



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



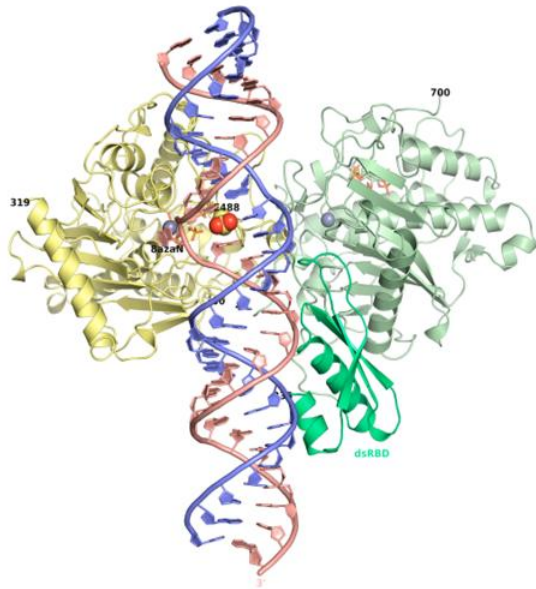
Disclosures

- 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)

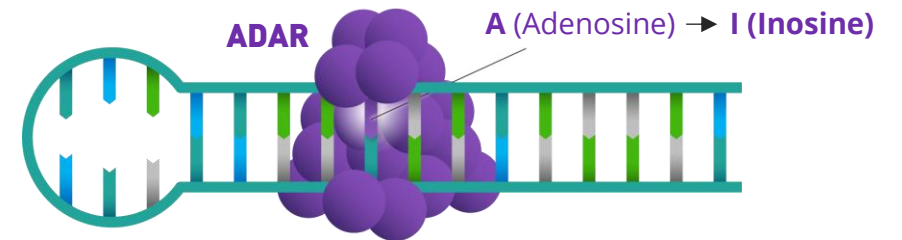


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing**. During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing (A-to-I)

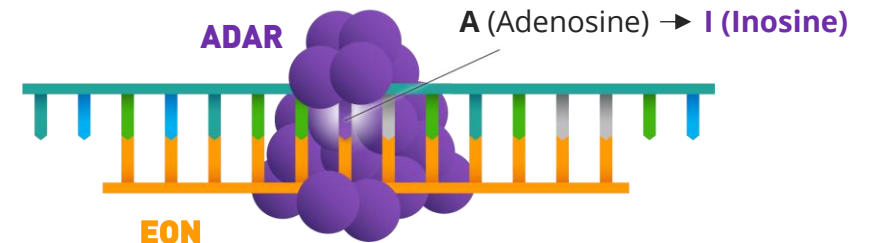
Natural ADAR editing (A-to-I)

RNA
Double
stranded



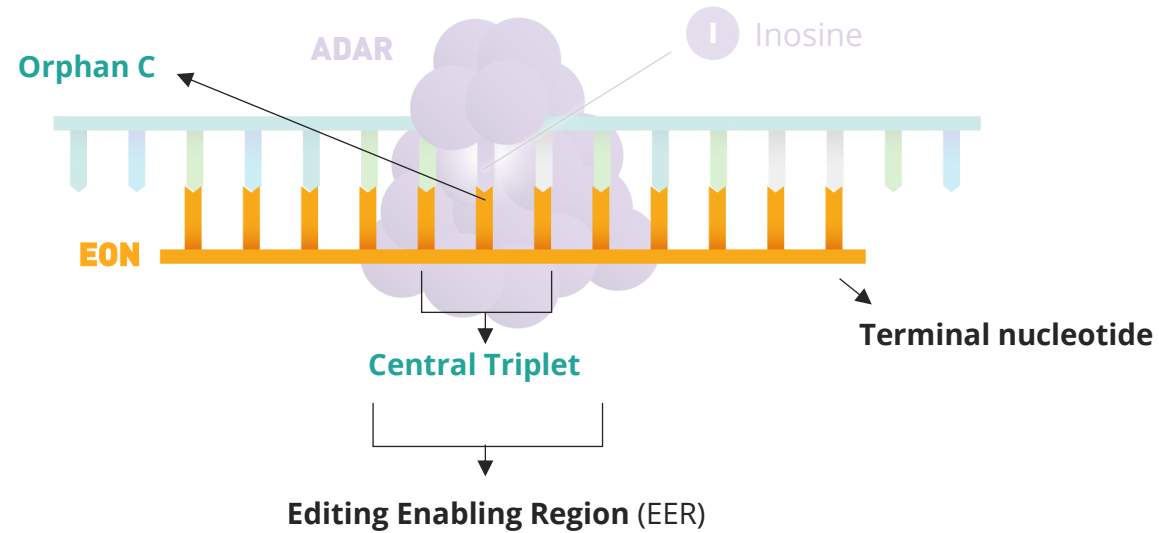
Editing Oligonucleotide (EON)-directed therapeutic editing (A-to-I)

RNA+EON
Double
stranded

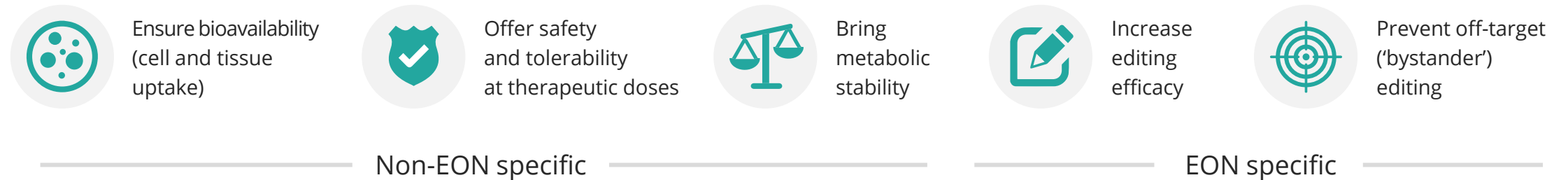


Driving the evolution of therapeutic EONs

Locations of importance

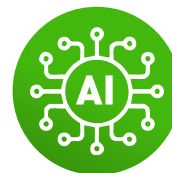
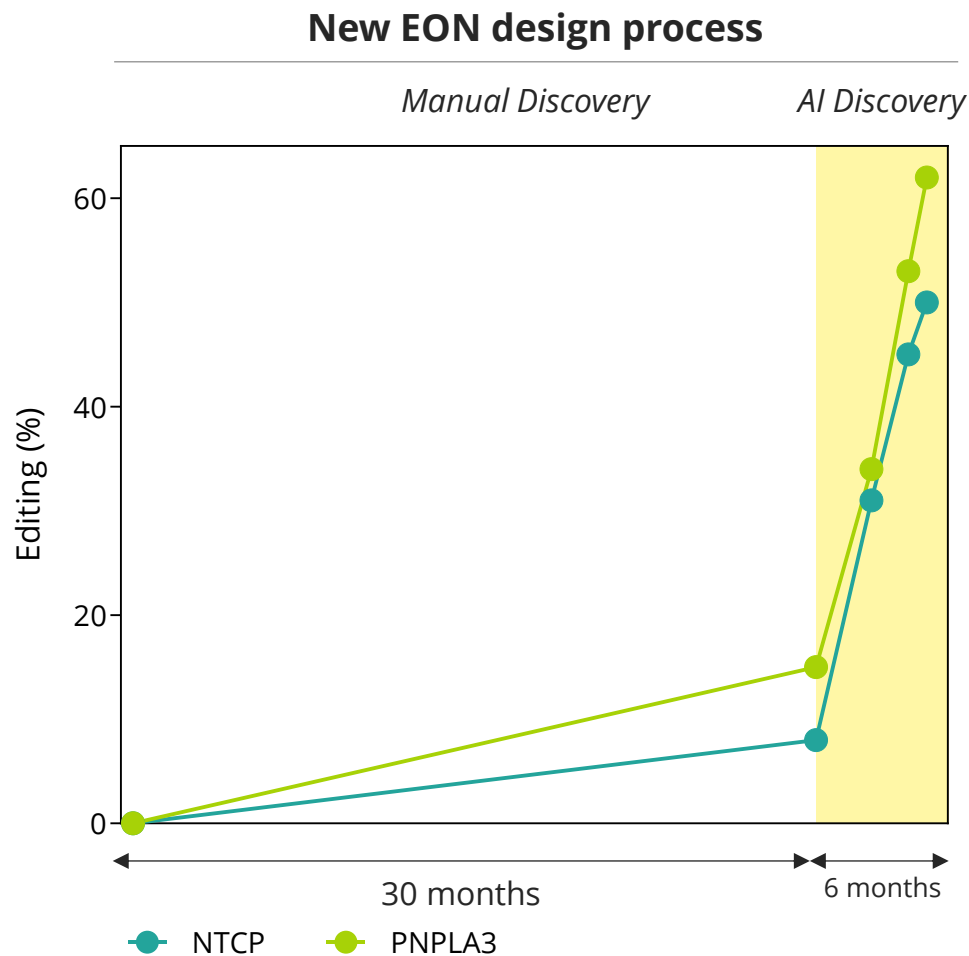


Optimized sequence and chemistry define functionality: EONs are not unlike other ASO types



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**




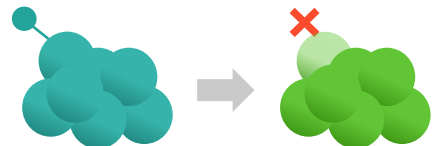
Models trained on
our in-house data
generate EONS
with higher editing
efficiency and
greater sequence
diversity





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

ProQR development pipeline

	TARGET	AXIOMER APPLICATION	DISCOVERY	NON-CLINICAL	CLINICAL	MILESTONES	ESTIMATED POPULATION
DEVELOPMENT PIPELINE							
AX-0810 <i>for Cholestatic diseases</i>	NTCP	<i>Modulate</i>				Target engagement data 1H 2026	~100K patients
AX-0811 <i>for Cholestatic diseases</i>	NTCP	<i>Modulate</i>				Target engagement data in 2026	
AX-0422 <i>for Hurler Syndrome</i>	IDUA	<i>Correct</i>				CTA filing early 2027; Clinical biomarkers in H1 2027	~500-1000 patients
AX-2911 <i>for MASH</i>	PNPLA3	<i>Correct</i>				FIH H1 2027	~8M patients
AX-2402 <i>for Rett syndrome</i>	MECP2 R270X	<i>Correct</i>					 ~5K
PARTNERED PIPELINE							
10 undisclosed targets (option to expand to 15)			<i>Progress undisclosed</i>				

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: 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

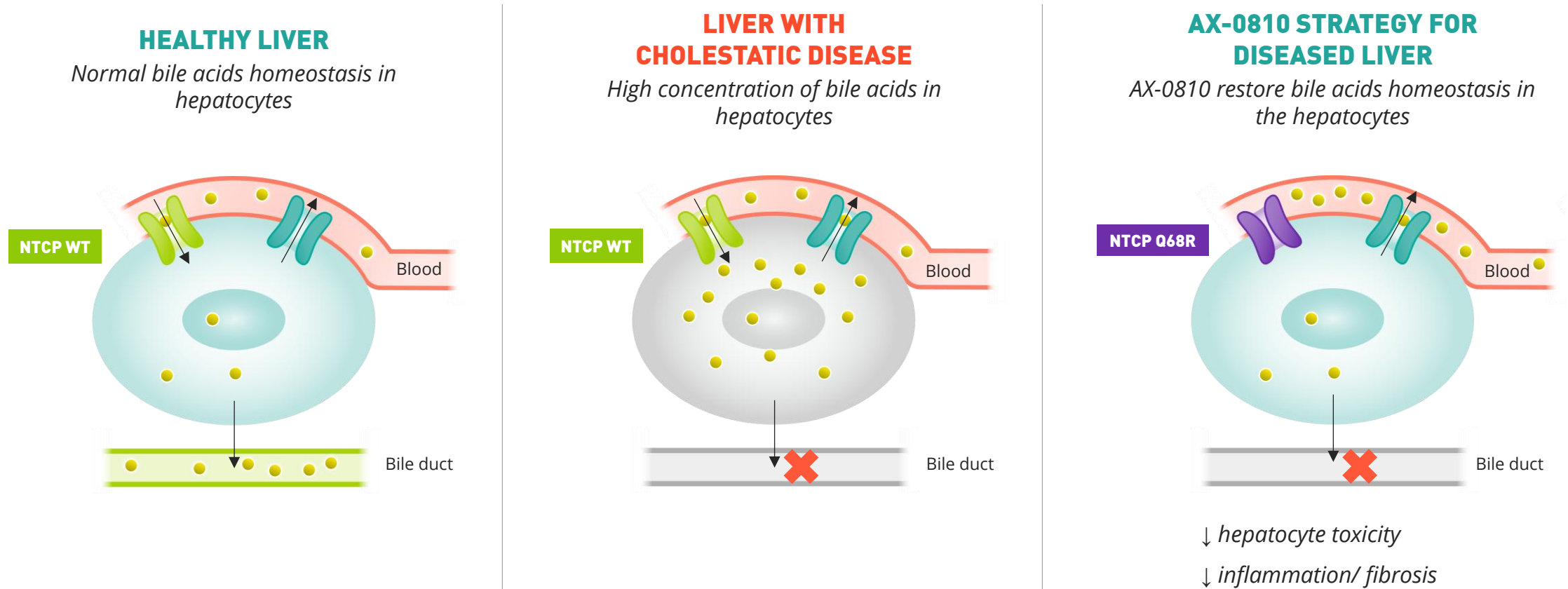
Clinical PoC with bulevirtide in Ph3 Hepatitis D trial, for which liver improvement occur in patients, even without virologic response⁶⁻⁸



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.

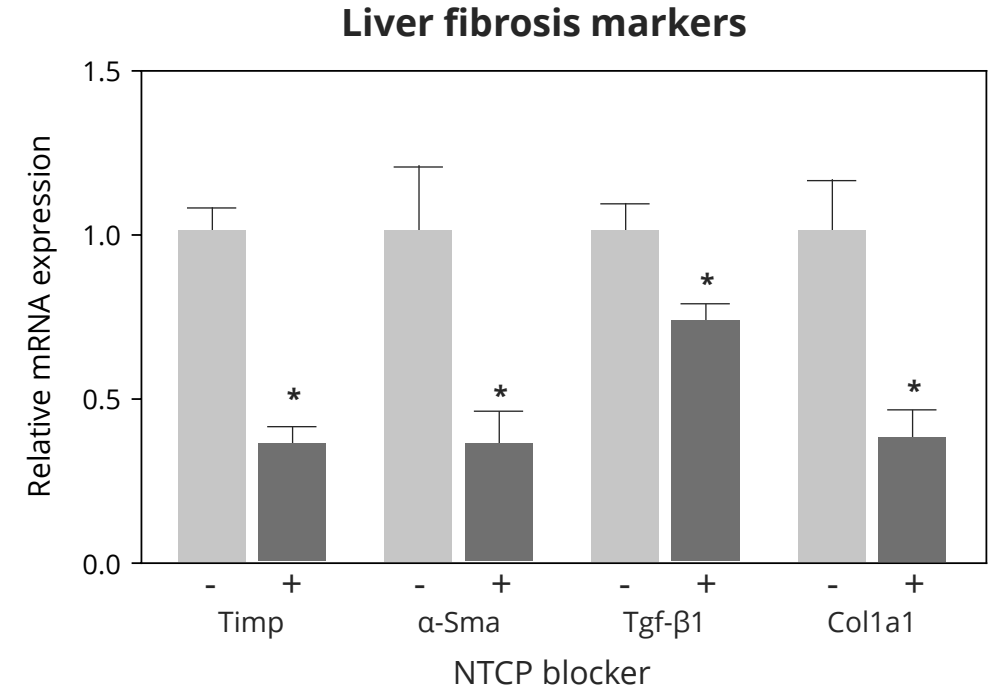
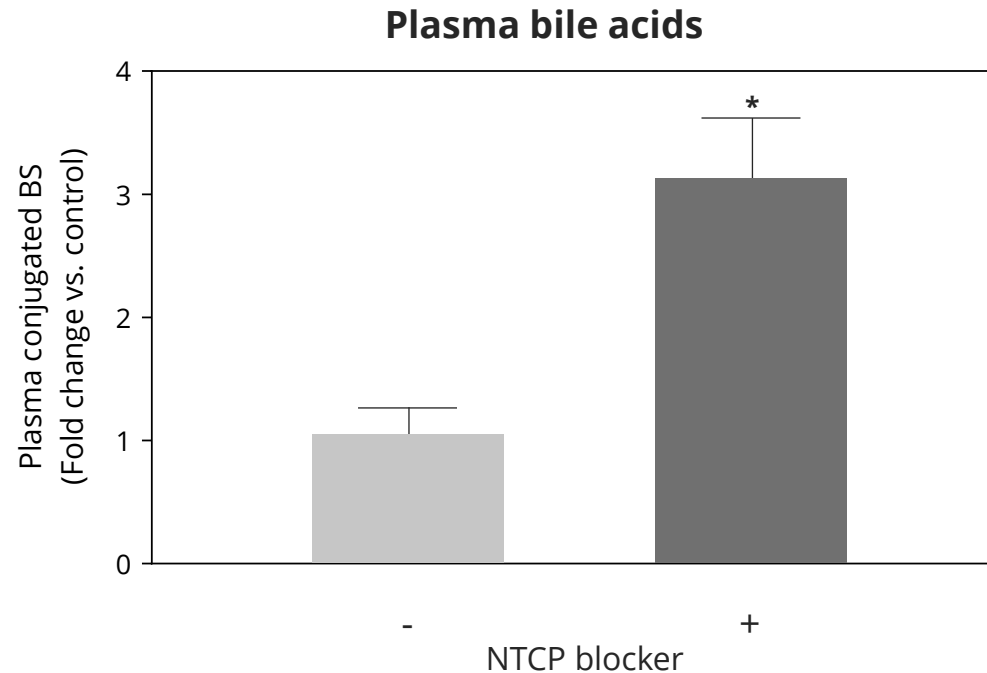
¹Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-22; ²Vaz FM, et al. Hepatology. 2015 Jan;61(1):260-7; ³Schneider AL, et al. Clin Res Hepatol Gastroenterol. 2022 Mar;46(3):101824; ⁴Sljepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069; ⁵Salhab A, et al. Gut. 2022 Jul;71(7):1373-1385; ⁶Wedemeyer 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.

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



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

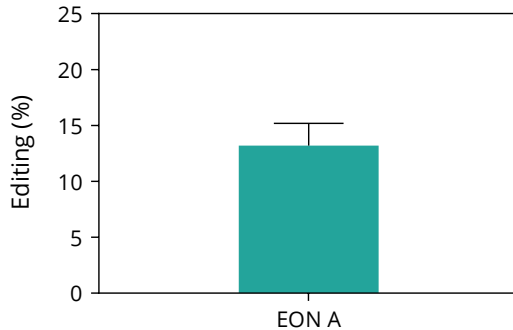
Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069.

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

EDITING EFFICIENCY

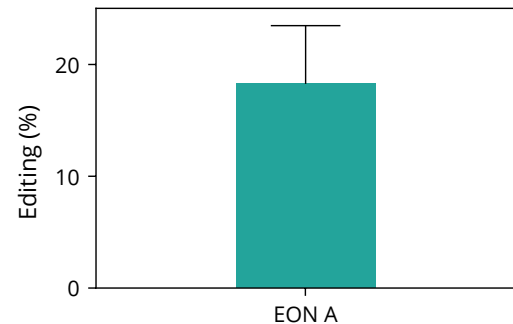
NTCP RNA Editing in Humanized Mice

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



NTCP RNA Editing in NHP

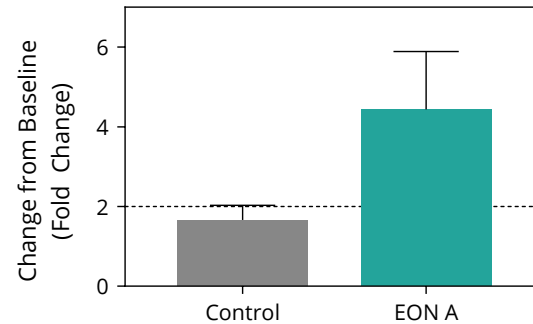
(N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D46, ddPCR)



PLASMA TOTAL BILE ACIDS

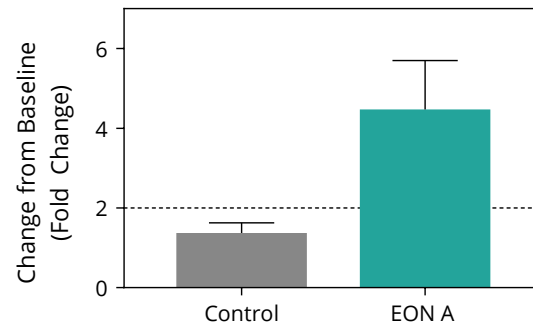
Plasma TBA in Humanized Mice

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



Plasma TBA in NHP

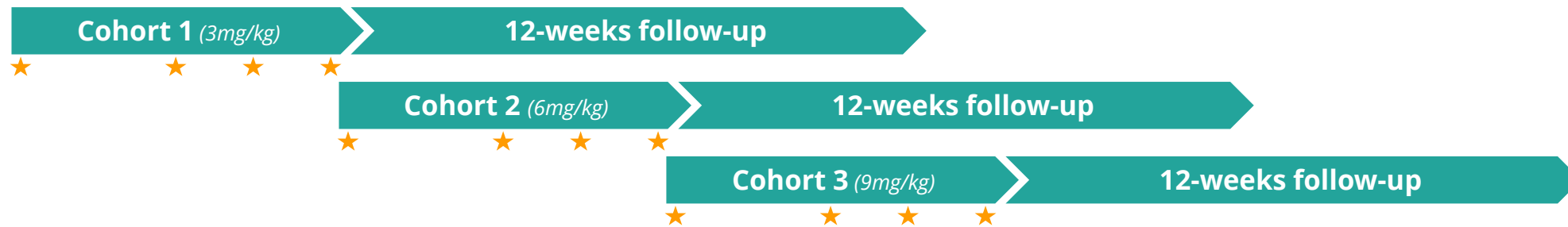
(N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D39)



- 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 options¹ highlight the significant unmet medical need, particularly in lean MASH patients



PNPLA3 I148M

Patatin-like phospholipase domain-containing³ variant

- Strongest genetic risk factor for disease progression
- ~50% of MASH patients²⁻⁴
- Associated with higher liver fat, NASH risk, and fibrosis progression
- Carriers may show reduced response to GLP-1 agonists⁵



RESTORING WT-LIKE PNPLA3

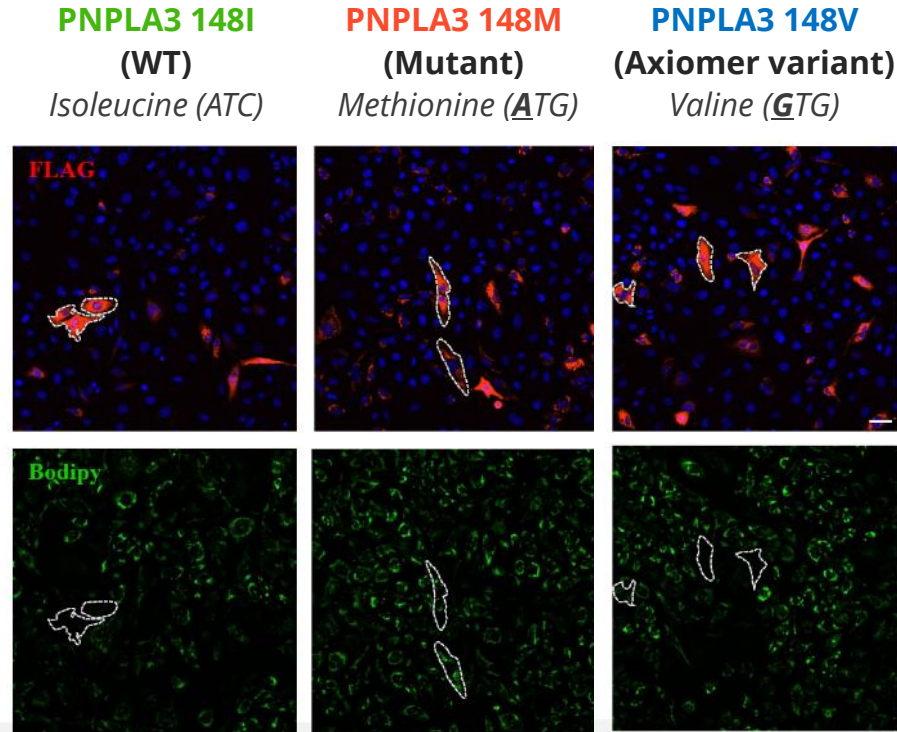
- AX-2911 restores PNPLA3 I148M (Met→Val) function
- Targets MASH primary genetic driver, unlike metabolic therapies
- Broad potential, including GLP-1-low response and lean MASH patients



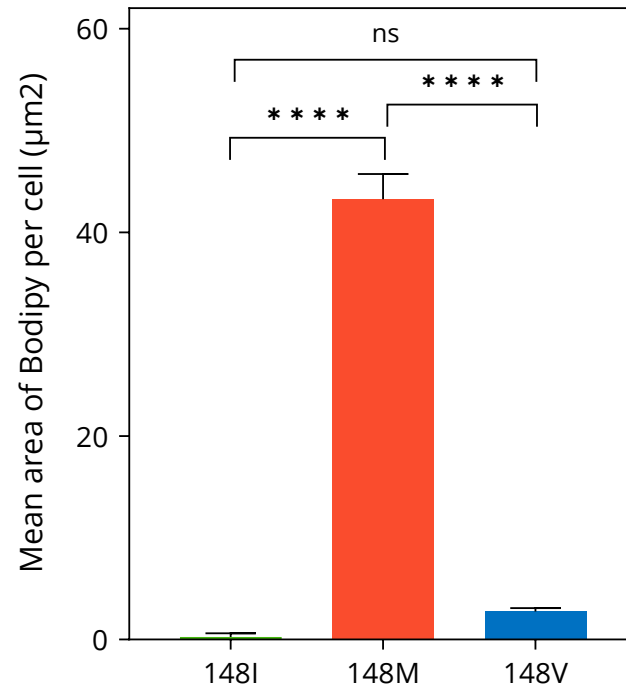
¹Sandireddy R, et al. Front Cell Dev Biol. 2024 Jul 16;12:1433857; ²Tsedendorj Yumchinsuren et al., 2025; ³Sookoian Silvia et al., 2011; ⁴Souza Matheus et al., 2024; ⁵Chen, Yunzhi et al, 2020

AX-2911 to restore WT-like PNPLA3 function

148I and 148V show comparable lipid droplet sizes



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.

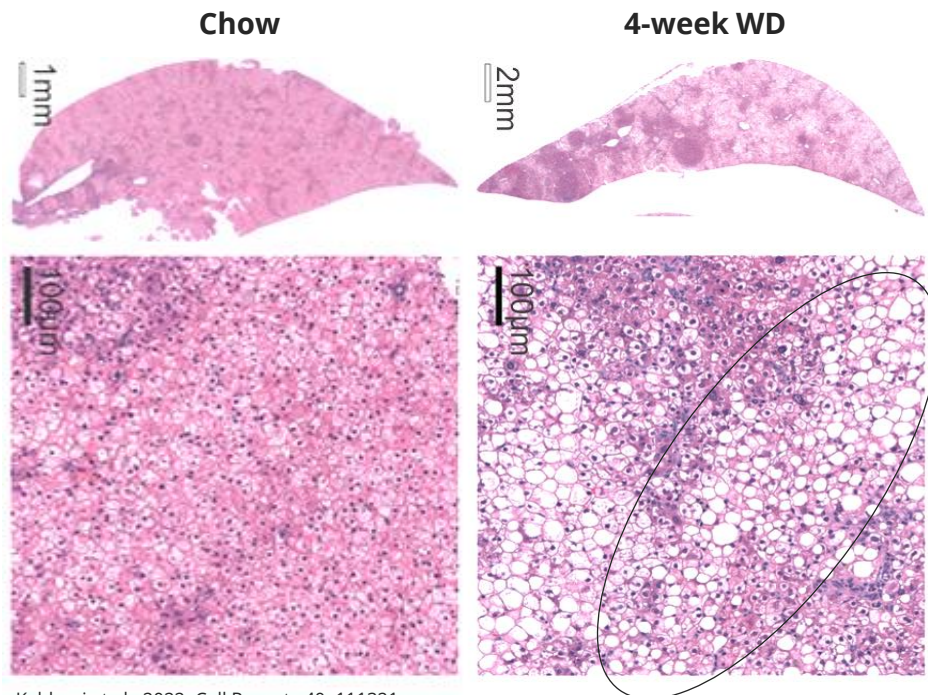
Treatment conditions: HeLa cells, plasmid, transfection, 250uM linoleic acids, 24h, cell lipase activity by IF One-way ANOVA, ****, P<0.0001; Mean, SEM.

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

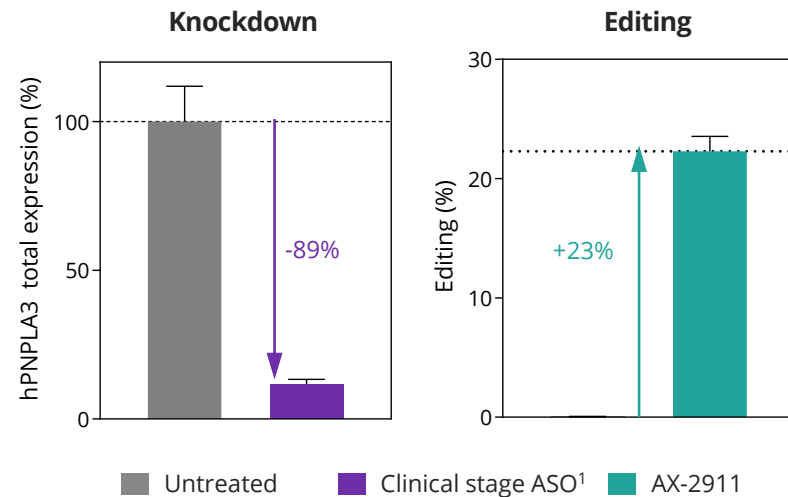
- Engrafted with PNPLA3 I148M primary human hepatocytes
- Recapitulates the human lipid-handling defect
- Translational relevance
- Industry-standard Western Diet
- Rapid, robust steatosis (4 weeks)

Editing has functional advantage over knockdown

AX-2911 substantially reduces liver fat vs clinical-stage ASO²

mRNA

hPNPLA3 I148M in livers of humanized FRG mice under WD¹ dPCR (Qiagen), AVG±SEM

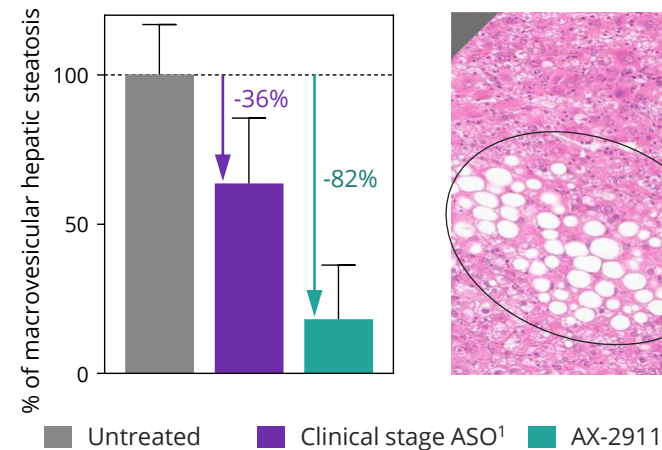


Clinical-stage ASO²:
~89% mRNA reduction
via knockdown of
hPNPLA3

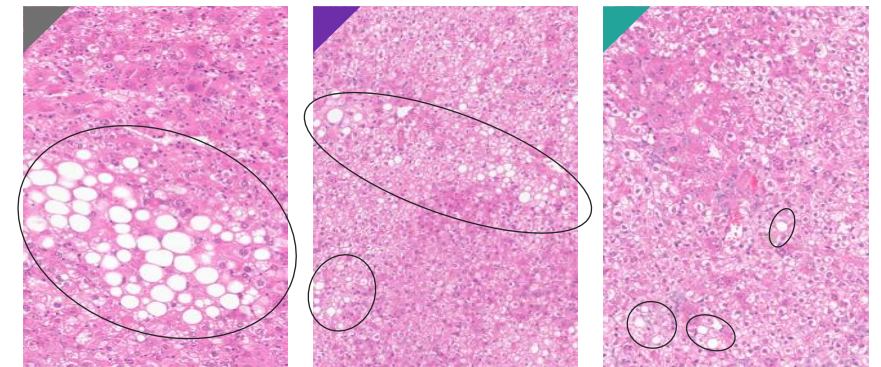
AX-2911 leads to **23%**
editing of
hPNPLA3 mRNA

LIVER FUNCTION (steatosis)

Macrovesicular steatotic incidence scoring¹ (%)
AVG±SEM



Liver sections of steatosis mouse model treated with ASO² or AX-2911¹
PNPLA3 I148M humanized FRG mouse, WD 4W+4W



82% reduction of
macrovesicular lipid
droplets

Untreated

Clinical-stage
ASO²

AX-2911

¹N=4-6, 20mg/kg, 14 doses, GalNAc conjugated-AX-2911 or 0.7mg/kg, 14 doses, AZ AZD2693 treatment, SC, readout at day D28; ²AZ 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 phenotype¹
- 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: glycosaminoglycans; 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



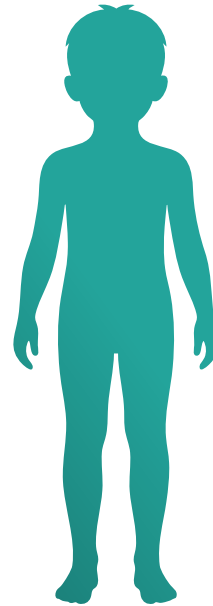
Cardiac involvement



Hepato-splenomegaly (liver & spleen)



Skeletal/Joint disease



NEUROLOGICAL



Progressive CNS impairment



Subcutaneous (SC) delivery: Liver

- Drives systemic IDUA expression
- Targets peripheral organs pathology



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

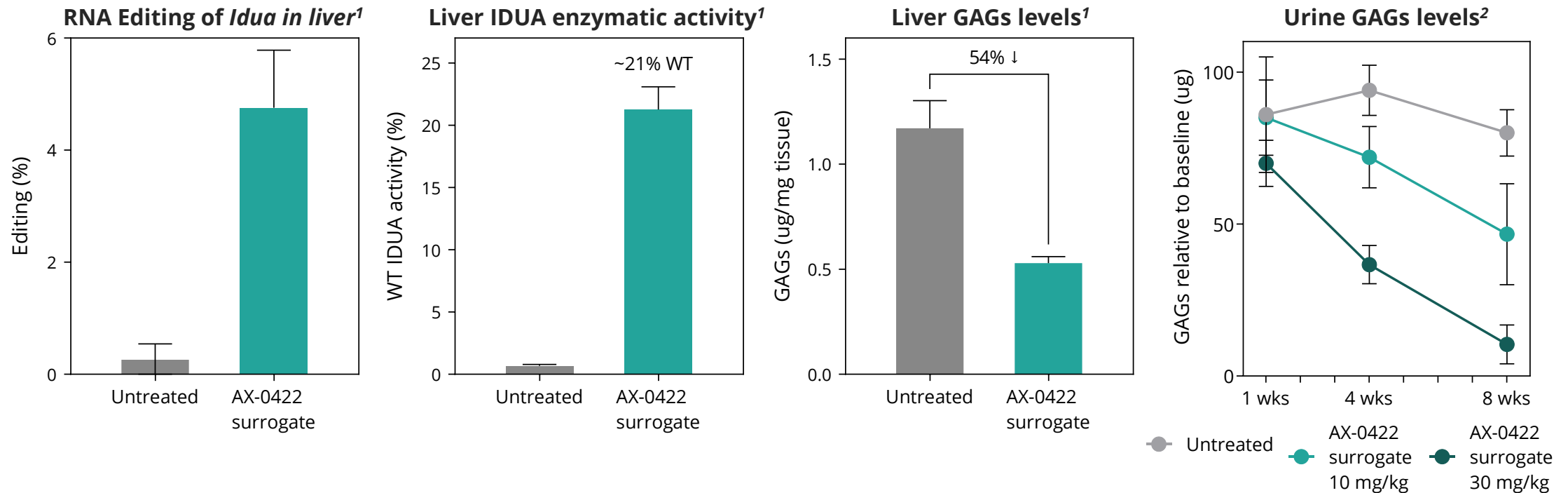
Severity →

	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 function² can improve phenotype

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

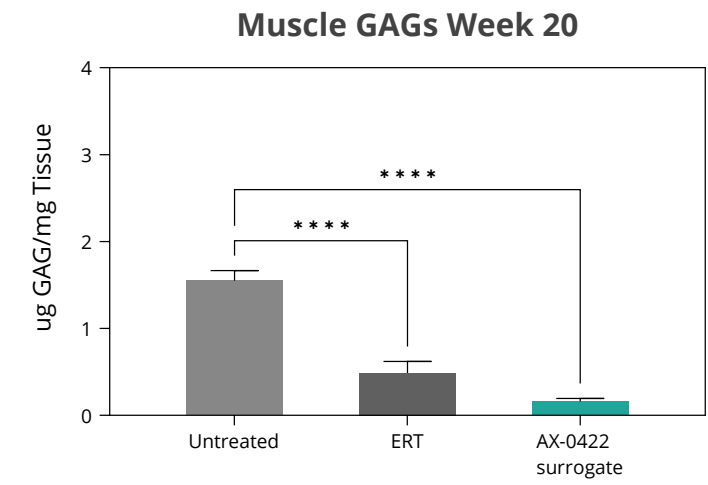
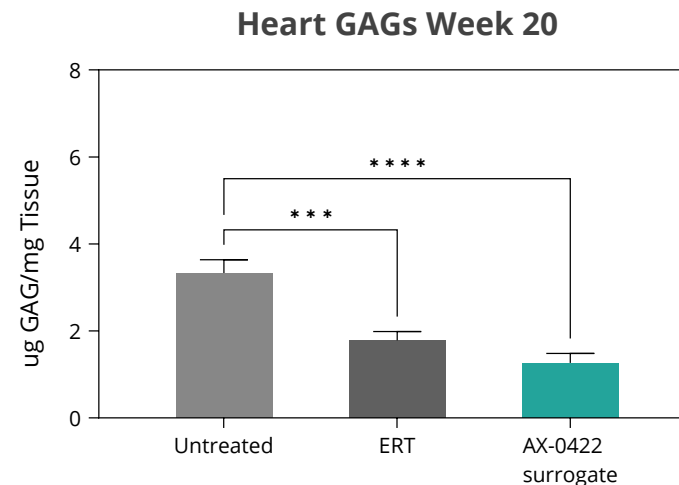
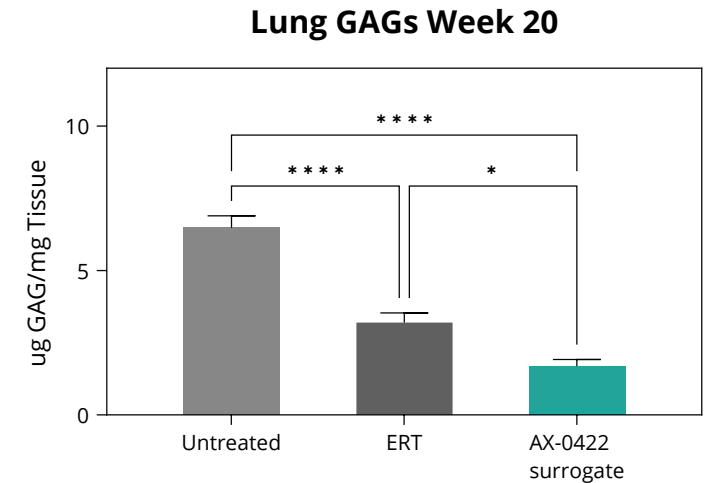
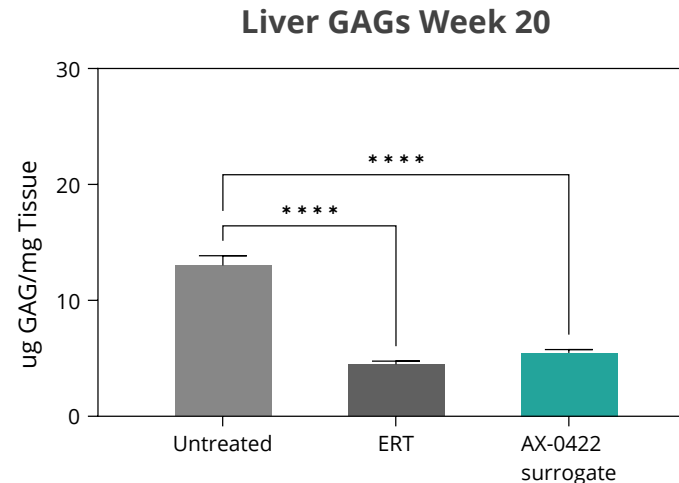
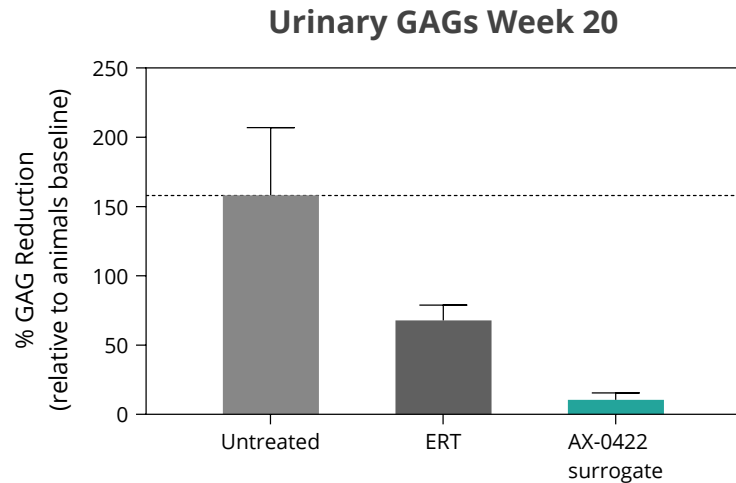
RNA editing achieves therapeutically meaningful enzyme restoration in *Idua* mouse model



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**

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

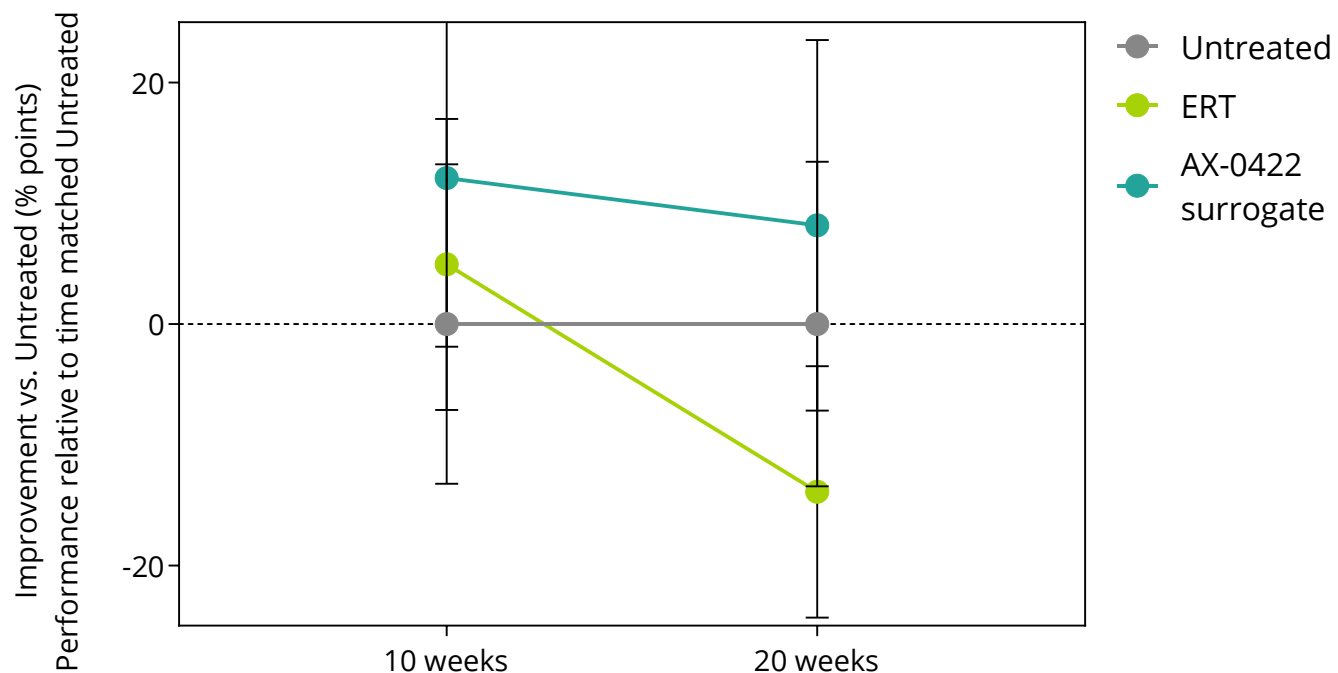
ERT: Enzyme replacement therapy; GAGs: Glycosaminoglycans; SoC: Standard of care. Treatment conditions; Idua-W392X mice, AX-0422 surrogate treatment: SC, 30 mg/kg, ERT (Laronidase) treatment: IV, 0.58 mg/kg, Q1W until 4 wks, n=6, mean, SEM. One-way ANOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$,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

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



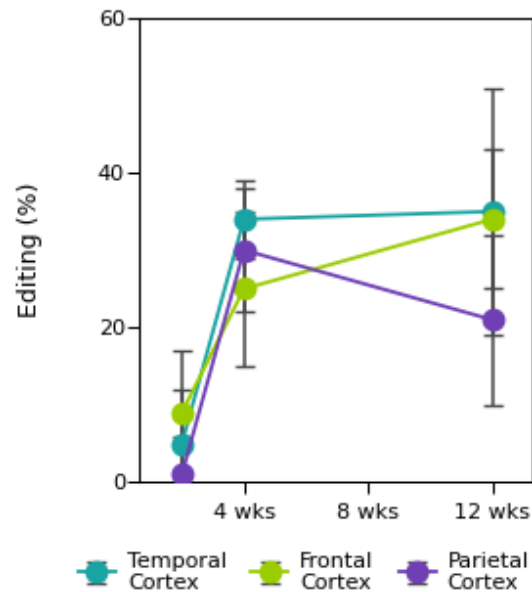
- Durable functional stabilization observed with EON through 20 weeks
- Transient stabilization with ERT followed by decline
- ERT data consistent with clinical data showing deterioration in 6-MWT in patients who develop inhibitory ADAs¹

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

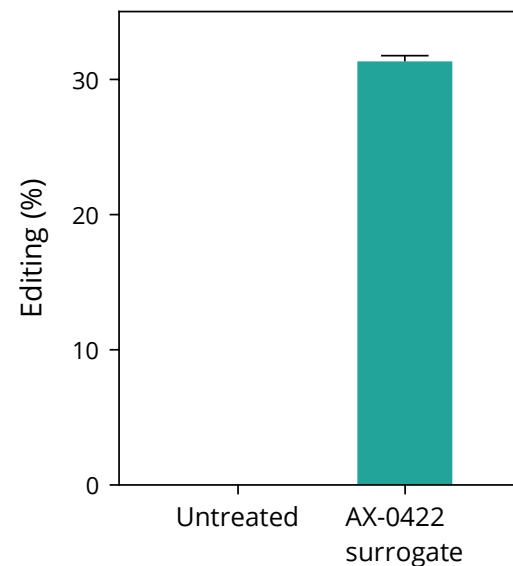
AX-0422 achieves robust, durable CNS editing with functional enzyme restoration



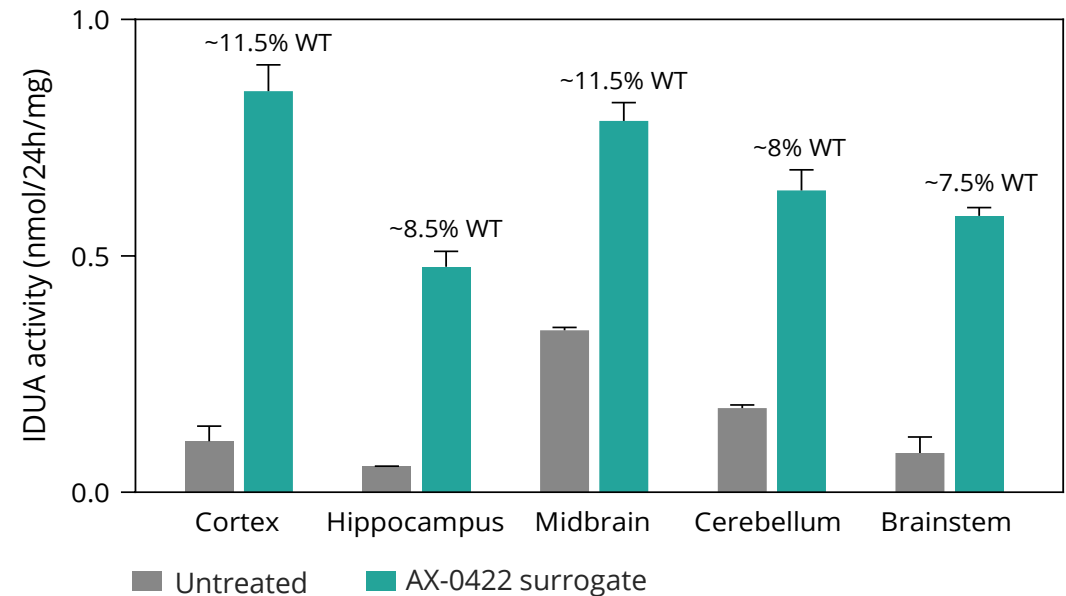
Durable RNA editing of ACTB in cortex of NHP²



RNA Editing of *Idua* in cortex of *Idua*-W392X mice¹



IDUA enzymatic activity in the brain of *Idua*-W392X mice¹ (% WT recovery)



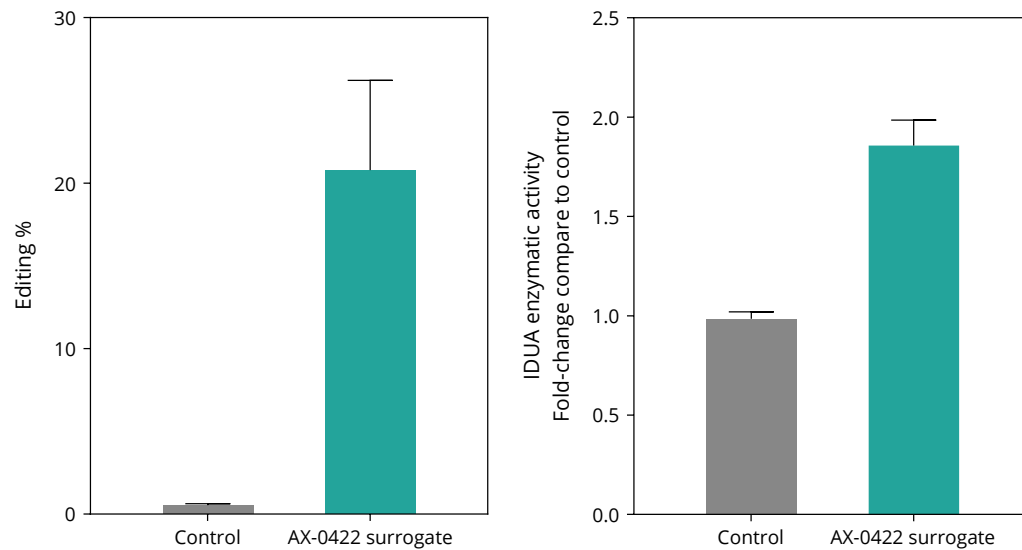
- Axiomer results in durable CNS editing of up to 12 weeks (single dose, NHP)
- Following ICV delivery, efficient editing in Hurler disease model leads to broad enzyme restoration across brain regions (~7–12% of WT)
- Levels consistent with disease-modifying potential in Hurler syndrome

¹AX-0422 surrogate treatment of *Idua*-W392X mice ICV, 250µg, single dose, n=6, 4 weeks, ddPCR, mean, SEM / western blot, mean, SEM; ²IT 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

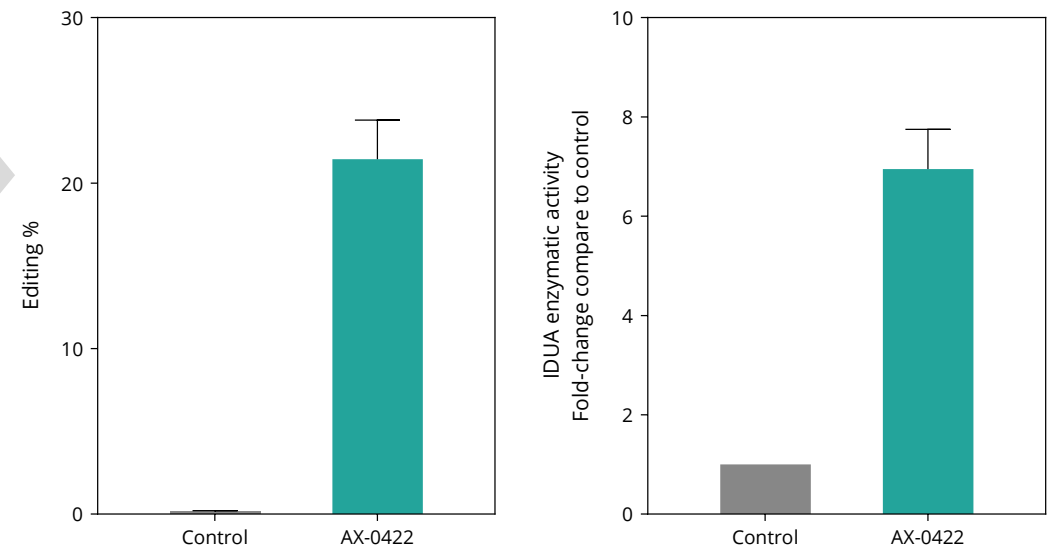
Mouse Idua W392X Mouse Embryonic Fibroblasts

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

Subcutaneous administration for Liver



Intrathecal administration for CNS



- 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



**IT'S IN
OUR RNA**