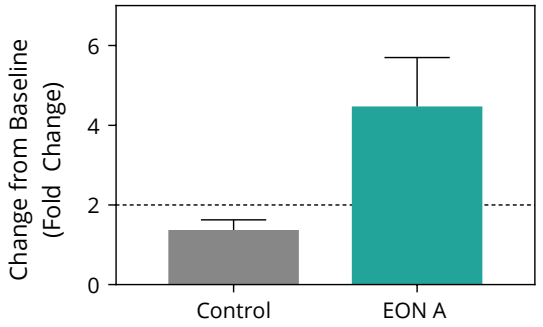
### Plasma TBA in Humanized Mice

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




### Plasma TBA in NHP

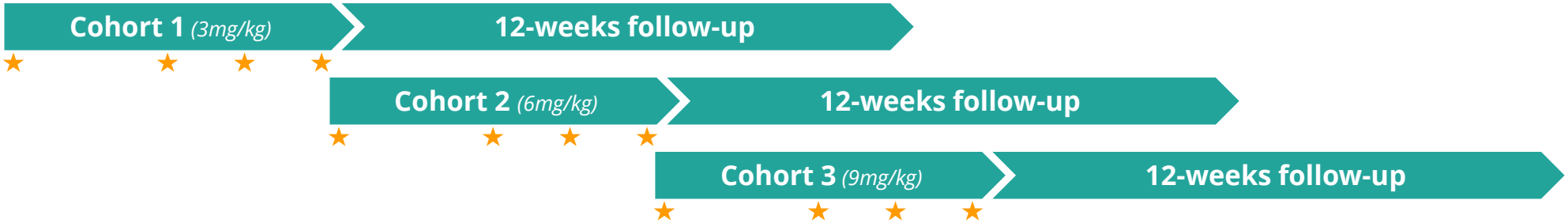
*(N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D39)*




- 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

# Assessing Safety, PK and Target Engagement of AX-0810 in First-in-Human Trial

**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 demonstrate no safety signals and pharmacokinetics consistent with non-clinical models
- Target engagement data on track for H1 2026

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

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

## MASH

- Highly prevalent and increasing worldwide
- Progression to cirrhosis, liver cancer and liver-related mortality
- Limited treatment options[1] highlight the significant unmet medical need, particularly in lean MASH patients

## PNPLA3 I148M

*Patatin-like phospholipase domain-containing[3] variant*

- Strongest genetic risk factor for disease progression
- ~50% of MASH patients[2-4]
- Associated with higher liver fat, NASH risk, and fibrosis progression
- Carriers may show reduced response to GLP-1 agonists[5]

## RESTORING WT-LIKE PNPLA3

- AX-2911 restores PNPLA3 I148M (Met→Val) function
- Targets MASH primary genetic driver, unlike metabolic therapies
- Broad potential, including GLP-1-low response and lean MASH patients


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

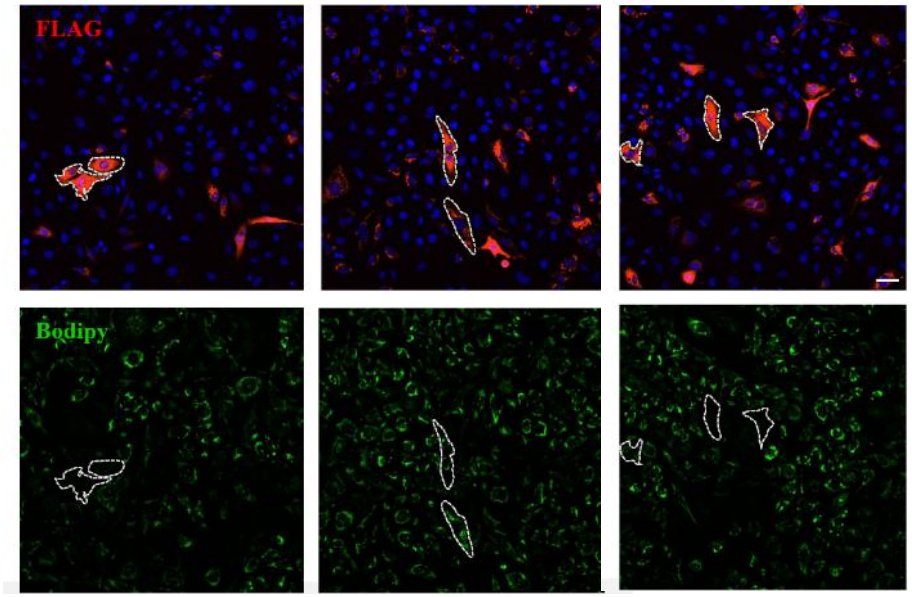
# AX-2911 to restore WT-like PNPLA3 function

*148I and 148V show comparable lipid droplet sizes*

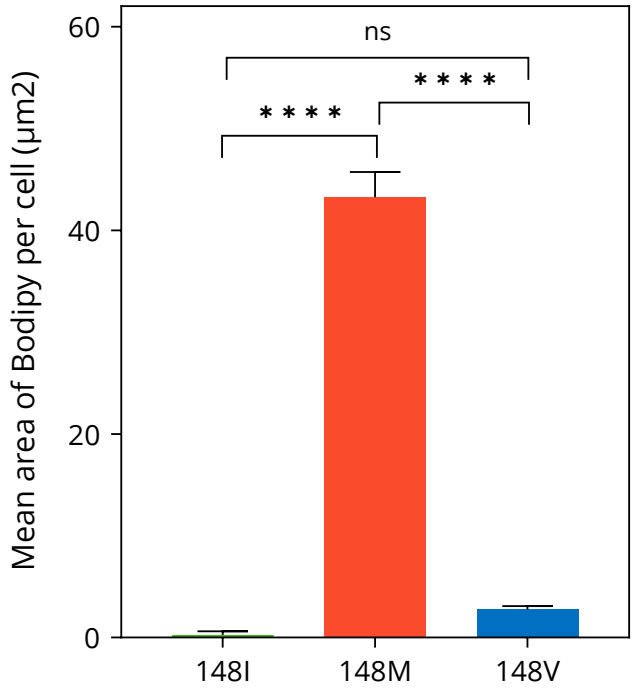
**PNPLA3 148I**
**(WT)**
*Isoleucine (ATC)*

**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 wildtype-like droplet sizes, suggesting a similar effect on lipid accumulation to 148I.

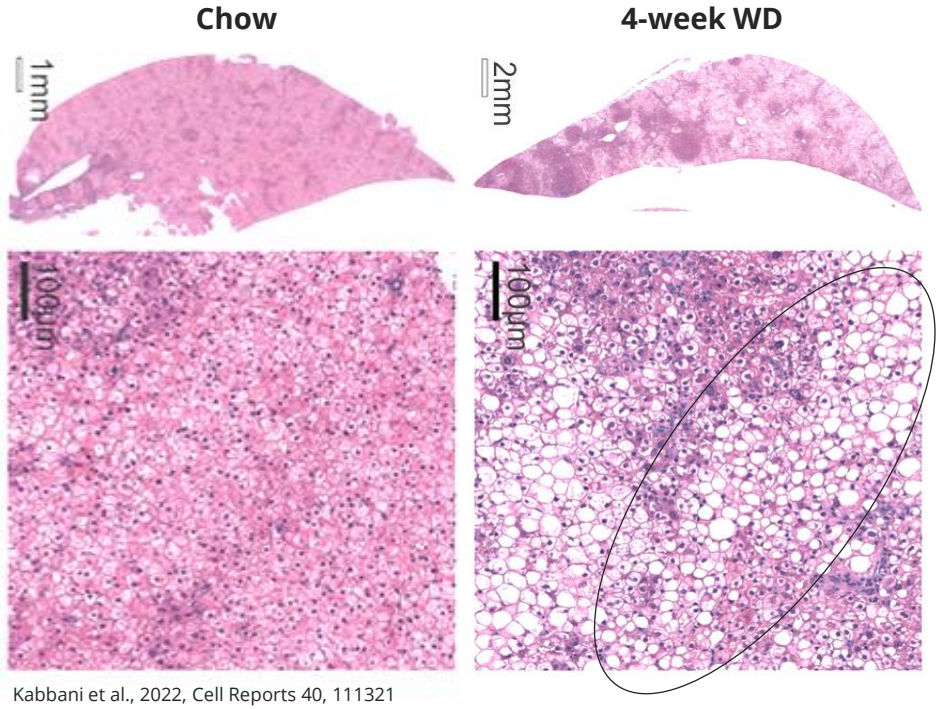
Treatment conditions: HeLa cells, plasmid, transfection, 250uM linoleic acids, 24h, cell lipase activity by IF One-way ANOVA, ****, P<0.0001; Mean, SEM.

# 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**

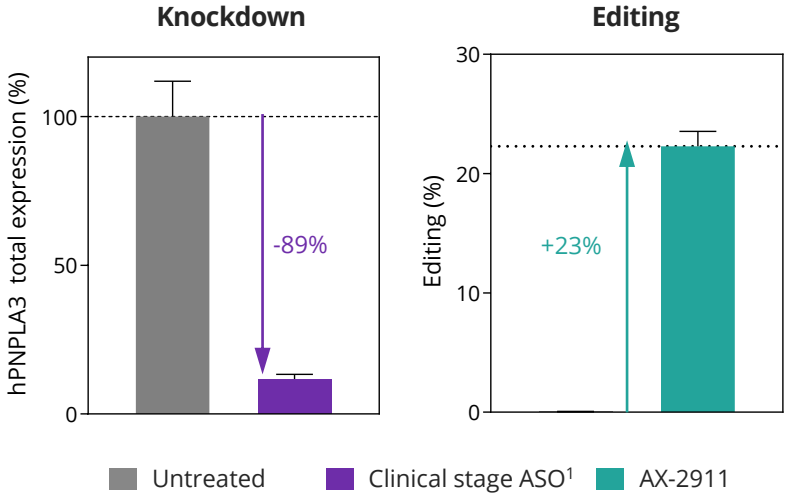
- Engrafted with PNPLA3 I148M primary human hepatocytes
- Recapitulates the human lipid-handling defect
- Translational relevance
- Industry-standard Western Diet
- Rapid, robust steatosis (4 weeks)

# Editing has functional advantage over knockdown

*AX-2911 substantially reduces liver fat vs clinical-stage ASO[2]*

## mRNA

***hPNPLA3* I148M in livers of humanized FRG mice under WD[1]** *dPCR (Qiagen), AVG±SEM*



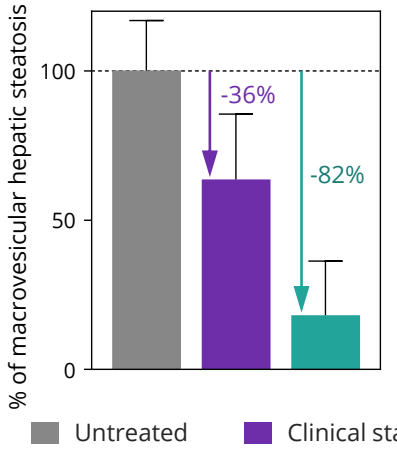

Clinical-stage ASO[2]: **~89%** mRNA reduction via knockdown of *hPNPLA3*

AX-2911 leads to **23%** editing of *hPNPLA3* mRNA

## LIVER FUNCTION *(steatosis)*

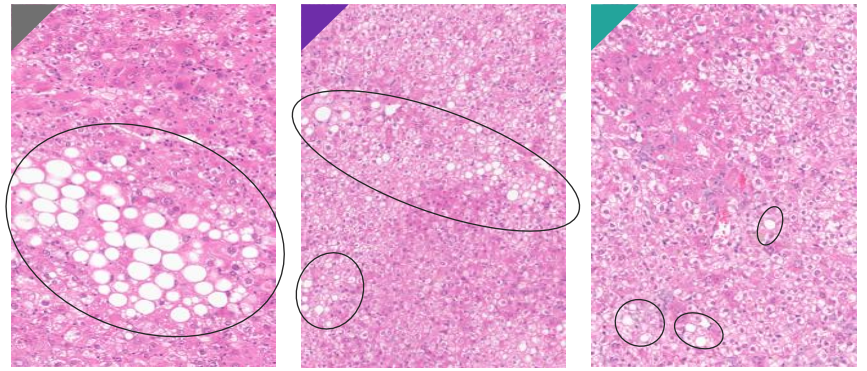
**Macrovesicular steatotic incidence scoring[1] (%)**

*AVG±SEM*




**Liver sections of steatosis mouse model treated with ASO[2] or AX-2911[1]**

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



**82%** reduction of macrovesicular lipid droplets

Untreated

Clinical-stage ASO[2]

AX-2911

[1]N=4-6, 20mg/kg, 14 doses, GalNAc conjugated-AX-2911 or 0.7mg/kg, 14 doses, AZ AZD2693 treatment, SC, readout at day D28; [2]AZ AZD2693 previously evaluated in Phase 2b

# Generating early clinical data to derisk AX-2911 development

## EXPLORING AN INVESTIGATOR-INITIATED TRIAL (IIT)

*Generate early proof-of-concept in patients by H1 2027*

*De-risk the program and inform future clinical development*

## PARALLEL PREPARATION FOR GLOBAL CTA / IND DEVELOPMENT

# AX-0422 RNA editing therapy

*to address Hurler Syndrome*

## HURLER SYNDROME

- Early onset, multi-symptom disease
- Progressive deterioration, high morbidity
- Current therapies do not address all comorbidities and have limitations

## IDUA DEFICIENCY

- W402X variant (**c. 1293G>A; p.W402X**) is present in up to 60% of patients with severe phenotype[1]
- Causes IDUA deficiency, leading to toxic accumulation of GAGs

## CLINICAL DE-RISKING

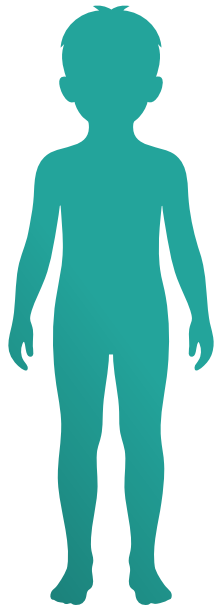
- AX-0422 corrects the W402X mutation back to WT
- Restores endogenous enzyme production, leading to GAGs clearance
- Potential to impact systemic and CNS disease


GAGs: glycosaminogylcans; MPS1: Mucopolysaccharidosis type I. 1Baldo G, et al, 2018, https://doi.org/10.1111/cge.13224

# Hurler is the most severe form of MPS I spectrum with multi-organ involvement

## SYSTEMIC

- Respiratory involvement
- Cardiac involvement
- Hepato-splenomegaly (liver & spleen)
- Skeletal/Joint disease



**Subcutaneous (SC) delivery: Liver**

- Drives systemic IDUA expression
- Targets peripheral organs pathology

## NEUROLOGICAL

- Progressive CNS impairment

**Intrathecal (IT) delivery: CNS**

- Direct CNS exposure
- Targets neurological manifestations

*AX-0422 is positioned to address systemic and neurological symptoms*

# Increases in IDUA enzymatic activity drive meaningful clinical impact

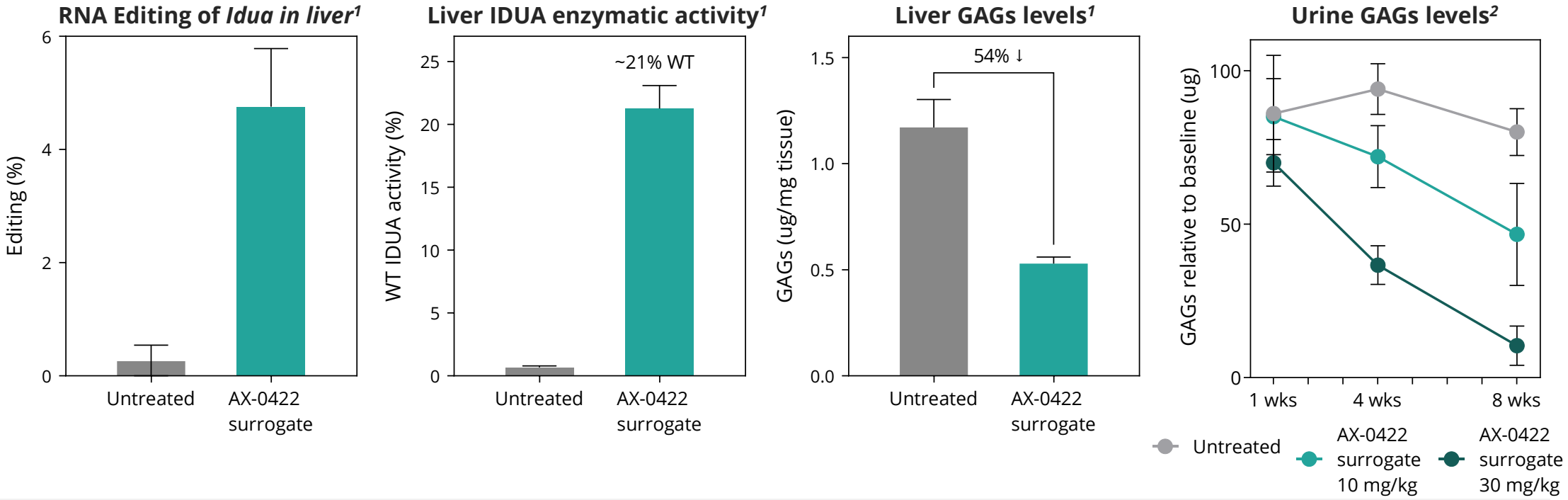
Severity →

| | Scheie | Hurler-Scheie | Hurler |
|---|---|---|---|
| Diagnosis | Teens | Childhood | < 18 months |
| Life expectancy | Normal | 20 yo | 10 yo |
| Enzymatic activity in fibroblasts (% of WT)[1] | ***0.8%*** | ***0.3%*** | ***0.2%*** |

A restoration of 1-15% of normal IDUA enzymatic function[2] can improve phenotype

[1]Oussoren E, et al. Mol Genet Metab. 2013 Aug;109(4):377-81; [2]Kakkis ED, et al. N Engl J Med. 2001 Jan 18;344(3):182-8.

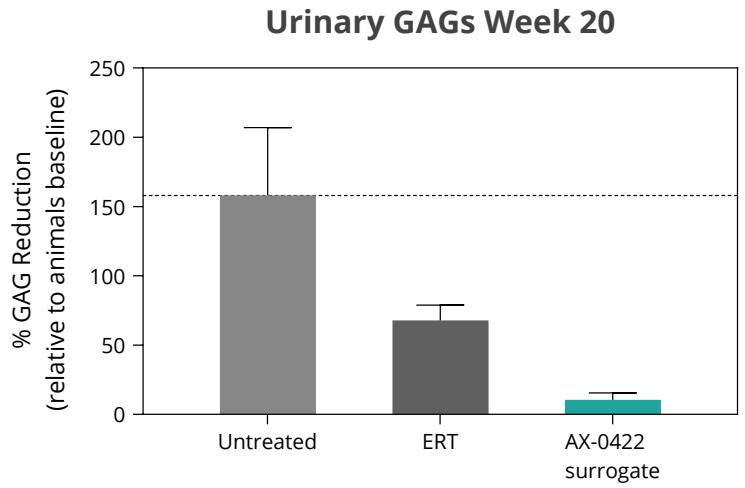
# RNA editing achieves therapeutically meaningful enzyme restoration in *Idua* mouse model

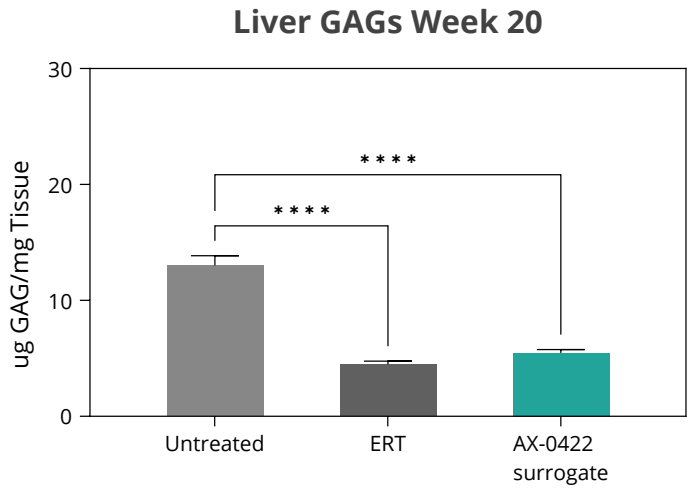


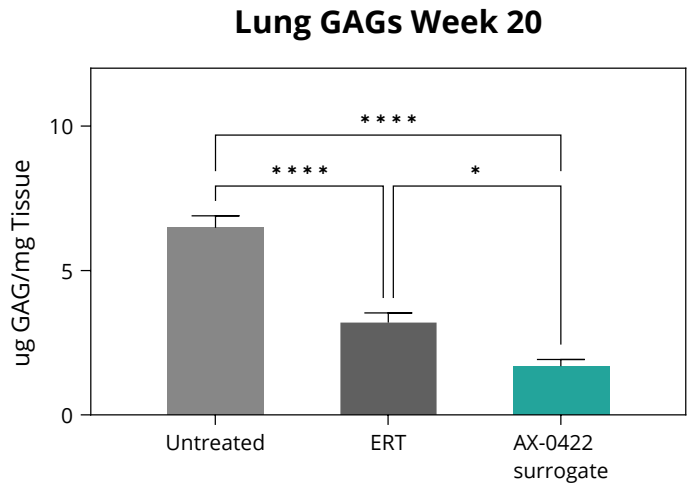

Following SC delivery, targeted editing of the nonsense mutation restores ~21% IDUA activity, driving substantial liver GAG reduction and dose-dependent normalization of urinary GAGs - **supporting potential for disease-modifying benefit**

*[1]AX-0422 surrogate treatment of Idua-W392X mice, SC, 30 mg/kg, Q1W until 8 wks, data at 8 weeks, n=6, mean, SEM; [2]AX-0422 surrogate treatment of Idua-W392X mice, SC, 10 and 30 mg/kg, Q1W until 4 wks, n=4-6, mean, SEM*

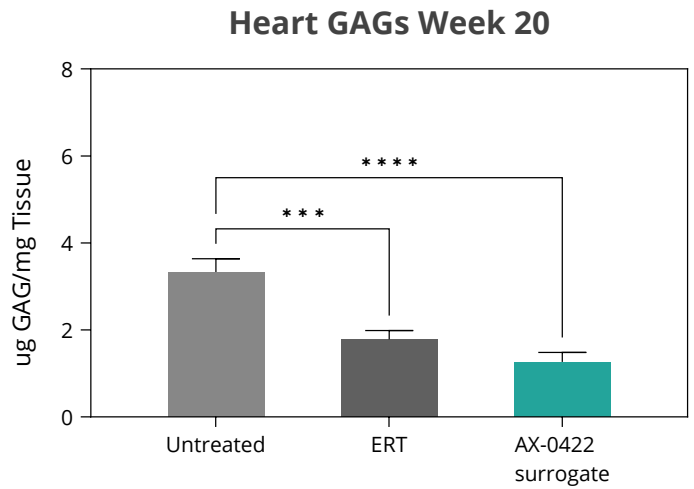
# AX-0422 surrogate leads to systemic reduction in GAGs versus SoC

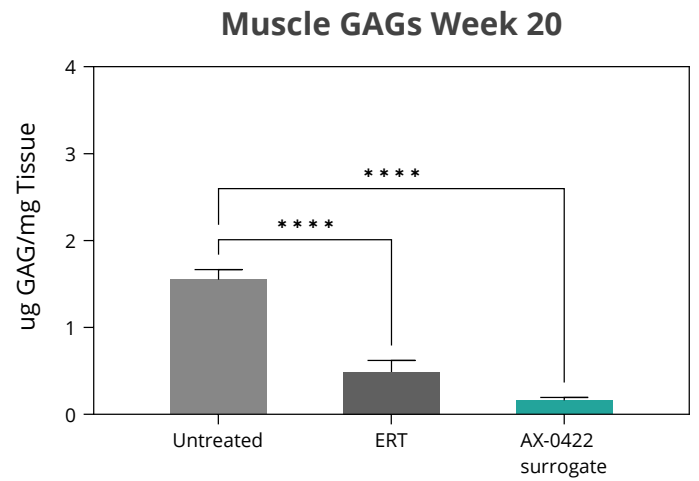



- 20-weeks after initiation of treatment, AX-0422 surrogate leads to reduced GAGs in urine and in organs of interest
- Equivalent or improved systemic reduction in GAGs vs. ERT



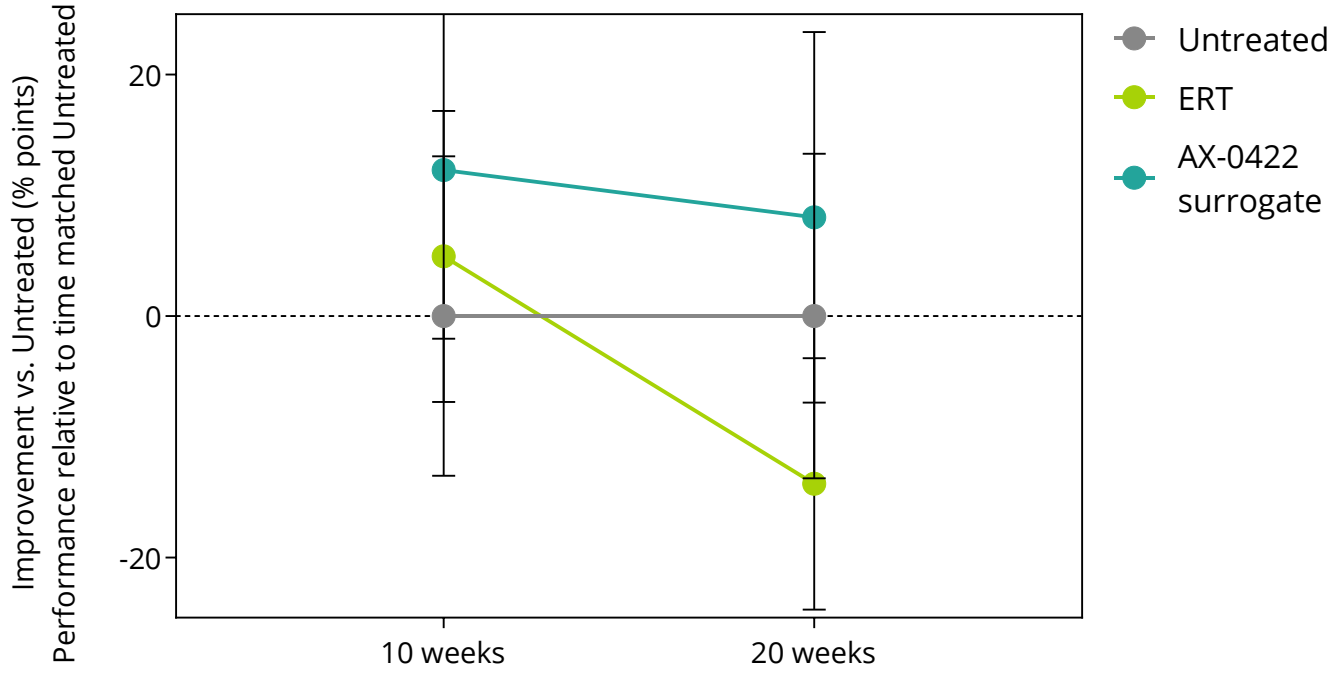




*ERT: Enzyme replacement therapy; GAGs: Glycosaminoglycans; SoC: Standard of care. Treatment conditions; Idua-W392X mice, AX-0422 surrogate treatment: SC, 30 mg/kg, ERT (Laronidase) treatment: IV, 0.58 mg/kg, Q1W until 4 wks, n=6, mean, SEM. One-way ANOVA; * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001.*

# AX-0422 surrogate shows functional stabilization vs ERT in Idua mouse model

**Hang Test at 10 and 20 weeks**

*Idua-W392X mice, AX-0422 surrogate treatment: SC, 30 mg/kg, ERT (Laronidase) treatment: IV, 0.58 mg/kg, Q1W until 4 wks, n=6, mean, SEM*

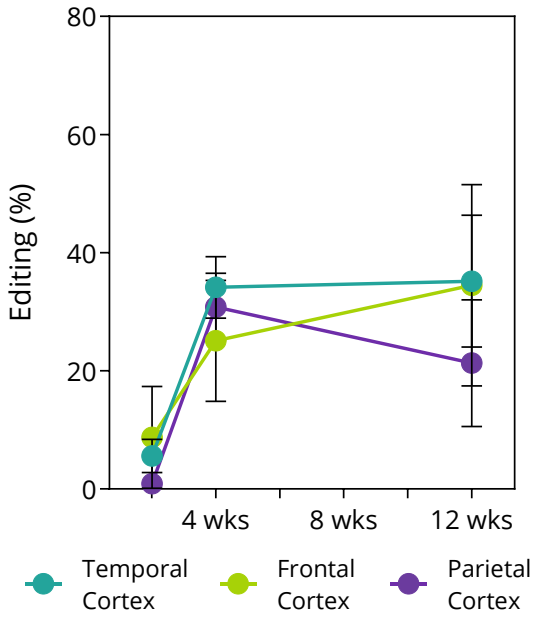



- Durable functional stabilization observed with EON through 20 weeks
- Transient stabilization with ERT followed by decline
- ERT data consistent with clinical data showing deterioration in 6-MWT in patients who develop inhibitory ADAs[1]

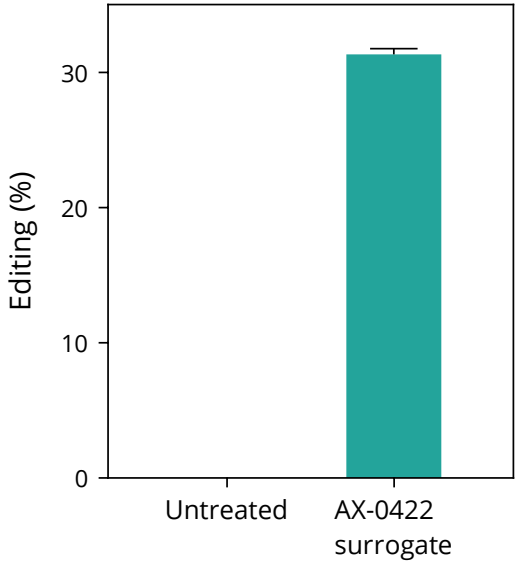
[1]Polgreen et .al. (2020) Clinical Trial of Laronidase in Hurler Syndrome after Hematopoietic Cell Transplantation. Pediatric Research.

# AX-0422 achieves robust, durable CNS editing with functional enzyme restoration

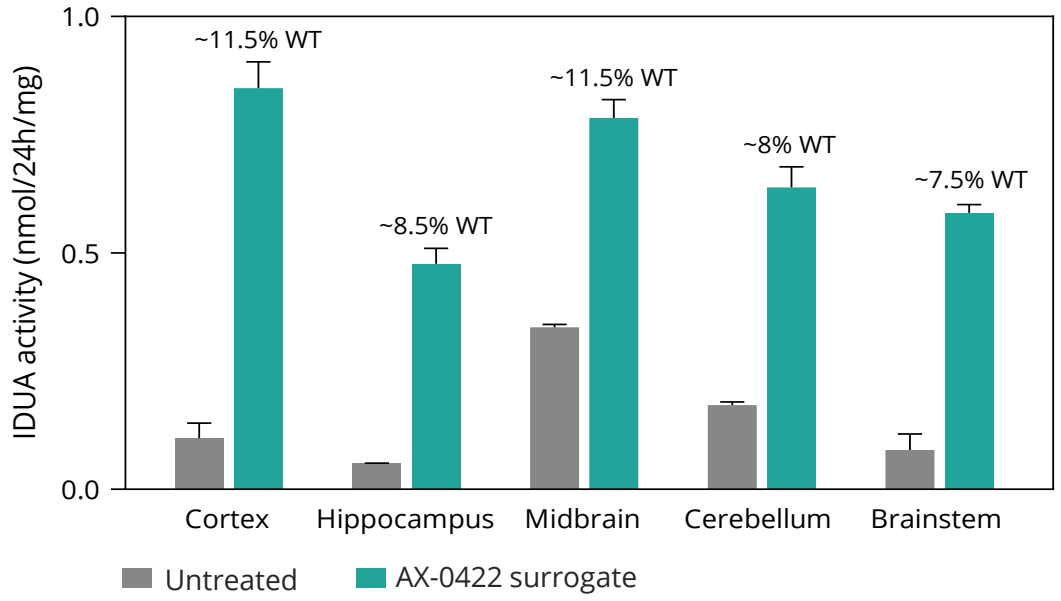
**Durable RNA editing of ACTB in cortex of NHP[2]**




**RNA Editing of *Idua* in cortex of Idua-W392X mice[1]**




**IDUA enzymatic activity in the brain of *Idua*-W392X mice[1] (% WT recovery)**



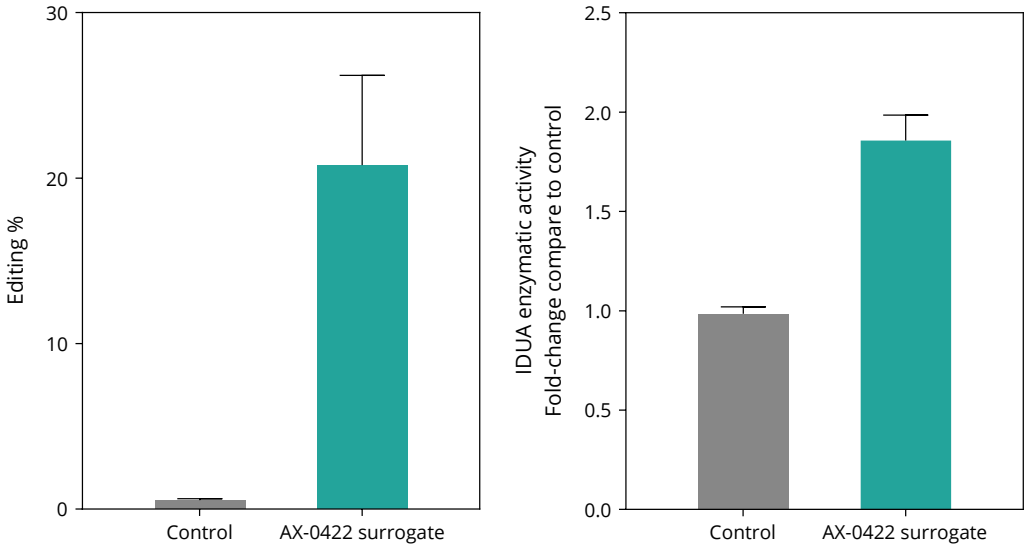

- Axiomer results in durable CNS editing of up to 12 weeks (single dose, NHP)
- Following ICV delivery, efficient editing in Hurler disease model leads to broad enzyme restoration across brain regions (~7–12% of WT)
- Levels consistent with disease-modifying potential in Hurler syndrome

*[1]AX-0422 surrogate treatment of Idua-W392X mice ICV, 250µg, single dose, n=6, 4 weeks, ddPCR, mean, SEM / western blot, mean, SEM; [2]IT administration, 10.6mg AX-0422 surrogate treatment, single dose, n=3, up to 12 weeks, ddPCR, mean, SD*

# AX-0422 surrogate leads to robust restoration of IDUA enzymatic activity

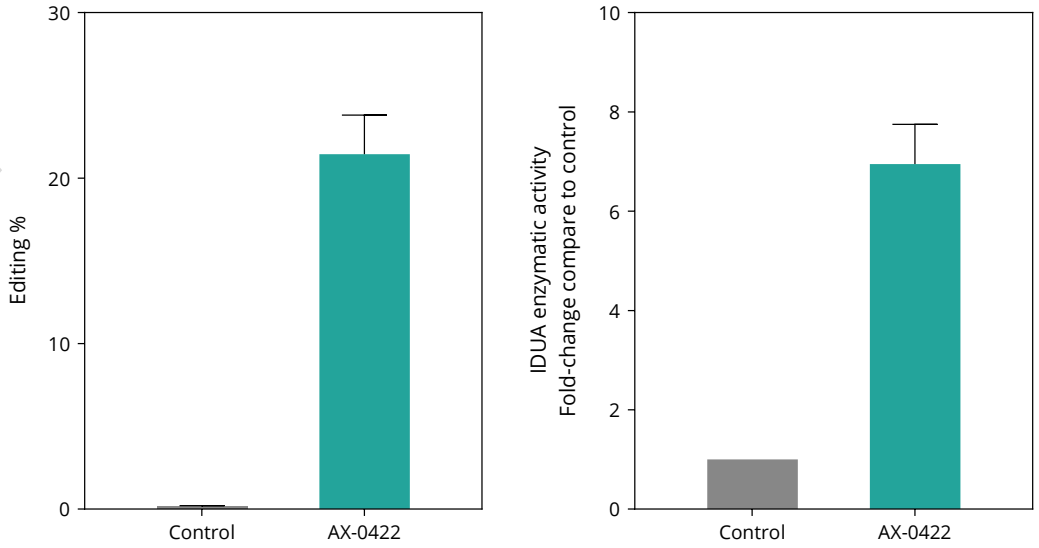
### Mouse Idua W392X Mouse Embryonic Fibroblasts

*AX-0422 surrogate, transfection, 100nM, n=2-3, 48h, ddPCR, mean, SEM / IDUA enzymatic activity assay, mean, SEM*




### Human IDUA W402X patient fibroblasts

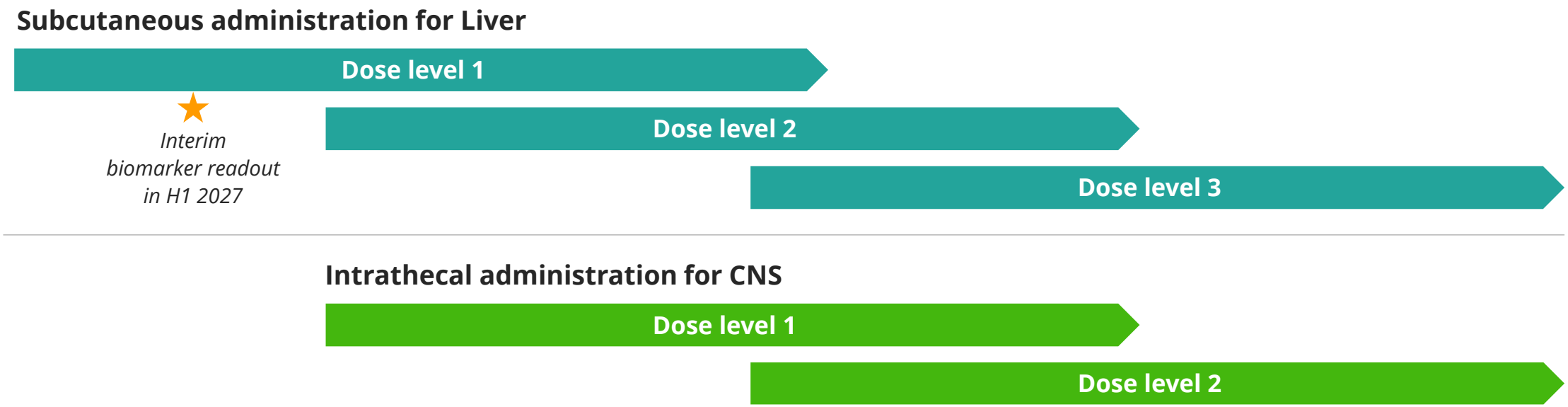
*AX-0422, transfection, 100nM, n=6, 48h, ddPCR, mean, SEM / n=2, IDUA enzymatic activity assay, mean, SEM*




Successful translation from AX-0422 mouse surrogate to AX-0422 human lead with robust editing efficiency and restoration of IDUA enzymatic across species

# AX-0422 preliminary clinical development

*A two-step approach with liver delivery followed by CNS delivery*




- Primary objective: safety, tolerability
- Secondary: pharmacokinetics
- Exploratory PD and clinical measures: plasma IDUA enzyme activity and protein level; HS and DS levels
- Development candidate selected
- CTA filing in early 2027
- First-in-human trial clinical biomarker data in patients in H1 2027

DS: dermatan sulfate; HS: heparan sulfate

# AX-0422 positioned to redefine the standard of care in Hurler Syndrome

*Positioned to deliver systemic and neurological benefit through a single, targeted mechanism*

## DIFFERENTIATED APPROACH

- Impact liver and neurological driven symptoms
- Convenient, infrequent dosing potential
- Avoids limitations of SoC

## HIGH AXIOMER PLATFORM POTENTIAL

- RNA editing restores endogenous enzyme production
- Preclinical data show relevant enzyme restoration, biomarker and functional improvement

# Axiomer™ RNA editing

*Broad Applicability in Precision Medicines*

## FIRST VALIDATION OF AXIOMER IN HUMANS

- Initial AX-0810 data demonstrate no safety signals and PK consistent with non-clinical models
- AX-0810 NTCP target engagement data expected H1 2026
- Biliary atresia selected as initial indication for AX-0810 in Phase 2

## PIPELINE EXPANSION

- AX-2911 for MASH (PNPLA3) advancing to FIH IIT in H1 2027
- AX-0422 for Hurler syndrome (IDUA) with potential to address systemic and neurological symptoms with CTA filing in early 2027

## CONTINUING TO ADVANCE AXIOMER

- AI-guided EON design accelerates discovery
- AX-0811 next generation NTCP program from AI-enabled discovery
- Axiomer RNA editing translating toward liver and CNS therapies

ProQR®

# IT'S IN OUR RNA