ProQR®

DEVELOPING RNA-EDITING MEDICINES

for patients in need

Nasdaq: PRQR

September 2026

Forward-looking statements

This presentation has been prepared by ProQR Therapeutics N.V. ("we", "us" or "our") and contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as “continue,” "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 business, technology, strategy, preclinical and clinical model data; our initial pipeline targets and the upcoming strategic priorities and milestones related thereto; the continued advancement of our lead development pipeline programs, including ongoing and planned clinical trials; expectations regarding the ongoing Phase 1 clinical trial of AX-0810 in NTCP for cholestatic diseases, including our ability to complete the Phase 1 clinical trial for AX-0810, biliary atresia as our primary indication for AX-0810 and/or AX-0811, and the anticipated timing of additional target engagement data readout for Phase 1 clinical trial in 2026 and the initiation of Phase 2 trial for AX-0810 and/or AX-0811 in mid-2027, subject to regulatory interactions, with first interim analysis expected by mid-2028; expectations regarding the safety and therapeutic benefits of AX-0810 and AX-0811, including the planned dosing levels and their efficacy; our ability to collaborate with investigators to execute and recruit for an investigator-initiated trial of AX-0810 or AX-0811 in China in pediatric participants with biliary atresia and to generate meaningful data therefrom, including the anticipated timing of initial data readout in the first half of 2027; risks and uncertainties associated with conducting clinical trials in China, including evolving regulatory requirements; our pipeline targets, including the planned Phase 1 clinical trial of AX-0811 in NTCP for cholestatic diseases; our ability to complete a Phase 1 clinical trial for AX-0811, including initial data readout by early January 2027; the anticipated first-in-human study of AX-0422 targeting IDUA for MPS I Hurler syndrome, with a CTA filing expected in early 2027 and anticipated initial clinical data readout in the first half of 2027; the anticipated investigator-initiated study in China of AX-2911 targeting PNPLA3 for MASH in the first half 2027; our expectations regarding clinical updates across multiple programs in 2026 and 2027; the therapeutic potential and development timeline regarding AX-0810, AX-0811, AX-0422, AX-2911 and AX-2402; the continued development and advancement of our Axiomer platform; the therapeutic potential of our Axiomer RNA editing oligonucleotides and product candidates; the timing, progress and results of our preclinical studies and other development and pipeline activities, including the release of data related thereto; our patent estate, including our anticipated strength and our continued investment in it, as well as the timing of our clinical development; our AI strategy and expectations regarding AI’s ability to accelerate Axiomer discovery; our partnership with Ginkgo and the anticipated benefits thereof; our collaboration with Lilly and the intended benefits thereof; our ability to selectively form new partnerships and enter into future collaborations; our financial position and cash-runway; and the potential of our technologies and product candidates. 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 expressed or implied by 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 most recent annual report filed on Form 20-F. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies and clinical trials 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 chains and logistics in the global market, economic sanctions and international tariffs; the likelihood of our preclinical and clinical programs being initiated and executed on timelines provided and our reliance on our contract research organizations and predictability of timely enrollment of subjects and patients to advance our clinical trials and maintain their own operations; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; the potential for future data to alter initial and preliminary results of early-stage clinical trials; the unpredictability of the duration and results of the regulatory review of applications or clearances that are necessary to initiate and continue to advance and progress our clinical programs; 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; and risks related to macroeconomic conditions and market volatility resulting from global economic developments, geopolitical events and conflicts, inflationary pressures, fluctuating interest rates, tariffs and potential for significant changes in U.S. policies and regulatory environment. 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.

Advancing multi-asset Axiomer™ clinical pipeline

	TARGET	AXIOMER APPLICATION	DISCOVERY	NON-CLINICAL	CLINICAL	ANTICIPATED MILESTONES	ESTIMATED POPULATION
DEVELOPMENT PIPELINE							
AX-0810 *for Cholestatic diseases*	NTCP	*Modulate*				Phase 1 full results YE 2026	~100K patients
AX-0811 *for Cholestatic diseases*	NTCP	*Modulate*				Target engagement data in early January 2027	
AX-0422 *for Hurler Syndrome*	IDUA	*Correct*				CTA filing early 2027; Initial patient data 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

FIRST CLINICAL VALIDATION OF AXIOMER RNA EDITING

Initial AX-0810 target engagement data
Biliary atresia selected as initial indication for NTCP

HIGH IMPACT PARTNERSHIP

Ongoing execution across $3.9B collaboration with Eli Lilly

ADVANCE AXIOMER PLATFORM

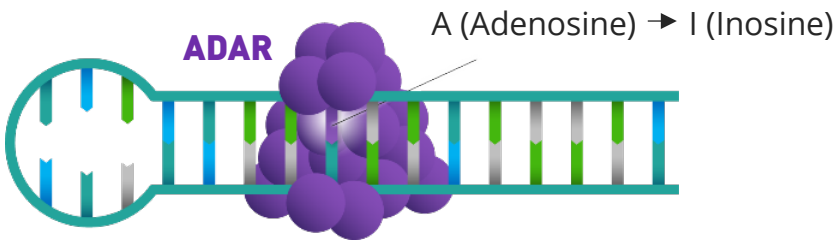
ProQR's AI-enabled discovery; autonomous HTS with Ginkgo Bioworks

RUNWAY THROUGH MID 2028

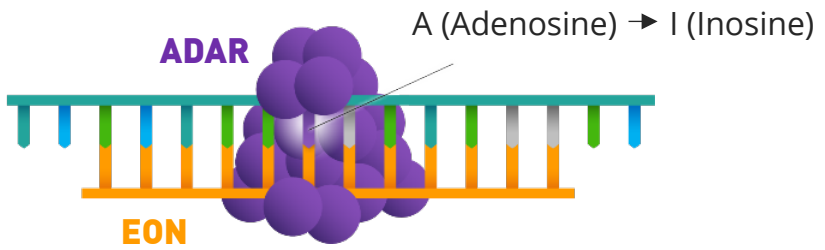
***€117.1M** cash and cash equivalents as of end Q2 2026; multiple upcoming clinical catalysts*

How Axiomer™ edits RNA

NATURAL ADAR EDITING



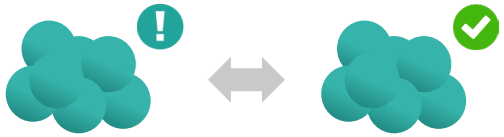
EDITING OLIGONUCLEOTIDE *(EON)-directed* EDITING



MODULATE

Modify protein function

CORRECT



Correct disease-causing mutations

PROTECT

Introduce protective variants

Addressing unmet need in cholestatic diseases through NTCP modulation

CHOLESTATIC DISEASE

- Biliary Atresia affects pediatrics early in life (~20,000 patients worldwide)
- 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 STRATEGY

- 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 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]

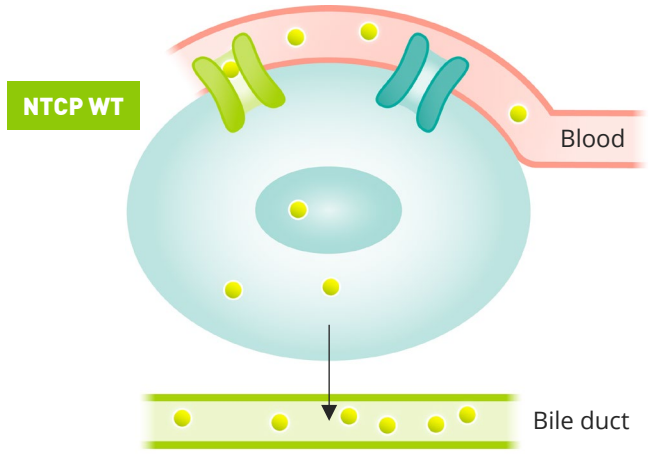
Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. NTCP channel is a known transporter for bile acids and hepatitis virus from bloodstream to the liver.

[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

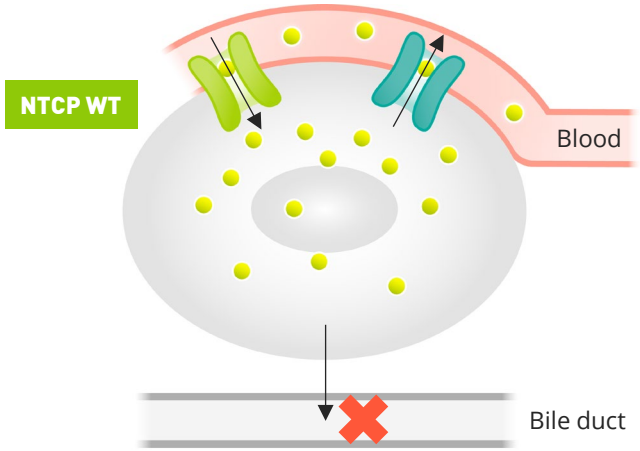
HEALTHY LIVER

Normal bile acids homeostasis in hepatocytes



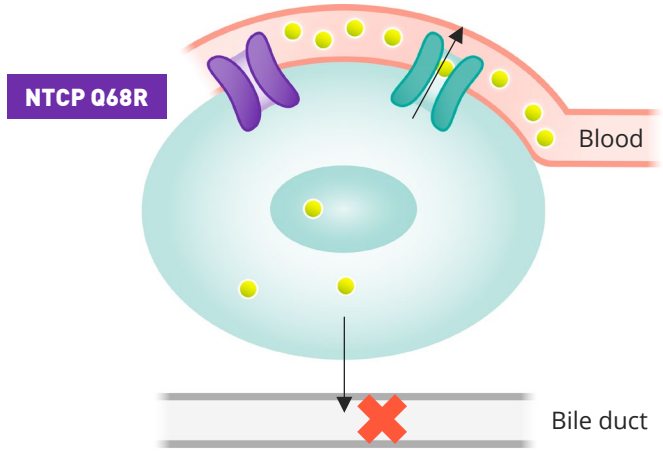
LIVER WITH CHOLESTATIC DISEASE

High concentration of bile acids in hepatocytes



AX-0810 STRATEGY FOR DISEASED LIVER

AX-0810 restore bile acids homeostasis in the hepatocytes



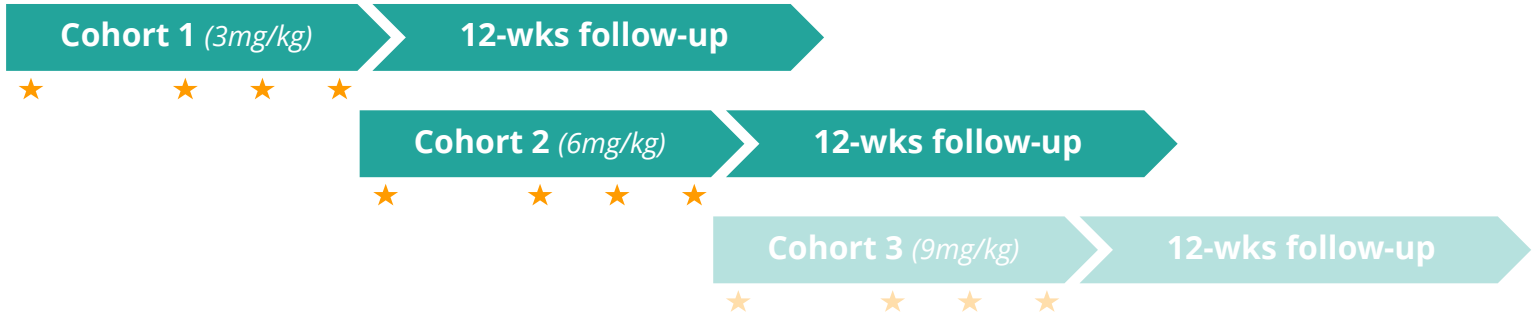
↓ *hepatocyte toxicity*

↓ *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.

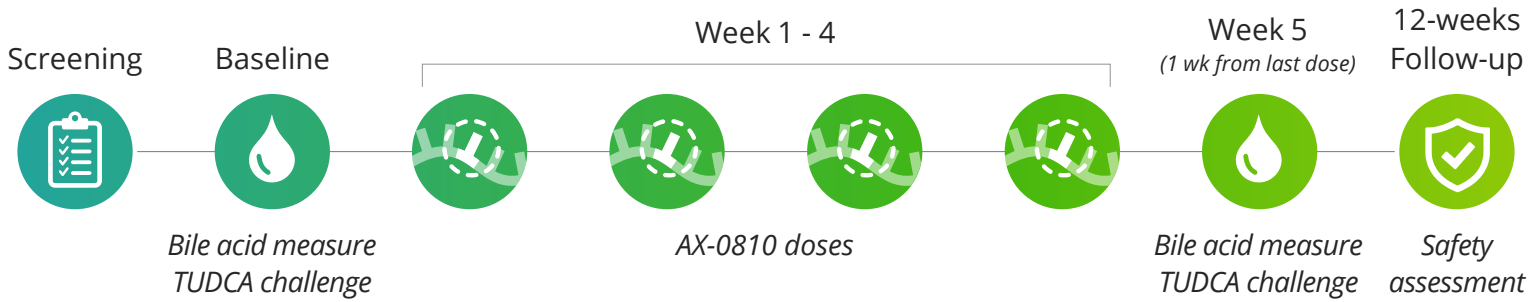
AX-0810 FIH Phase 1 study

Multiple ascending dose (MAD) *N=33 healthy volunteers (24 on treatment, 9 on placebo)*



DMC safety reviews before proceeding to next dose and dose escalation is sequential during the dosing phase; Cohort 3 ongoing

Study timeline



Objectives

- Assess safety, tolerability, and PK of AX-0810
- Confirm target engagement as measured by biomarkers

Key biomarkers of target engagement

- Change in bile acid levels
- Bile acids profile
- TUDCA challenge

Key features of study design

- Controlled challenges: Standardized meal + TUDCA procedures
- Bile Acid Profiling: Robust bile-acid bioanalytical coverage
- Serial Sampling: 12-hour continuous data collection on study days

DMC, Data Monitoring Committee; MAD, Multiple Ascending Dose; PK, Pharmacokinetics; NTCP, sodium taurocholate co-transporting polypeptide; TUDCA, Tauroursodeoxycholic acid; AX-0810 CTA approved in Europe (Oct 2025)

Baseline characteristics AX-0810 Phase 1

Characteristic	**Placebo** *(Cohort 1 + 2, n=6)*	**3 mg/kg** *(Cohort 1, n=8)*	**6 mg/kg** *(Cohort 2, n=8)*
Age, years (mean ± SD)	40.8 ± 8.98	40.9 ± 9.36	40.1 ± 11.4
Age, years (min–max)	27 – 50	26 – 55	27 – 54
Male, n (%)	*5* (83%)	8 (100%)	8 (100%)
Female, n (%)	*1* (17%)	0	0
Weight, kg (mean ± SD)	80.1 ± 10.4	80.6 ± 10.1	78.5 ± 10.2
Weight, kg (min–max)	66 – 97	67.1 – 98.1	67.9 – 95.7
BMI, kg/m² (mean ± SD)	24.1 ± 2.46	25.1 ± 1.91	24.4 ± 2.48
BMI, kg/m² (min–max)	22.3 – 29	22.8 – 28.4	20.1 – 27.4
TBA, µmol/L (mean ± SD)	2.2 ± 1.7	3.2 ± 1.3	1.9 ± 1.0
TBA, µmol/L (min-max)	1.1 - 5.5	1.9 – 5.9	0.8 - 3.8

The two cohorts are well balanced with respect to age, body weight, and BMI

AX-0810 demonstrated favorable profile

Category	3 mg/kg AX-0810 + placebo (N=11), blinded, *n (%)*	6 mg/kg AX-0810 + placebo (N=11), blinded, *n (%)*	Overall (N=22) *n (%)*
Number of all AEs	35	16	51
Participants with ≥1 AE	7 (63.6)	6 (54.5)	13 (59.1)
AEs by relationship			
AEs related to study drug	1 (9.1)	3 (27.3)	4 (18.2)
AEs unrelated to study drug	6 (54.5)	3 (27.3)	9 (40.9)
AEs by severity			
Mild	5 (45.5)	6 (54.5)	11 (50.0)
Moderate	2 (18.2)	0	2 (9.1)
Severe	0	0	0
SAEs	0	0	0
AEs leading to study drug withdrawal	0	0	0
AEs leading to early termination	0	0	0

No safety or tolerability issues to date

- No discontinuations
- No SAE's reported

NTCP modulation mechanism as expected

- No clinically significant changes in liver enzymes
- No pruritus
- No changes in hormone or vitamin D levels
- No changes in bilirubin (no OATP off-target)

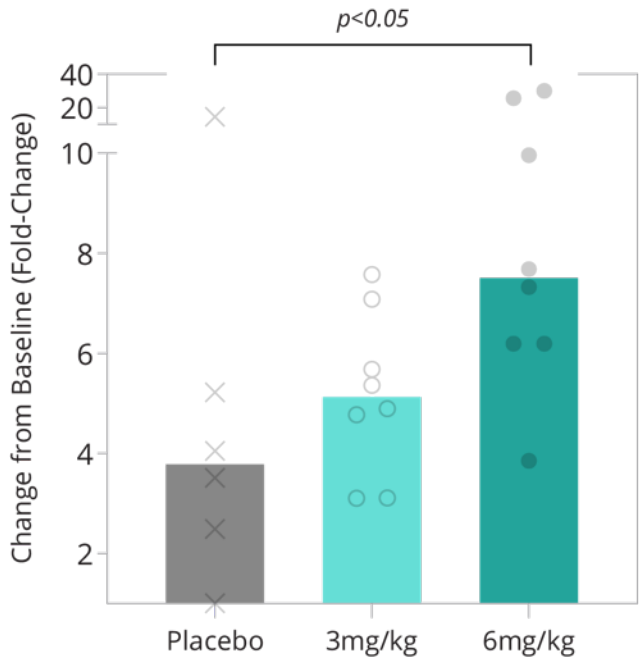
PK in line with expected profile

- AX-0810 has a half-life in human of 8 weeks

AEs, Adverse events; SAEs, Serious adverse events. Values represent n (%) of participants unless otherwise stated. Data shown through the cutoff date (May 26, 2026 for AEs summaries, and June 1, 2026 for Laboratory data); covers 30 days on treatment and additional post-treatment follow-up. PK half-life based on available data (3mg/kg)

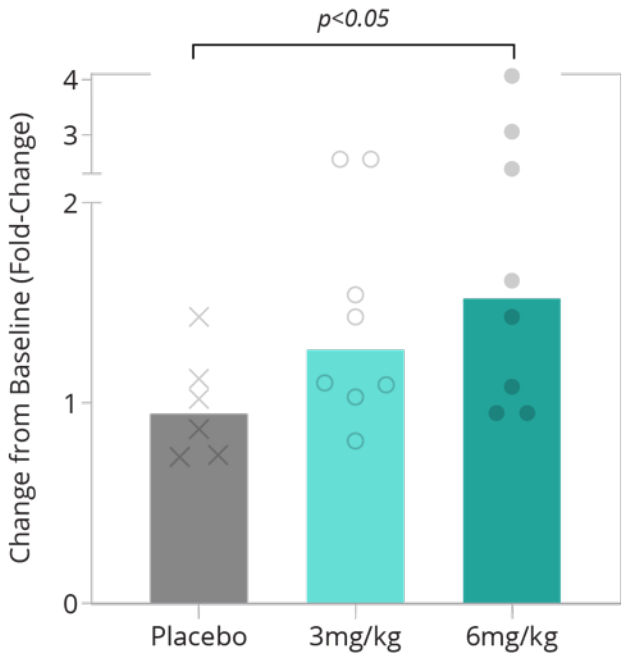
All 3 biomarkers confirmed target engagement

Total bile acids (TBA)



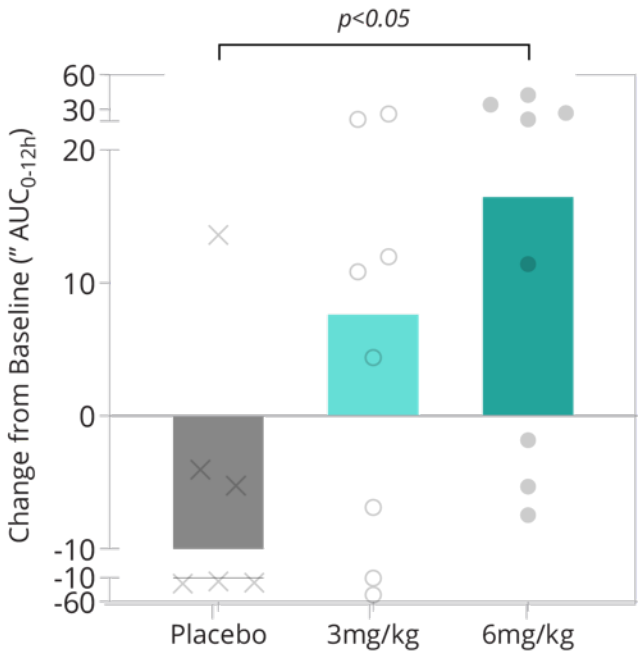
Up to **8-fold increase in TBA** in serum showed bile acids uptake modulation

TUDCA



Increased circulating TUDCA **confirmed NTCP specificity**

Conjugated bile acids

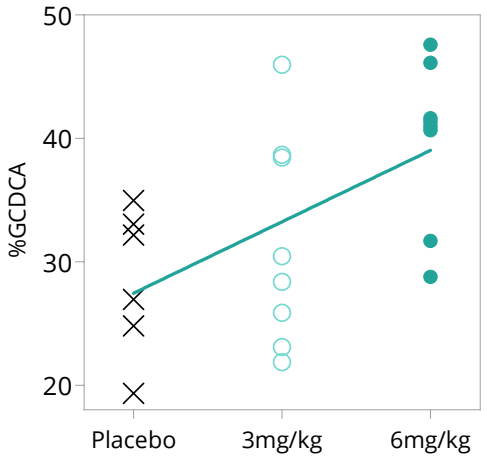


Selective increase in conjugated bile acids showed specific NTCP modulation

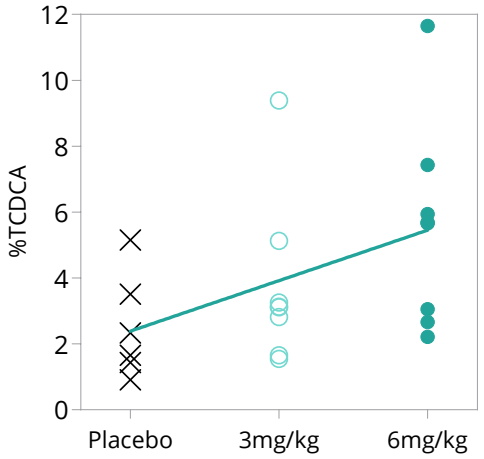
Figures: median + individual values. Total Bile Acids (TBA) and TUDCA: Cmax week 5 / baseline. Conjugated bile acids: ΔAUC0-12h (µmol/L x h) (week 5 – baseline). Post-hoc statistical analyses.
N=22 (n=6 Placebo, crosses; n=8 Cohort 1 | 3mg/kg, circles; n=8 Cohort 2 | 6mg/kg, dots); 4 doses AX-0810; GalNAc conjugation; Subcutaneous

Concordant changes with conjugated bile acids

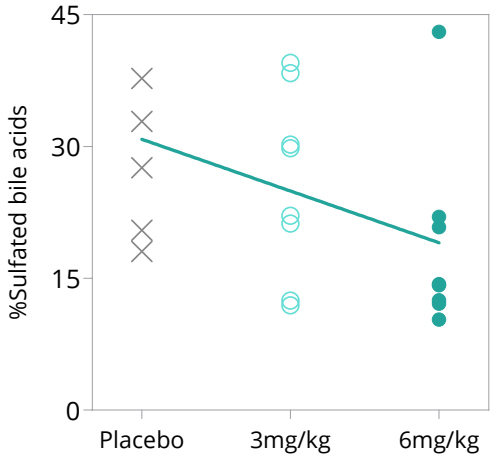
GCDCA
r=0.56, p = 0.007



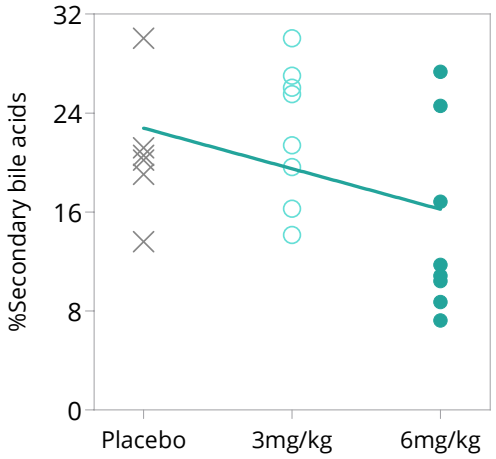
TCDCA
r=0.48, p = 0.024



Sulfated BAs
r= -0.42, p = 0.052



Secondary BAs
r= -0.37, p = 0.086



Increase in serum levels of hepatotoxic BAs

Decrease in serum sulfated BAs produced in the liver

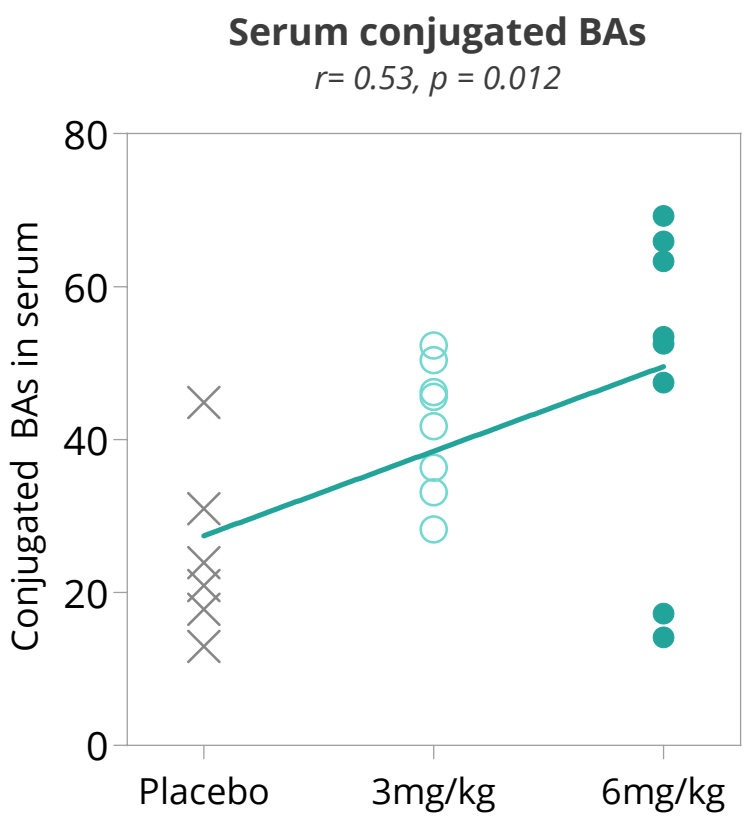
Decrease in serum BAs produced by intestinal bacteria

DECREASE IN LIVER EXPOSURE TO TOXIC CONJUGATED BILE ACIDS

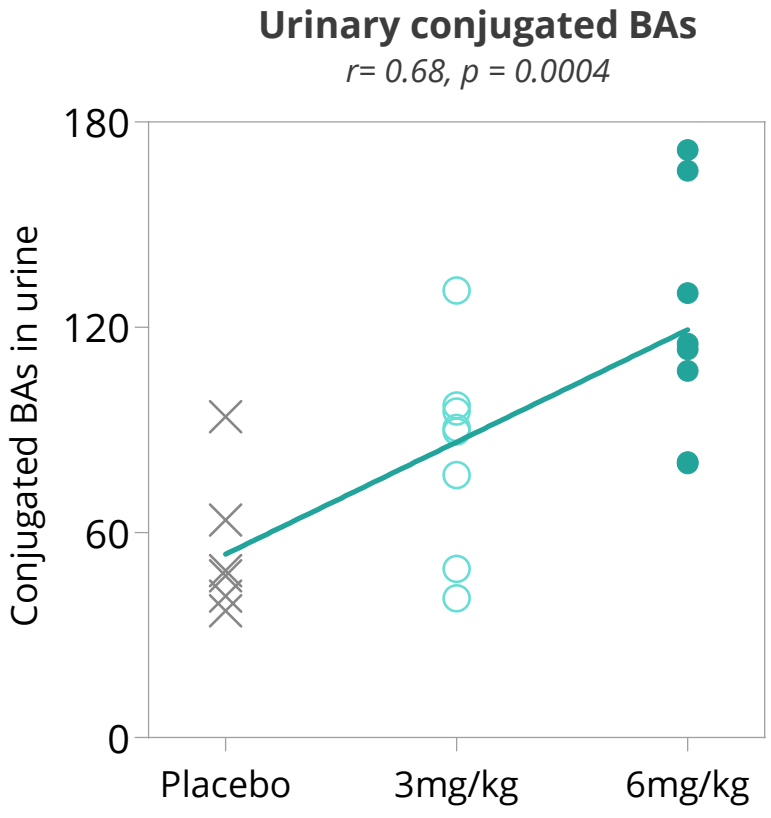
DECREASE IN GUT EXPOSURE TO HEPATIC BILE ACIDS

BA, bile acids; GCDCA, Glycochenodeoxycholic acid; TCDCA, Taurochenodeoxycholic acid. Values represent the median of the % measured in serum from 0-12h on Week 5. Pearson correlation calculated and significance indicated. Post-hoc statistical analyses. N=22 (n=6 Placebo, crosses; n=8 Cohort 1 | 3mg/kg, circles; n=8 Cohort 2 | 6mg/kg, dots); 4 doses AX-0810; GalNAc conjugation; Subcutaneous

Urine excretion of conjugated bile acids



Conjugated bile acids are cleared from the plasma into the urine



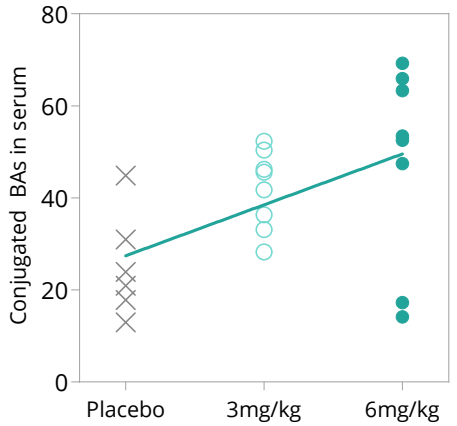
In serum, values represent each individual AUC (in serum from 0-12h) on Week 5 (µmol/L x h). In urine, represented total amount cleared 0-24h on week5 (nmol/L x h). Pearson correlation calculated and significance indicated. Post-hoc statistical analyses.
N=22 (n=6 Placebo, crosses; n=8 Cohort 1 | 3mg/kg, circles; n=8 Cohort 2 | 6mg/kg, dots); 4 doses AX-0810; GalNac conjugation; Subcutaneous

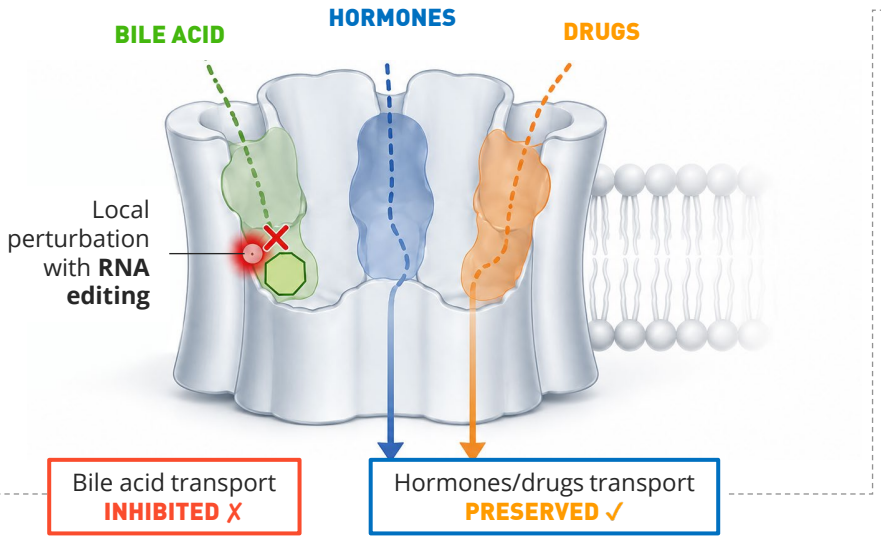
AX-0810 only edits NTCP's bile acid function

Increase in conjugated bile acids in circulation

Serum conjugated BAs

r= 0.53, p = 0.012

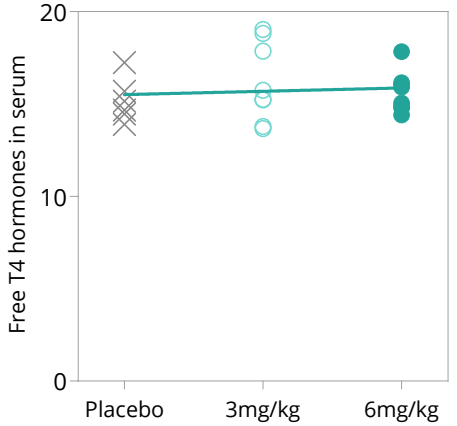




No change in hormone levels in circulation

Free T4 hormones

r= 0.15, p = NS



RNA editing is designed to modulate NTCP bile acid reuptake and maintain its other functions

- NTCP protein transports bile acids and hormones through distinct binding sub-pockets
- AX-0810 only edits the sub-pocket that transports bile acid, leaving the sub-pocket that transports hormones functional

AX-0810 Phase 1 clinical data demonstrates that hormonal levels are unchanged Important to maintain NTCP's other functions

- Mitigates thyroid dysfunction, growth and neurodevelopmental concerns associated with full NTCP inhibition
- Maintains normal drug metabolism
- Enables safer, longer-term therapy for chronic cholestasis patients

Conjugated BAs values represent each individual AUC (in serum from 0-12h) on Week 5 (µmol/L x h). Free T4 hormones values represent each individual at week 5 (pmol/L) NS, not significant. References: Ruggiero MJ, et al. J Biol Chem. 2021 Jan-Jun;296:100047; Park JH, et al. Nature. 2022 Jun 30;606(7916):1027-1031; Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-7222.

AX-0810 FIH trial confirmed target engagement

AX-0810 Phase 1

- AX-0810 achieved its pharmacodynamic objectives – concordant, statistically significant, dose-dependent target engagement across 3 predefined biomarkers:
  - Up to 8-fold increase in total bile acids in serum
  - TUDCA and conjugated bile acids confirmed NTCP specificity
- AX-0810 demonstrated favorable safety and tolerability profile to date
- Subcutaneous AX-0810 showed expected pharmacokinetics, half-life 8-weeks
- Hepatotoxic conjugated bile acids redirected away from the liver and excreted through urine

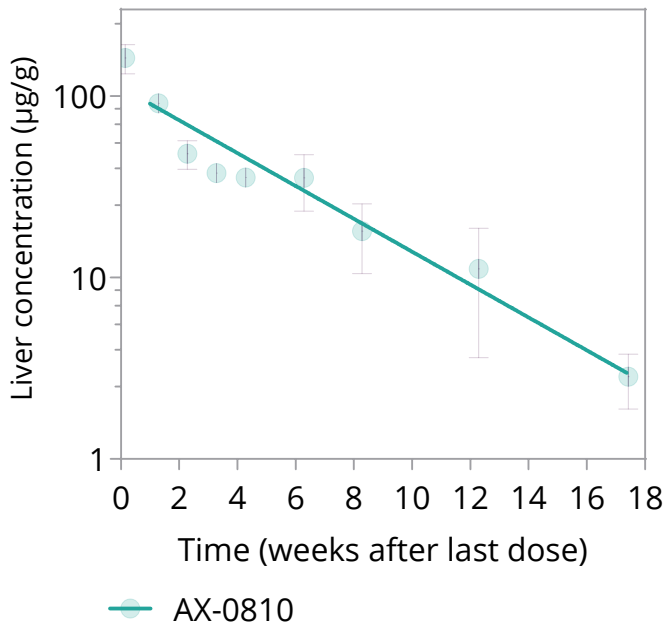
Next steps

- AX-0810 Cohort 3 data and 12-week follow-up data expected by year-end 2026
- Initial Phase 1 clinical data will be generated with AX-0811 in healthy volunteers by early January 2027

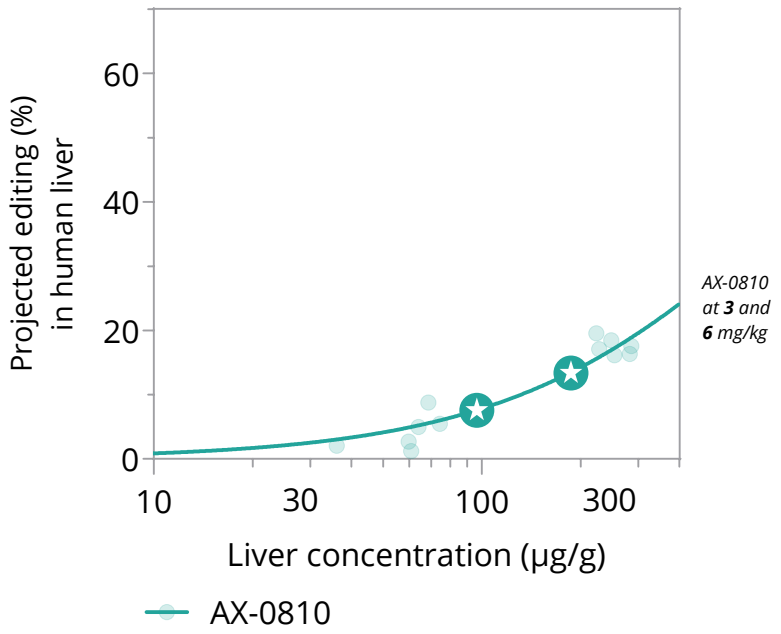
PK half-life based on available data (3mg/kg)

AX-0810 PK predicts 10-15% editing in humans

AX-0810 liver concentration in NHP



AX-0810 projected editing in human liver based on liver concentration

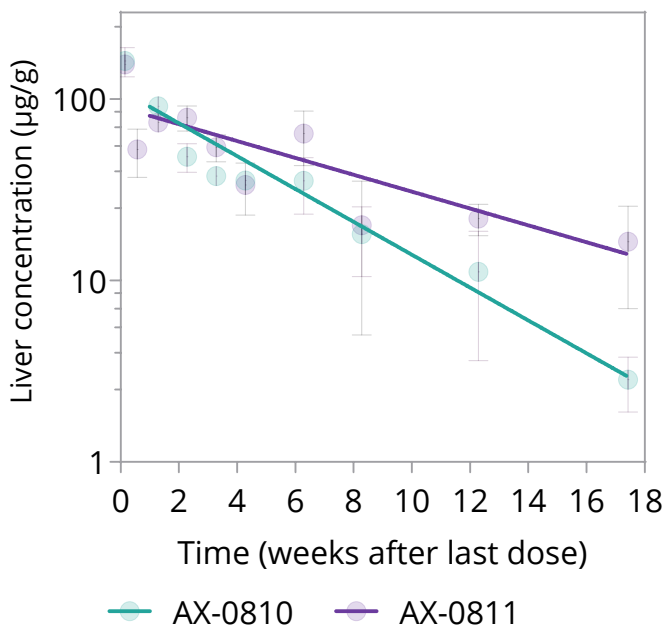


Human AX-0810 PK correlation to preclinical data suggests **3 and 6mg/kg** doses achieve **10 and 15% editing** in human, respectively.

Treatment conditions: left, NHP treated with SC administration of AX-0810 2mg/kg at D1, D3 and D5. n=4 - sparse sampling ; right, humanized mice treated with SC administration of AX-0810 at 50 mg/kg, 1-13x doses, n=12, HPLC

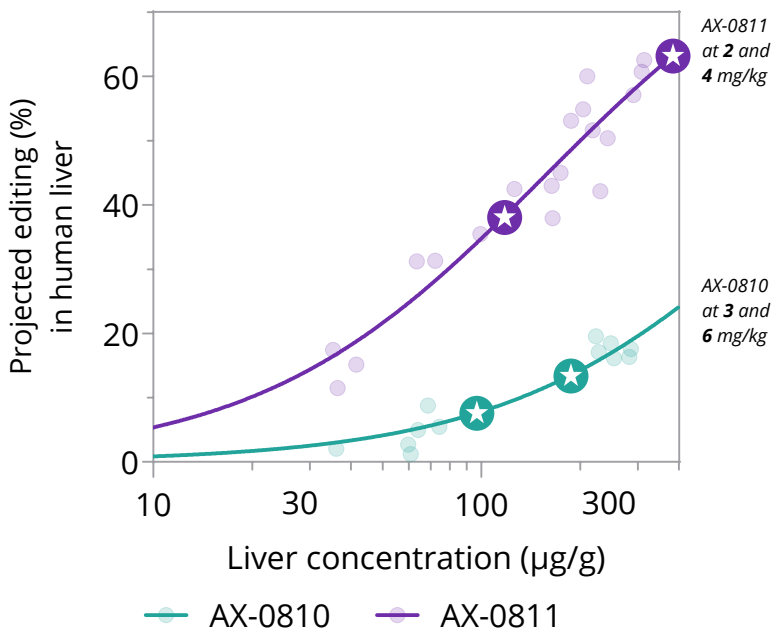
AX-0811 projected to achieve up to 65% editing

AX-0810 and AX-0811 liver concentration in NHP



AX-0811 has 1.6-fold longer half life

AX-0810 and AX-0811 projected editing in human liver based on liver concentration



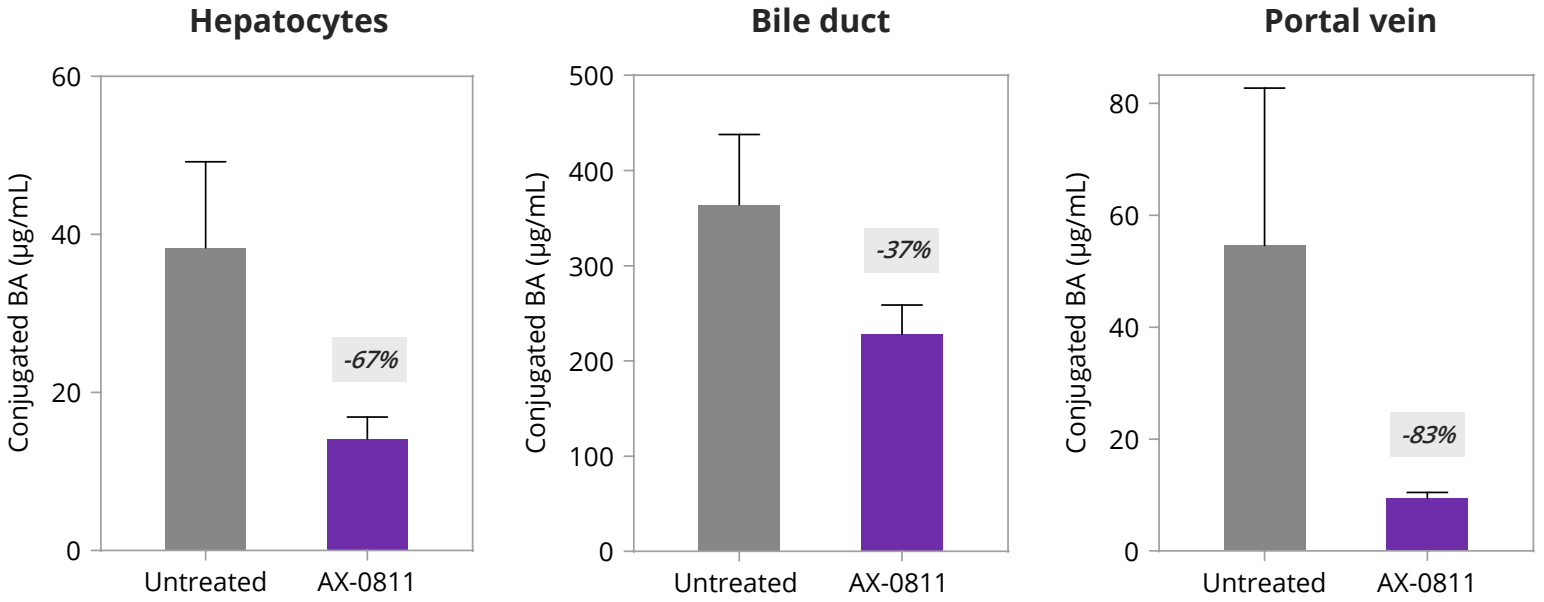
AX-0811 has >4x greater potency *in vivo*

- Based on the AX-0810 human PK correlation, AX-0811 PK modeling predicts **40 and 65% editing in human** at doses of **2 and 4 mg/kg** respectively
- AX-0811 is projected to have
  - 3+ month half-life
  - lower dose levels
  - less frequent dosing

Treatment conditions: left, NHP treated with SC administration of AX-0810 2mg/kg at D1, D3 and D5 or AX-0811 2 mg/kg at D1, D4 and D7. n=4 per treatment - sparse sampling; right, humanized liver mice treated with SC administration of AX-0810 at 50 mg/kg, (1, 4 and 13 injections) and 30 mg/kg (10 injections), n=12, HPLC, and AX-0811 at 3.75 - 30 mg/kg (8 injections), n=19, hECLIA. PK half-life based on available data (3mg/kg)

AX-0811 improved cholestasis *in vivo*

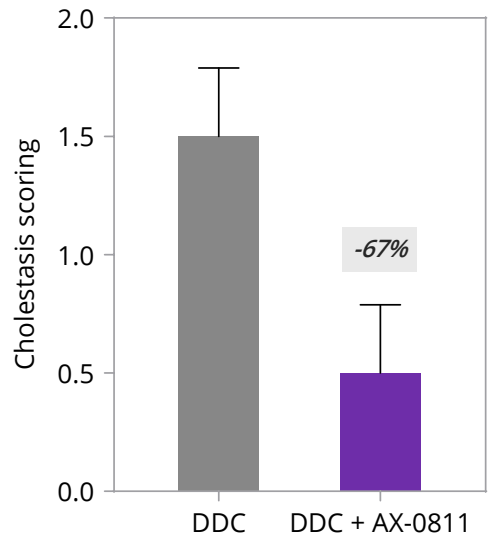
AX-0811 REDUCED BILE ACID UPTAKE THAT DRIVES LIVER TOXICITY



AX-0811 led to >60% decrease in periportal bile acid uptake

Lower intrahepatic load reduced downstream bile acid levels

AX-0811 IMPROVED CHOLESTASIS

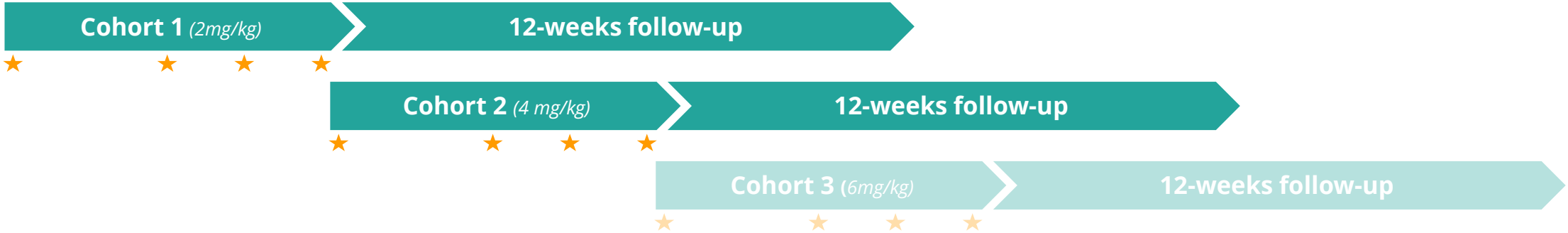


AX-0811 improved cholestasis by ~67% in cholestatic animals

Conjugated bile acid (BA) reported is relative quantification of taurocholic acid (TCA) compared to internal standard, the primary substrate for NTCP-mediated hepatic uptake in mice, and is consistently detected above the quantification threshold, enabling reliable spatial measurements across the porto-central axis. Treatment conditions: left 3 graphs, humanized mice treated with SC administration of AX-0811 at 30 mg/kg, 10 doses, n=2, Maldi MS Imaging, Mean, SEM; Right, Humanized mice treated with SC administration of AX-0811, 30 mg/kg, 12 doses, n=4, D31, Mean, SEM

AX-0811 FIH Phase 1 study

Multiple ascending dose (MAD) N=33 healthy volunteers (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-0811 GalNAc conjugated editing oligonucleotide

Objectives

- Assess safety, tolerability, and PK of AX-0811
- Confirm target engagement as measured by biomarkers

Key biomarkers of target engagement

- Bile acids profile
- TUDCA challenge
- Change in bile acid levels

Dosing underway

- Initial target engagement data expected by early January 2027

CTA, Clinical Trial Application; DMC, Data Monitoring Committee; FIH, First in Human; MAD, Multiple Ascending Dose; PK, Pharmacokinetics; TUDCA, Tauroursodeoxycholic acid

AX-0811 summary & next steps

AX-0811 preclinical data demonstrated robust profile on biomarkers and cholestasis

- 4-fold more potent compared to AX-0810 in preclinical animal models
- Led to 60% editing *in vivo* in animal models
- Reduced cholestasis by 67% in cholestatic disease animal model
- Reduced periportal uptake of bile acids in preclinical animal models
- AX-0811 half-life in human projected to be 3+ months

Expected next steps

- Reporting initial Phase 1 clinical data with AX-0811 in healthy volunteers by early January 2027
- IIT in pediatric biliary atresia patients with AX-0810 or AX-0811 to report initial data in H1 2027
- Phase 2 trial in biliary atresia with AX-0810 or AX-0811 expected to start in mid-2027

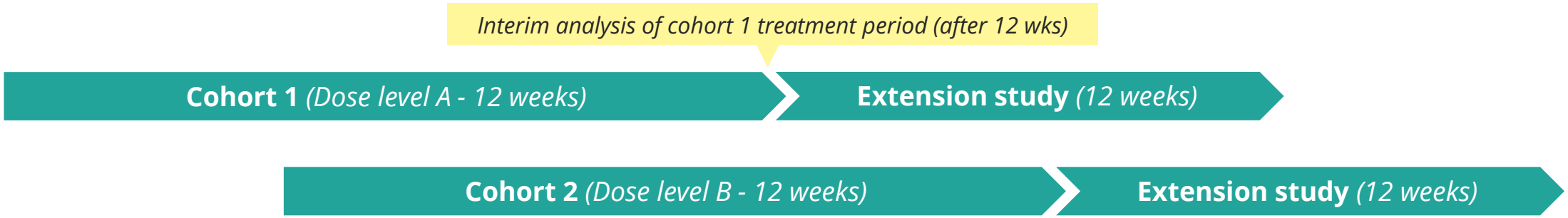
PK half-life based on available data (3mg/kg)

Biliary atresia as primary indication for AX-0810

BILIARY ATRESIA				
SEVERITY AND UNMET NEED	**BIOLOGICAL RATIONALE**	**CLINICAL DE-RISKING**	**CENTRALIZED CARE**	**REGULATORY PATHWAY**
Leading cause of pediatric liver transplantation and no approved therapies	AX-0810 targets the key driver of liver injury in the disease	No comorbidities and limited confounding factors	Patients concentrated in specialized centers	Pediatric guidance and orphan designation potential

Biliary atresia Investigator-Initiated Trial (IIT)

Multiple ascending dose (MAD) *N=10 (5 patients in each dose level); open label, comparison with external natural history data*



DMC safety reviews before proceeding to next dose and dose escalation is sequential during the dosing phase

Treatment

AX-0810 or AX-0811 GalNAc conjugated editing oligonucleotide

Objectives

- Assess safety, tolerability and PK of AX-0811
- Assess PD signal as measured by parameters related to liver health

Key endpoint

Improvement of liver health parameters

- Liver function
- Fibrosis biomarkers
- Bile acid biomarkers
- liver-related clinical events

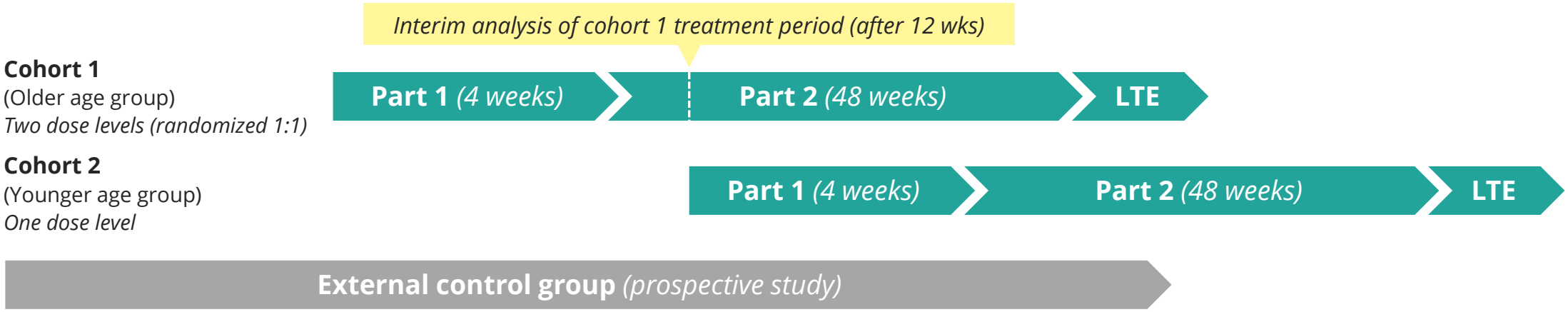
Target population

- Children 5–11 years with biliary atresia post-Kasai with native liver
- Active disease enrichment (e.g., abnormal liver enzymes, presence of liver fibrosis, and abnormal bile acids level)

DMC, Data Monitoring Committee; MAD, Multiple Ascending Dose; PK, Pharmacokinetics; PD, pharmacodynamic

Preliminary phase 2 trial design in biliary atresia

Randomized, open-label, adaptive design study with external control group *(up to 24 months old)*



Sample size: 60 subjects in total; dosing frequency to be determined based on PK/PD modeling and extrapolation from early phase studies; DMC to evaluate the safety, dose selection and transition to younger cohort

Target population

BA patients post-Kasai procedure, excluding those with decompensated liver disease or prior liver transplantation.

Objectives (Part 1)

Assess safety, tolerability and PK of AX-0810 or AX-0811 to identify age-appropriate dose level.

Potential registration enabling (Part 2)

Assess efficacy of AX-0810 or AX-0811 as measured by combination of clinical outcomes and biomarkers. Subject to alignment with health authorities.

BA, Biliary atresia; DMC, Data Monitoring Committee; LTE, Long-term evaluation; PK, Pharmacokinetics; PD, pharmacodynamic

AX-0422 RNA editing therapy

to address Hurler Syndrome

HURLER SYNDROME

- Most severe form of MPS I
- Early onset, multi-symptom disease
- Progressive deterioration, high morbidity
- Current therapies do not address all comorbidities and have limitations

IDUA DEFICIENCY

- W402X mutation (**c. 1205G>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; MPS I: Mucopolysaccharidosis type I. 1Baldo G, et al, 2018, https://doi.org/10.1111/cge.13224

Increases in IDUA enzymatic activity drive meaningful clinical impact

Severity →

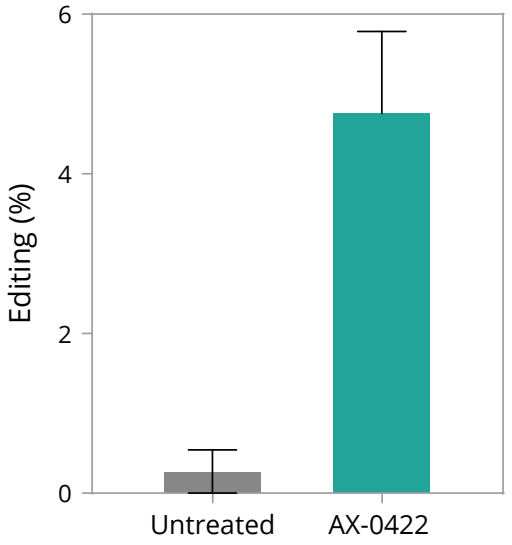
	Scheie	Hurler-Scheie	Hurler
Diagnosis	Teens	Childhood	< 18 months
Life expectancy	Normal	20 yo	10 yo
Enzymatic activity in fibroblasts (% of WT)[1]	***0.8%***	***0.3%***	***0.2%***

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

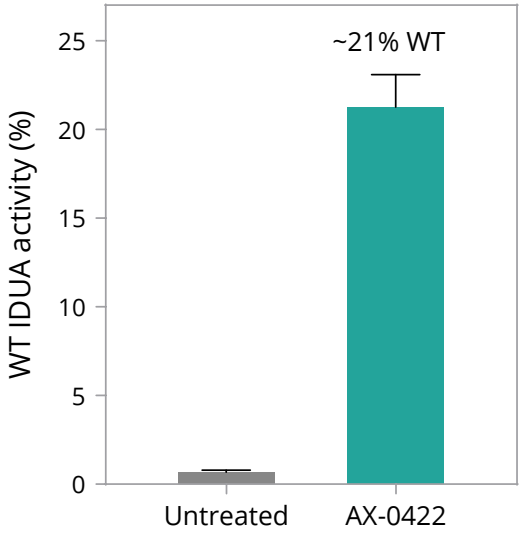
[1]Oussoren E, et al. Mol Genet Metab. 2013 Aug;109(4):377-81; [2]Kakkis ED, et al. N Engl J Med. 2001 Jan 18;344(3):182-8.

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

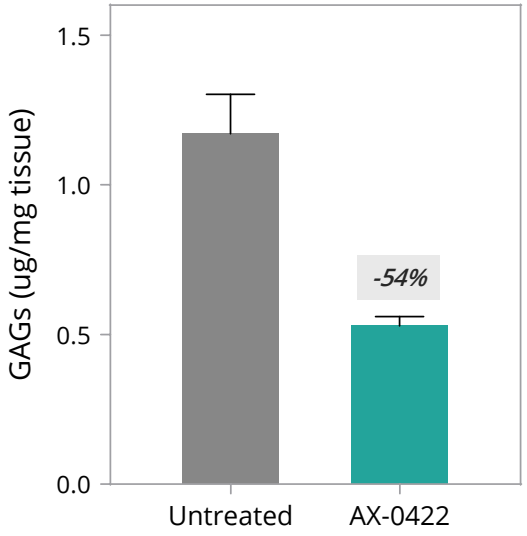
RNA Editing of *Idua in liver*[1]



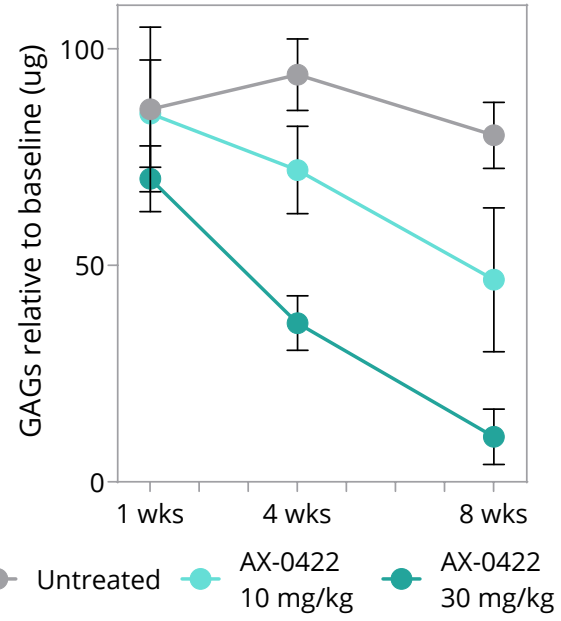
Liver IDUA enzymatic activity[1]



Liver GAGs levels[1]



Urine GAGs levels[2]



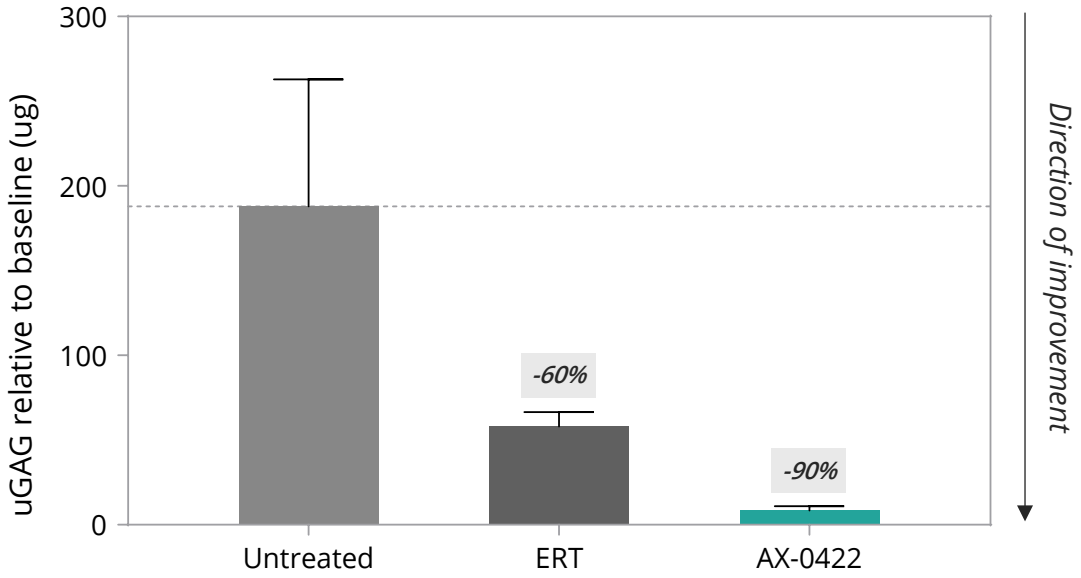
Following SC delivery, targeted editing of the nonsense mutation restores ~21% IDUA activity, driving substantial liver GAG reduction and dose-dependent normalization of urinary GAGs - **supporting potential for disease-modifying benefit**

[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

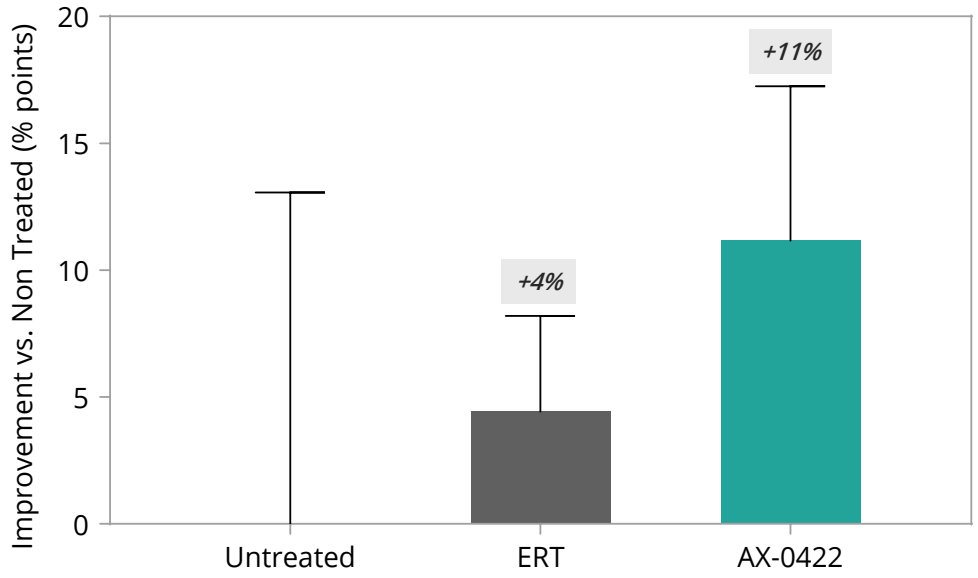
AX-0422 shows differentiated activity vs standard of care in *Idua* mouse model

Greater biomarker reduction and functional improvement vs ERT

Urine GAGs levels at 8 weeks[1]



Hang Test at 10 weeks[1]



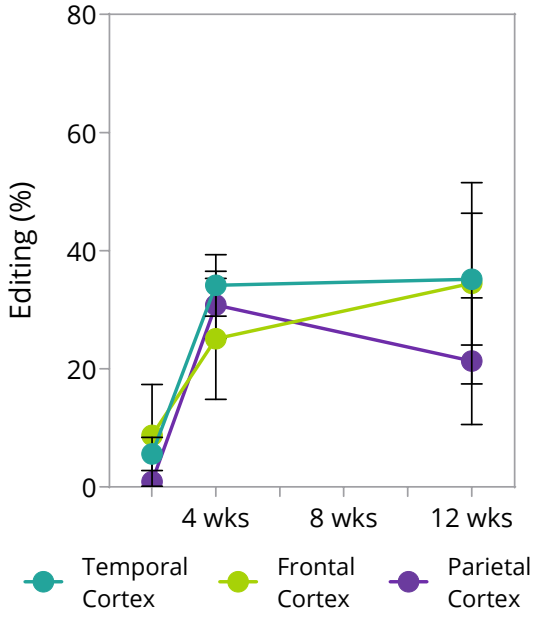
AX-0422 delivers reduction in urinary GAGs compared to ERT, approaching biomarker normalization

AX-0422 shows improvement in motor skills test compared to ERT

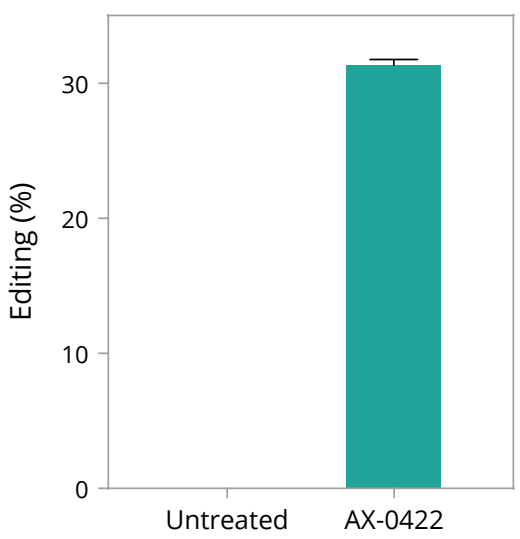
[1]Idua-W392X mice, AX-0422 surrogate treatment: SC, 30 mg/kg, ERT (Laronidase) treatment: IV, 0.58 mg/kg, Q1W until 4 wks, n=12, mean, SEM

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

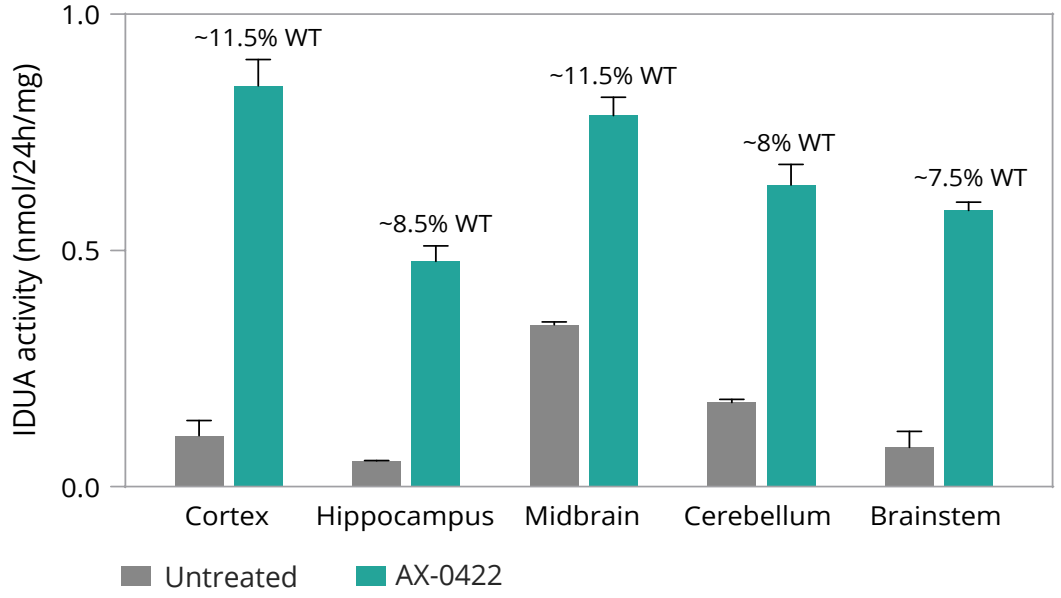
Sustained RNA editing of ACTB in cortex of NHP[2]



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



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

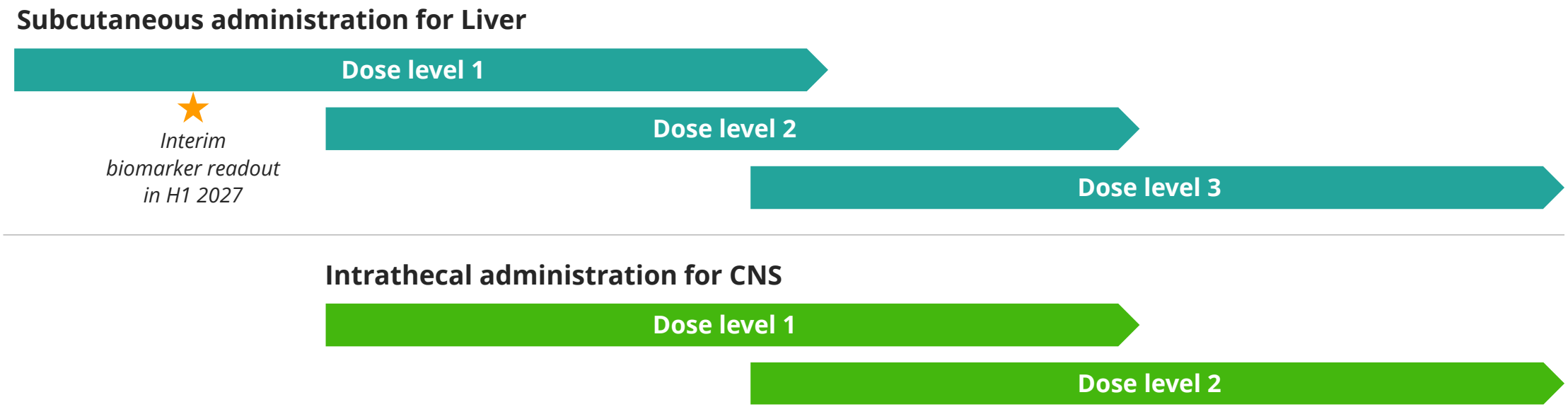


- Axiomer results in sustained CNS editing of up to 12 weeks (single dose, NHP)
- Following ICV delivery, efficient editing in Hurler disease model leads to broad enzyme restoration across brain regions (~7–12% of WT)
- Levels consistent with disease-modifying potential in Hurler syndrome

[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 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-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; 5Chen, Yunzhi et al, 2020

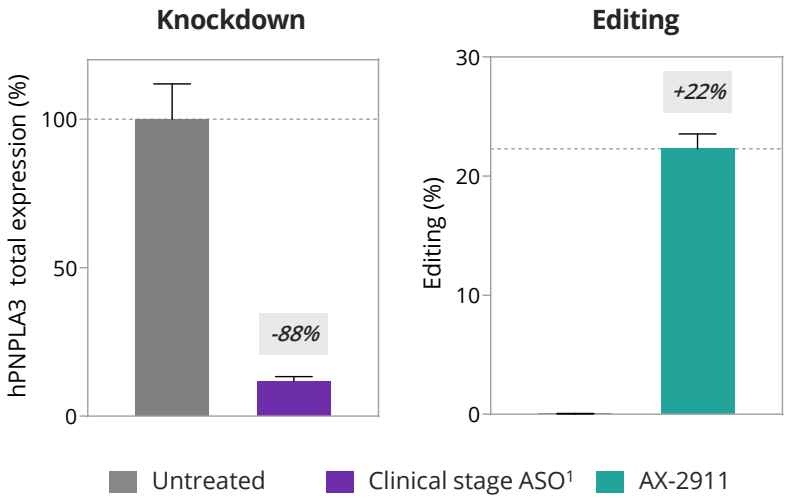
Editing has functional advantage over knockdown

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

mRNA

hPNPLA3 I148M humanized mouse liver model[1]

dPCR (Qiagen), AVG±SEM



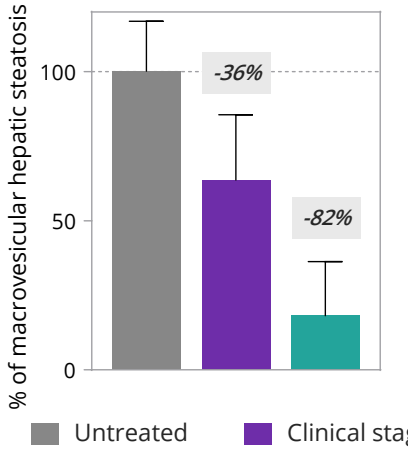
Clinical-stage ASO[2]: **~89%** mRNA reduction via knockdown of *hPNPLA3*

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

LIVER FUNCTION *(steatosis)*

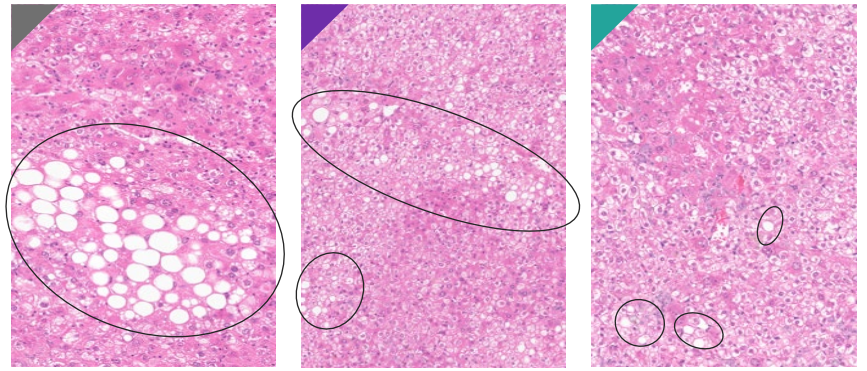
Macrovesicular steatotic incidence scoring[1] (%)

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

AX-2911 development strategy

Exploring an Investigator-Initiated Trial (IIT) in China

OBJECTIVE

Generate early proof-of-concept in patients

De-risk the program and inform development strategy

ACCELERATED APPROACH

Parallel preparation for global CTA/IND development

EXPECTED TIMELINE

FIH in H1 2027

Interim readouts to guide next steps

PNPLA3 driven MASH Investigator-Initiated Trial (IIT)

Multiple ascending dose (MAD) *N=12 (6 patients in each dose level); open label,*

Interim analysis of cohort 1 treatment period (after 6 wks)

Cohort 1 *(Dose 300mg - 24 weeks)*

Cohort 2 *(Dose 500mg - 24 weeks)*

DMC safety reviews before proceeding to next dose and dose escalation is sequential during the dosing phase

Treatment

AX-2911 GalNAc conjugated editing oligonucleotide

Objectives

- Assess safety, tolerability and PK of AX-2911
- Assess PD signal as measured by parameters related to liver health

Key endpoint

Improvement of liver health parameters and fat reduction

- Liver function
- Decrease in liver fat on MRI-PDFF
- Fibrosis biomarkers (ProC3, ELF score, Liver stiffness by VCTE)

Target population

- Adults with histological confirmation of MASLD/MASH (Lean and non-Lean)
- homozygous for PNPLA3 I148M (rs738409) as confirmed by genotyping at screening
- Liver fibrosis

Timing

- FIH in H1 2027

DMC, Data Monitoring Committee; MAD, Multiple Ascending Dose; PK, Pharmacokinetics; PD, pharmacodynamic

Summary & next steps

CLINICALLY VALIDATED PLATFORM WITH AN EXPANDING PIPELINE

Advancing wholly owned and partnered RNA editing programs across liver and CNS

- AX-0810 delivered first clinical validation of Axiomer with dose-dependent target engagement; next generation AX-0811 builds on this with greater potency, approx. 60% editing *in vivo* and disease modification in cholestatic models
- Wholly owned pipeline extends beyond NTCP to MPS I Hurler syndrome, PNPLA3-associated MASH
- Platform breadth further supported by Lilly collaboration and AI-enabled discovery capabilities

RICH CATALYST CALENDAR EXPECTED

NTCP

- AX-0810 Phase 1 Cohort 3 and 12-week follow-up full results: YE 2026
- AX-0811 initial HV data: early January 2027
- IIT initial data in Biliary Atresia patients: H1 2027
- AX-0810 or AX-0811 Phase 2 development expected to start: mid-2027 with IA: mid 2028

IDUA

- AX-0422 for MPS I Hurler syndrome initial human data: H1 2027

PNPLA3

- AX-2911 for PNPLA3 IIT: H1 2027

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IT'S IN OUR RNA