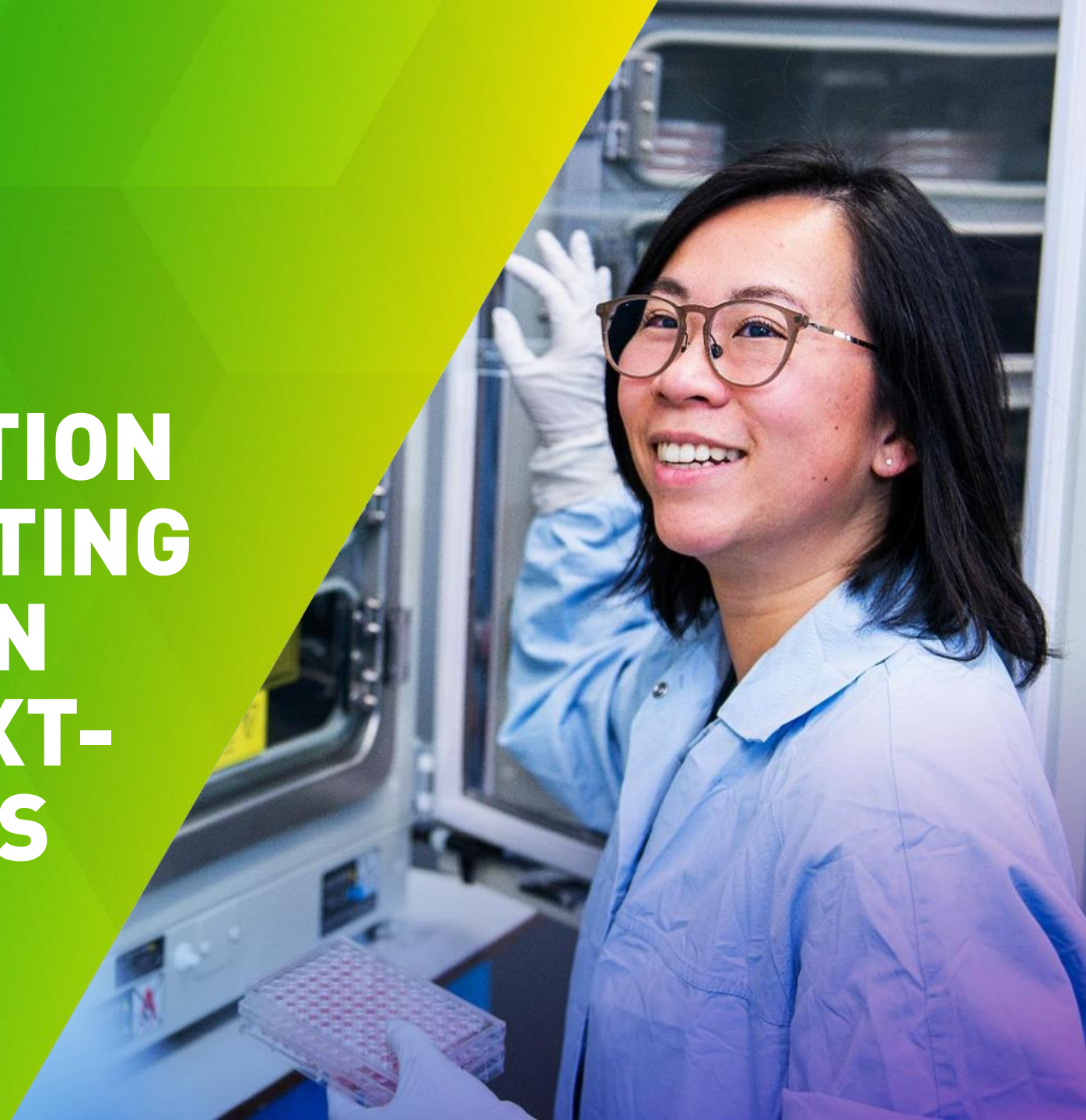
CLINICAL VALIDATION OF ADAR RNA EDITING AND TRANSLATION TO AI-DRIVEN NEXT-GENERATION EONS

Gerard Platenburg

TIDES Europe - Nov 3, 2026



Disclosure

- I am co-founder and current CSO of ProQR Therapeutics

Evolution of oligonucleotide drugs

Multiple single-stranded and siRNA approved drugs, RNA editing now in clinical development

	1998–2004	2013–2016	2018–2019	2020–2022	2023–2024	2025–2026
SINGLE-STRANDED OLIGONUCLEOTIDES						
RNase H ASOs Gapmers	• **fomivirsen** 1998	• **mipomersen** 2013	• **inotersen** 2018 • **volanesorsen** 2019		• **tofersen** 2023 • **eplontersen** 2023 • **olezarsen** 2024	• **donidalorsen** 2025 • **zilganersen** 2026 • **bepirovirsen** 2026
Splice modulation DMD exon skipping SMA exon inclusion		• **eteplirsen** 2016 • **nusinersen** 2016	• **golodirsen** 2019	• **viltolarsen** 2020 • **casimersen** 2021		
DOUBLE-STRANDED siRNAs			• **patisiran** 2018 • **givosiran** 2019	• **lumasiran** 2020 • **inclisiran** 2020 • **vutrisiran** 2022	• **nedosiran** 2023	• **fitusiran** 2025 • **plozasiran** 2025

RNA editing
2025-2026

ADAR-mediated A-to-I editing
Correct mutations or modulate protein function

Clinical-stage EONs (6 !)
WVE-006 / AX-0810 / AX-0811 / KRRO-121 / AIR-001 / RC001

First FDA or EU approval per molecule, including historical approvals. Other single-stranded approvals: pegaptanib 2004 / defibrotide 2013 / avacincaptad pegol 2023 / imetelstat 2024 / Status: 29 Oct 2026.

ProQR's Axiomer™ ADAR mediated RNA editing journey since 2022

2022	2023	2024	2025	2026	2027
ProQR pivots to solely focus on ADAR editing	ProQR demonstrates >50% editing in CNS and liver in NHP	First disease-relevant biomarker effect using Axiomer in NHP Initial clinical validation of ADAR editing	Platform expansion across liver, CNS and extrahepatic targets with translational models	AX-0810 Phase 1 clinical readout: dose-dependent target engagement and favorable profile	Initial clinical data from biliary atresia IIT (H1 2027) Phase 2 expected to start mid-2027
ProQR and Eli Lilly expand partnership to 10 targets worth ~$3.9B	ProQR announces pipeline targets in liver	AX-0810 enters clinical development and shows concordant target engagement across serum biomarkers	AX-0811 selected as next-generation NTCP lead based on 6-fold preclinical potency and longer projected duration	AX-0810 full Phase 1 results: December 2026 AX-0811 initial healthy-volunteer data: early January 2027	AX-0422 initial human data and AX-2911 IIT expected in 2027 NTCP Phase 2 interim analysis expected mid-2028

ADARs: Adenosine deaminases acting on RNA, EONs: Editing oligonucleotides

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 December 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

HIGH IMPACT PARTNERSHIP

ADVANCE AXIOMER PLATFORM

RUNWAY THROUGH MID 2028

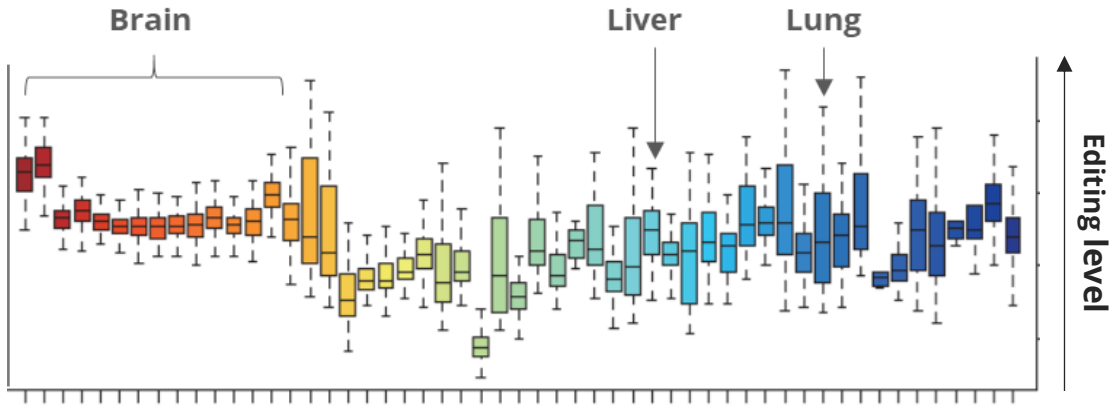
What is ADAR editing?

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 MEDIATED A-TO-I EDITING IN HUMAN TISSUES



Adapted from Tan et al. 2017 Nature 550:249-254

Known biological roles of A-to-I editing

- Recoding during the maturation of neurons
- Self vs. non-self discrimination
- Regulating genome stability
- Changing RNA processing (e.g., Splicing, miRNAs)

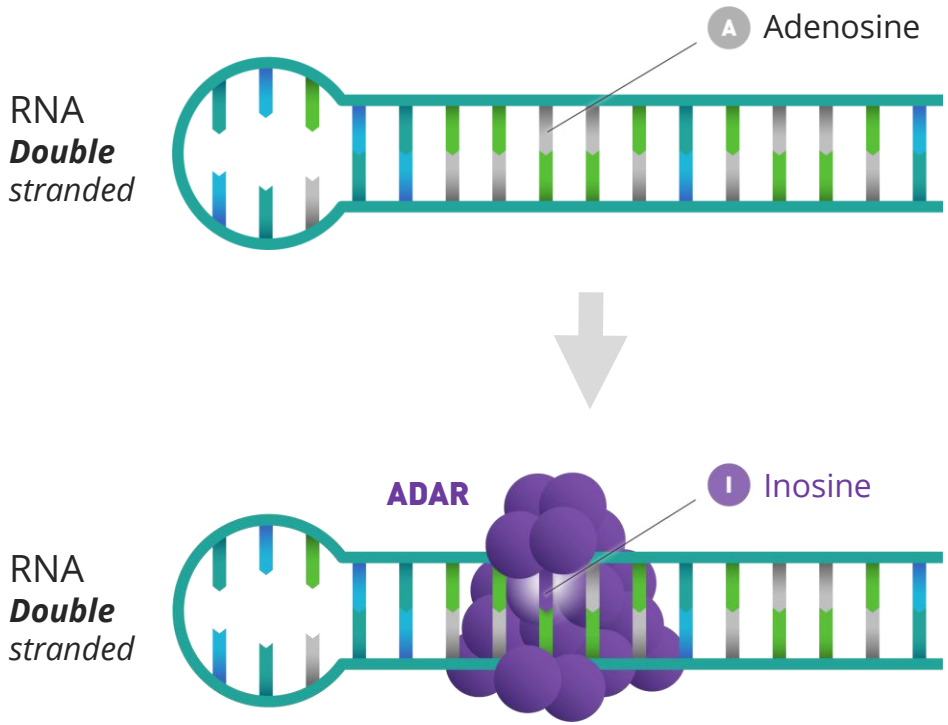
No sequence dependence

- 16 million A-to-I sites in the human transcriptome
- Extent of editing similar in most human tissues making therapeutic editing feasible in all disease areas

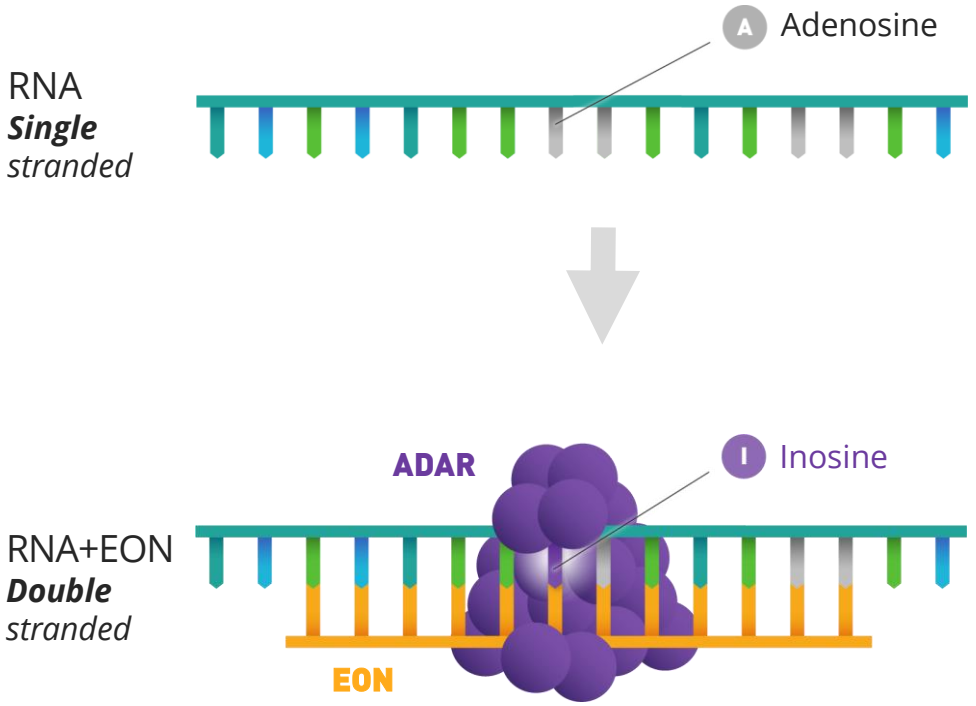
Axiomer™ EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

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

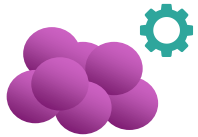
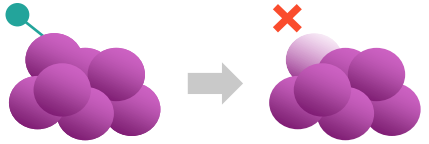


Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*



ADARs: Adenosine deaminases acting on RNA.

Creating a new class of medicines with broad therapeutic potential

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

ADAR RNA-editing platform technology

Versatile

- Ability to target multiple organs and a wide range of diseases with numerous applications
- Potential to include protective variants
- Designed to target a variety of RNA species (mRNA, miRNA, lncRNA)

Safety

- No permanent changes
- No irreversible DNA damages and less risk of permanent side effects

High specificity

- Highly targeted therapeutic with potential to minimize off-target effects and reduce the risk of adverse reactions

Transient

- Provide a long-lasting therapeutic effect that does not require frequent dosing
- Potential to target diseases for which permanent changes would be deleterious

No viral vector

- No risk of immunogenicity or capacity limitation due to the vector
- Efficient development and faster production increase the chance to reach market

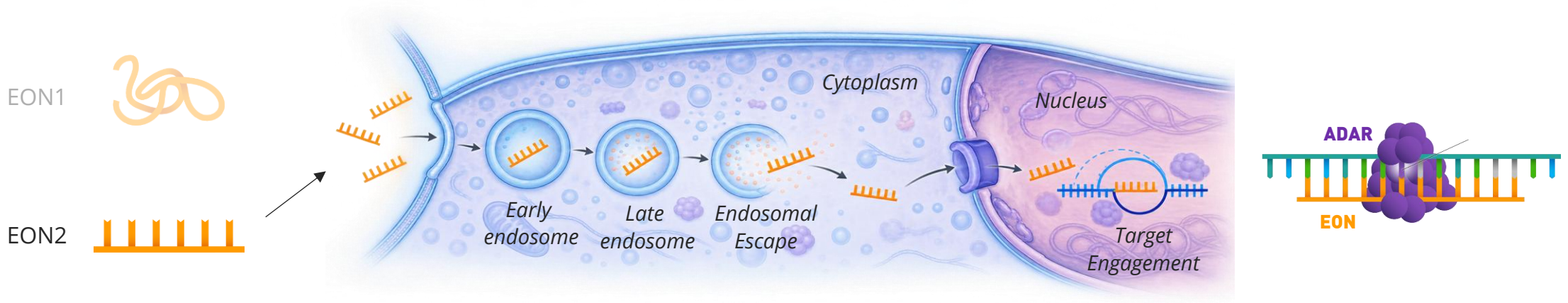
Endogenous ADARs

- Leverage body's potential to treat disease
- Less risk of off-target effect vs. exogenous ADARs

ADAR: Adenosine deaminase acting on RNA, mRNA: messenger RNA, miRNA: microRNA, lcRNA: long non-coding RNA

The EON journey: engineering productive RNA editing

CELLULAR UPTAKE	ENDOSOMAL ESCAPE	NUCLEAR ACCESS	TARGET ENGAGEMENT	ADAR MEDIATED EDITING
EON sequence and structure influences uptake efficiency	*EON design influences endosomal escape*	*Cytosol accessible EONs Can reach the nucleus*	*Nuclear accumulation Does not predict editing efficiency*	*Target mRNA editing occurs Co-transcriptionally*

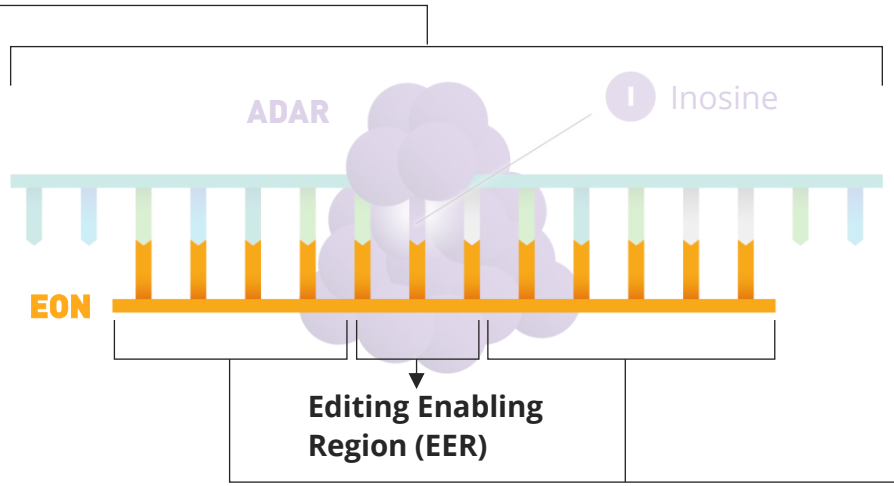


Editing depends on the full EON journey – rational design addresses each bottleneck to maximize productive editing

Driving the development of optimized EONs for therapeutic use

Sequence defines target
RNA binding and provides stability

EON total length
Between ~25 - 30 nt



ADAR-binding region (ABR)
Backbone modifications enable ADAR binding, and disable off-target editing

Optimized sequence and chemistry define functionality

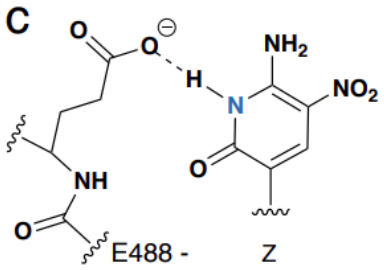
- Increase editing efficacy
- Bring metabolic stability
- Prevent off-target ('bystander') editing
- Ensure bioavailability (cell and tissue uptake)
- Offer safety and tolerability at therapeutic doses

ADAR: Adenosine deaminase acting on RNA, EON: Editing oligonucleotide, Nt: nucleotides

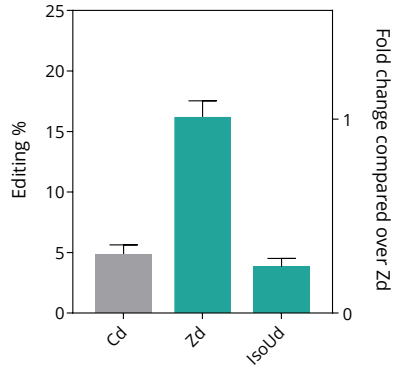
Leading research to optimize editing oligonucleotides for therapeutic use

MODIFICATION OF THE ORPHAN BASE

dZ in EER to increase ADAR activity

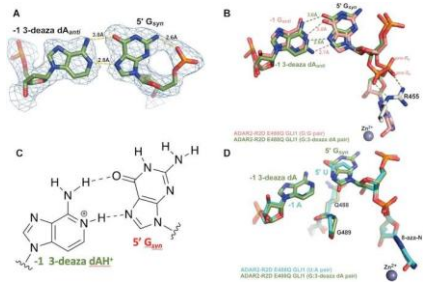


RNA editing of *Angptl3* in liver of C57BL/6JRj mice *SC, 1 µmol/kg, 3x dose (D0, D2, D4), N=4, Necropsy D7, dPCR analysis, mean, SEM*

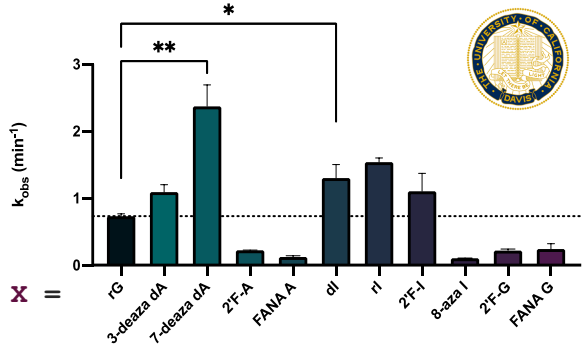


MODIFICATION OF THE BASE OPPOSITE TO 5'G

3-deaza-dA in EER to increase editing activity in 5'G unfavorable context



***In vitro* deamination kinetics for ADAR2 and duplex RNAs derived from *hMECP2* R255X** *10nM hybrid, 100nM ADAR2, 3 technical replicates, mean, SD. Two-tailed Welch's t test, *p<0.05, **p<0.01*

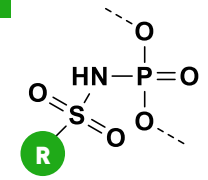


LINKAGE MODIFICATIONS IN THE ABR

PN and PMe linkages in the ABR to increase stability, EON liver concentration and target engagement

Phosphoroamidate linkage

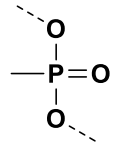
PN



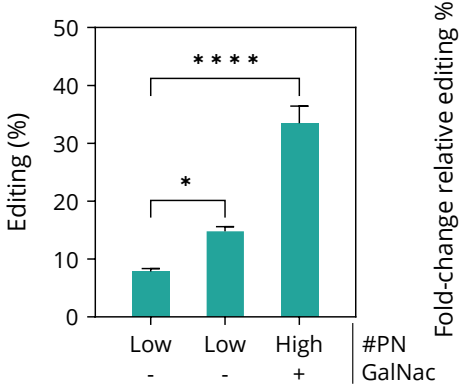
R = Me: Mesyl-PN

Methylphosphonate linkage

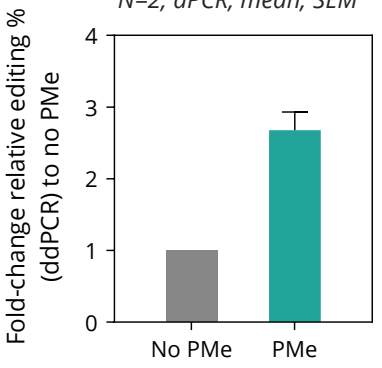
PMe



RNA editing of *ActB* in liver
C57Bl/6J mice, 7d, 3x10mg/kg, SC, N=4, dPCR, mean, SEM



RNA editing of *APP* in HepG2 cells
Gymnosis, 5d, 5µM single dose, N=2, dPCR, mean, SEM



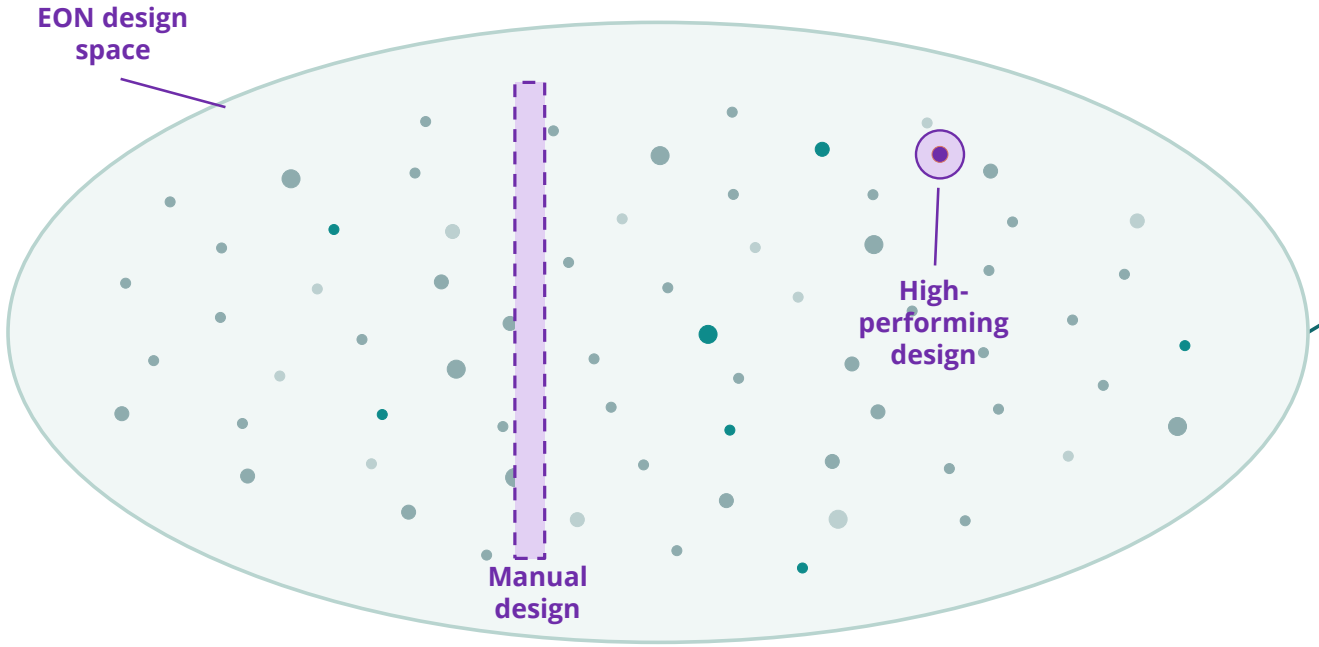
Adapted from Doherty EE, et al. Nucleic Acids Res. 2022;50(19):10857-10868. Statistical significance between groups was determined using one-way ANOVA with Tukey's multiple comparisons test or an unpaired t-test with Welch's correction; **P < 0.01; ***P < 0.001; ****P < 0.0001.

EON design space is too large for manual optimization

AI-guided HTS makes the EON design space searchable

MANUAL DESIGN, LOW-TRHOUGHPUT SCREEN

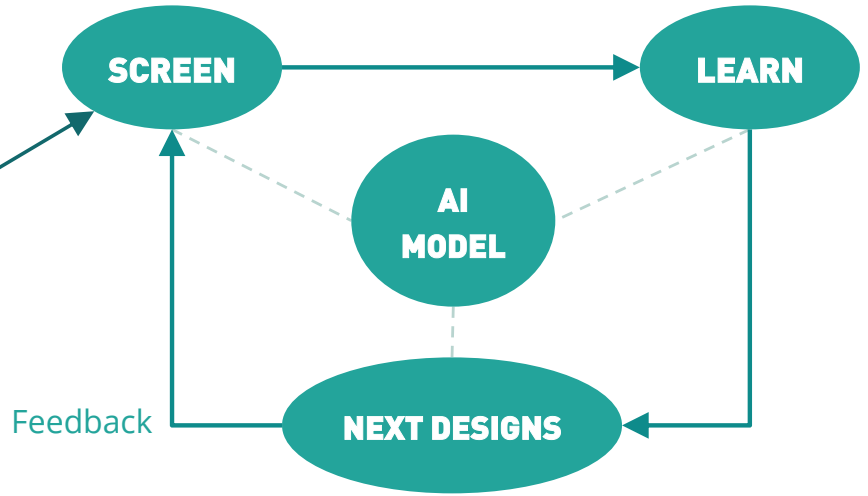
~10^{45} possible designs: target specific sequence, length, symmetry, chemistry



Manual optimization likely to miss the best candidates

AI DRIVEN DESIGN, HIGH-TROUGHPUT SCREEN

Systematic model-guided iteration

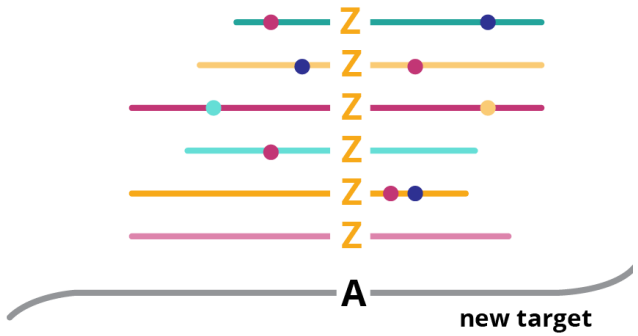


Expand the explored design space

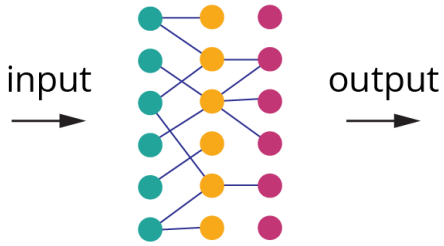
AI/ML-guided EON design accelerates discovery

Experimental data guide AI toward higher-performing EON designs

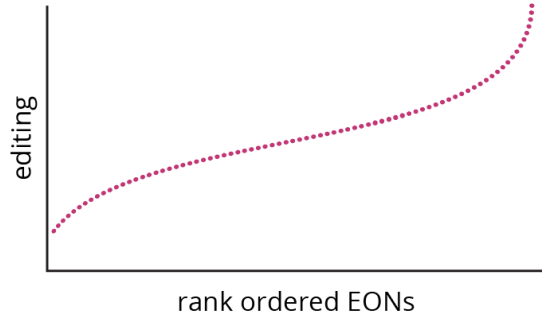
systematic GRID HT screen



AI/ML driven EON optimization



AI/ML optimized EONs - input for next AI/ML iteration

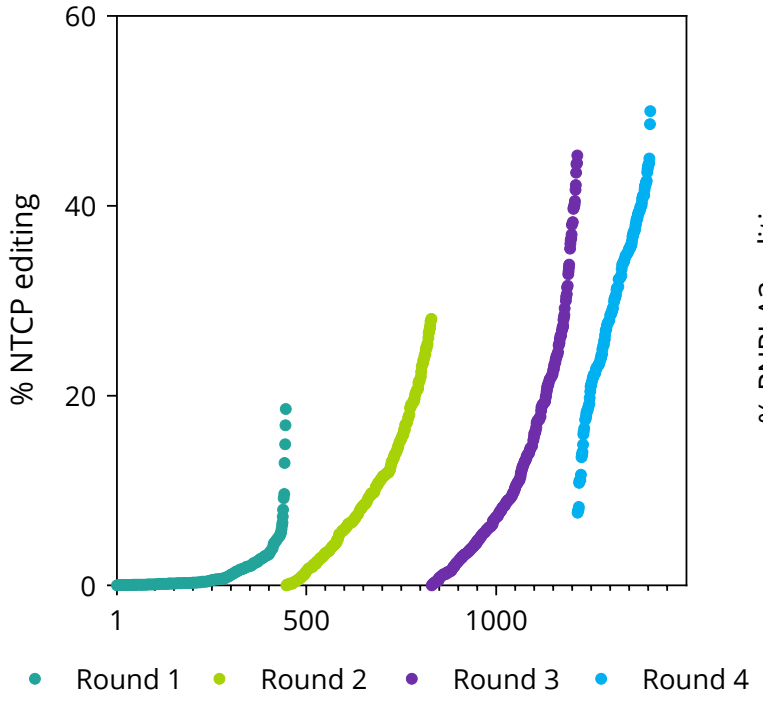


EXPLORE	LEARN	EXPLOIT
Structured diversity based on proprietary data: better variability and representation of EON designs	Experimental results identify which features correlate with editing, stability and safety readouts per target	AI proposes next-generation EONs predicted to improve performance and avoid liabilities

Successful optimization of EON design across liver and CNS targets

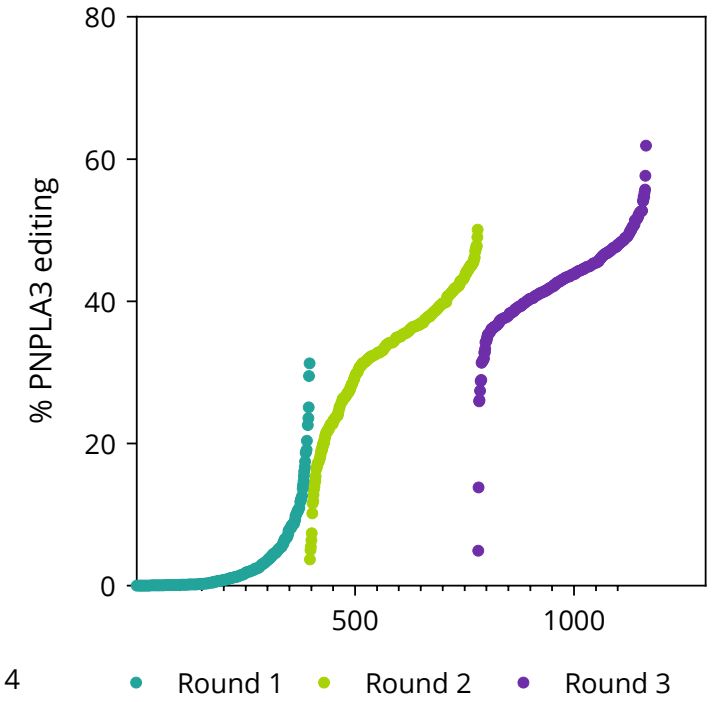
NTCP editing in PHH

Gymnosis, PHH, 5µM, 72h, N=2 biological, seed & treat, dPCR analysis (QiAcuity), AVG



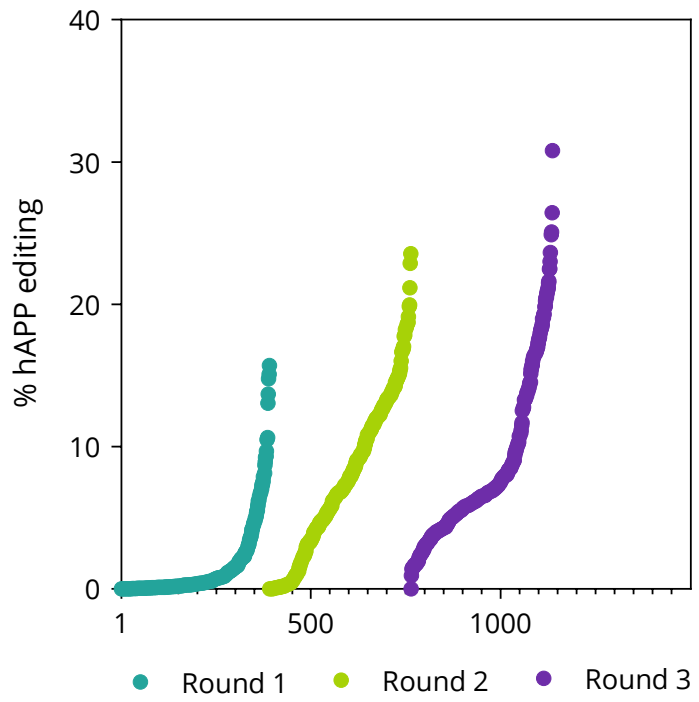
PNPLA3 editing in PHH

Gymnosis, PHH, 5µM, 72h, N=2 (biological, seed & treat, dPCR analysis (QiAcuity), AVG



APP in forebrain neurons

Gymnosis, iPSC neurons, 5µM, 1-week washout, N=1, dPCR analysis (QiAcuity), AVG



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 variants reduced bile acids uptake into liver in health population research

Healthy population discovered with NTCP variants that reduces bile acids uptake into liver[1-4]



Ethnicity-dependent Polymorphism in Na+-taurocholate Cotransporting Polypeptide (*SLC10A1*) Reveals a Domain Critical for Bile Acid Substrate Recognition*

Richard H. Ho‡§¶, Brenda F. Leake‡, Richard L. Roberts‖, Wooin Lee‡, and Richard B. Kim‡**

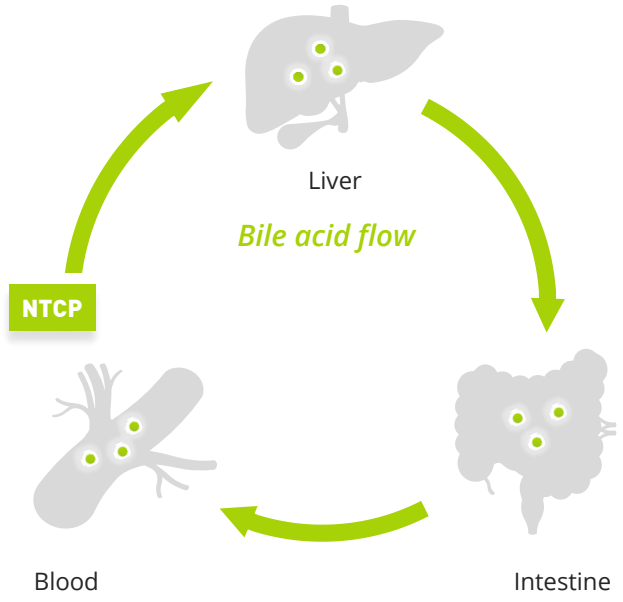
d D Viruses and Bile Salts
on Molecular Determinants on Sodium
Polypeptide

[1]Salhab A, et al. Gut. 2022 Jul;71(7):1373-1385; [2]Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-22; [3]Vaz FM, et al. Hepatology. 2015 Jan;61(1):260-7; [4]Schneider AL, et al. Clin Res Hepatol Gastroenterol. 2022 Mar;46(3):101824; [5]Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069; [6]Cai SY, et al. JCI Insight. 2017 Mar 9;2(5):e90780.

NTCP RNA editing redirects toxic bile acids away from the liver

HEALTHY LIVER

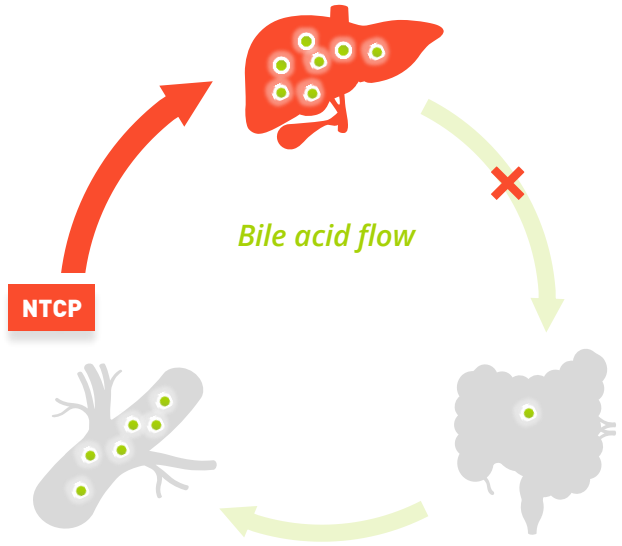
BAs homeostasis



Bile acids (BAs) homeostasis and recycling in the enterohepatic cycle

BILIARY ATRESIA

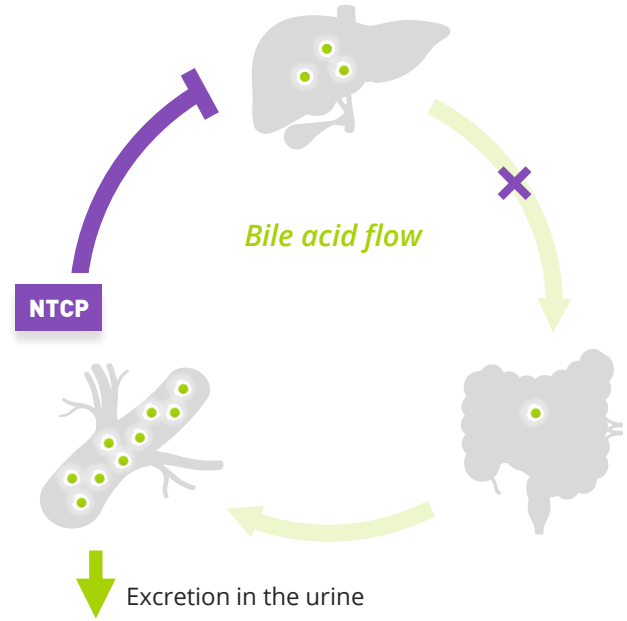
Toxic BAs lead to intrahepatic cholestasis



Deterioration of liver health biomarkers (increase in ALT, AST, GGT, bilirubin, INR), fibrosis biomarkers and negative clinical outcomes

NTCP MODULATION *with RNA editing*

Decrease in toxic BAs in liver



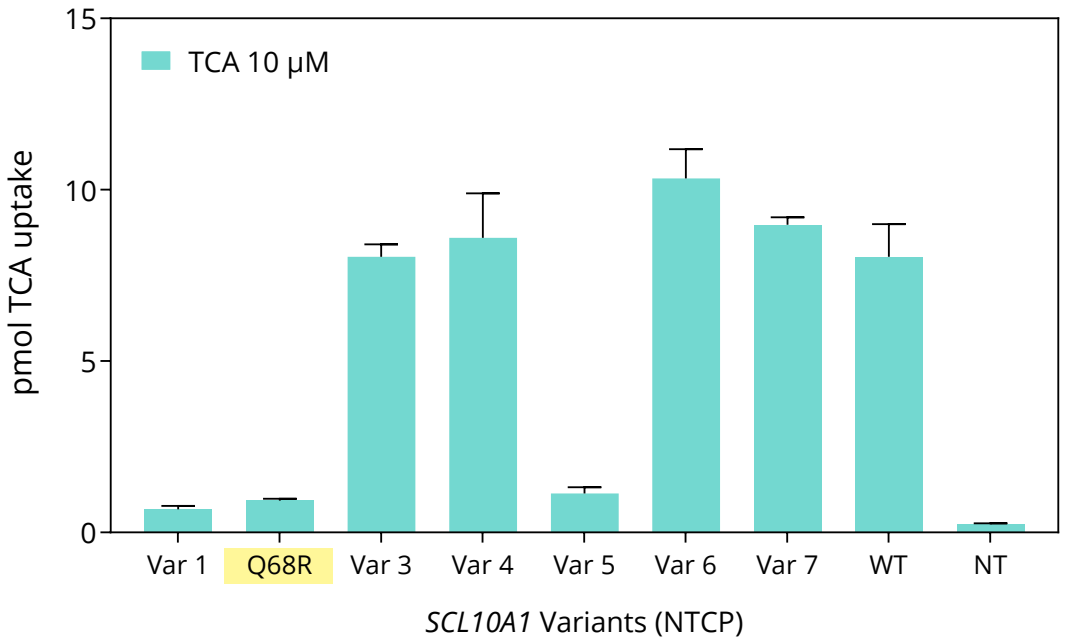
Improvement in liver health biomarkers
Positive clinical outcomes

Analysis of NTCP variants reveal a path to selective bile acid transport reduction

In silico analysis of 7 *SCL10A1* variants

Variants	Effect	
Variant 1	Probably effect	
Variant 2 (Q68R)	Probably effect	← *Lead variant*
Variant 3	Likely benign	
Variant 4	Likely effect	
Variant 5	Probably effect	
Variant 6	Likely effect	
Variant 7	Likely effect	

^{3}H-TCA uptake in transiently transfected U2OS cells



Model the NTCP-bile acid interaction

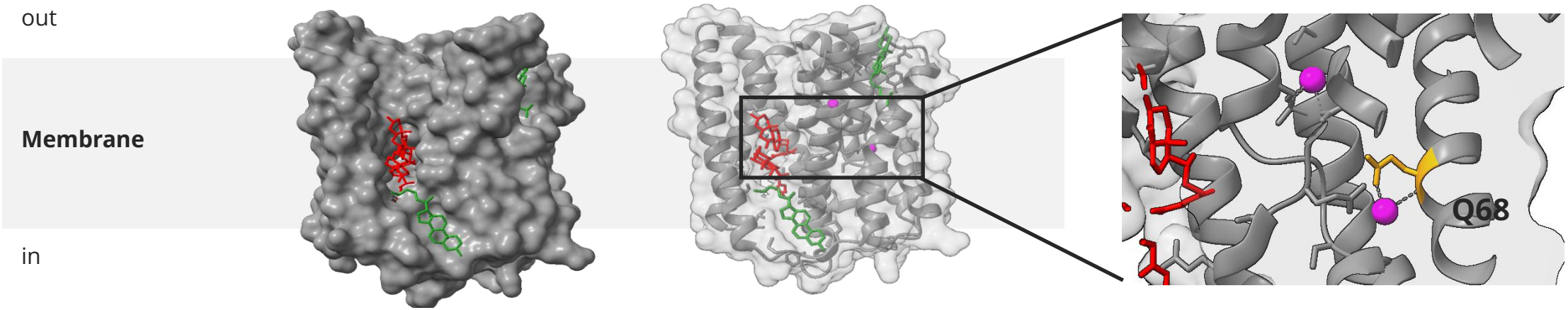
Rank variants by predicted transport impact

Advance the strongest candidates to in vivo testing

Best candidate: selective BA transport reduction

NTCP Q68 an amino acid of interest located in the Na^+ binding pocket

Structure of the human sodium/bile acid cotransporter (NTCP) and position of Q68 in the Na binding pocket

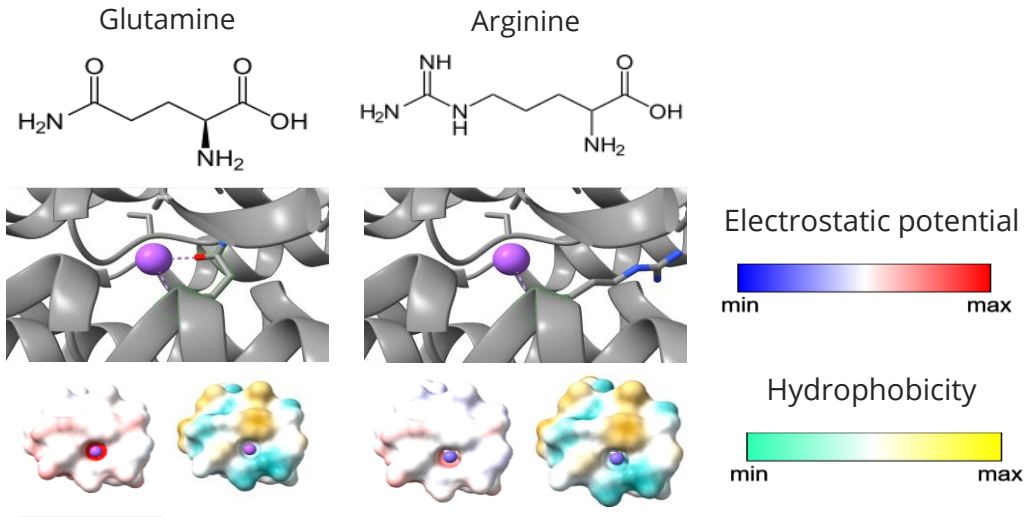


NTCP Q68 is located inside of a Na^+ binding pocket, and an amino acid change can indirectly affect NTCP function by altering the precise geometry required for Na^+ binding

BAs: Bile acids, NTCP: Na-taurocholate cotransporting polypeptide.

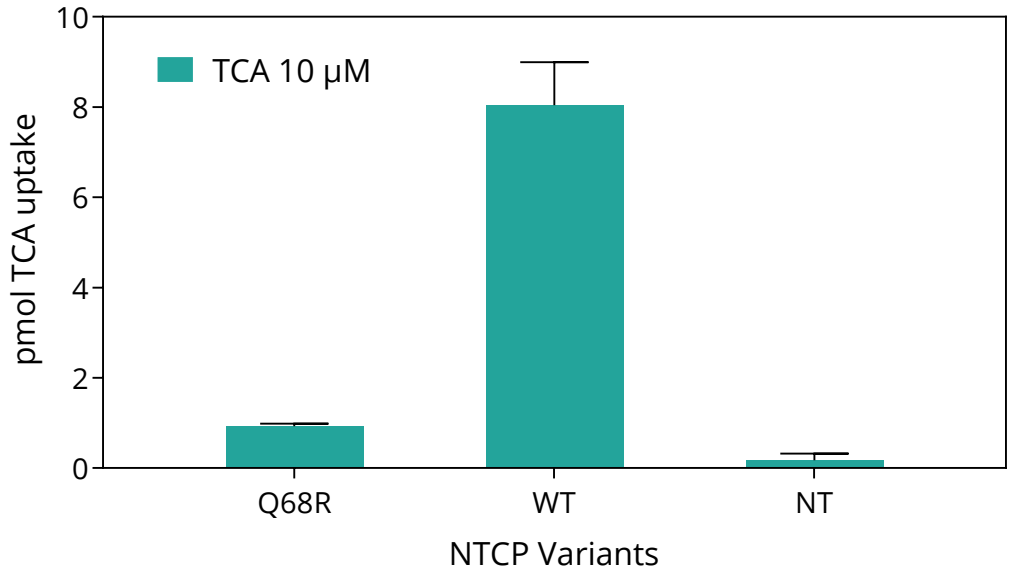
Introducing the Q68R variant leads to lowering of bile acids re-uptake

3D Model of Q68R variant impact on Na^+ binding pocket of NTCP



BAs uptake (TCA) *in vitro

n=3, mean±SEM



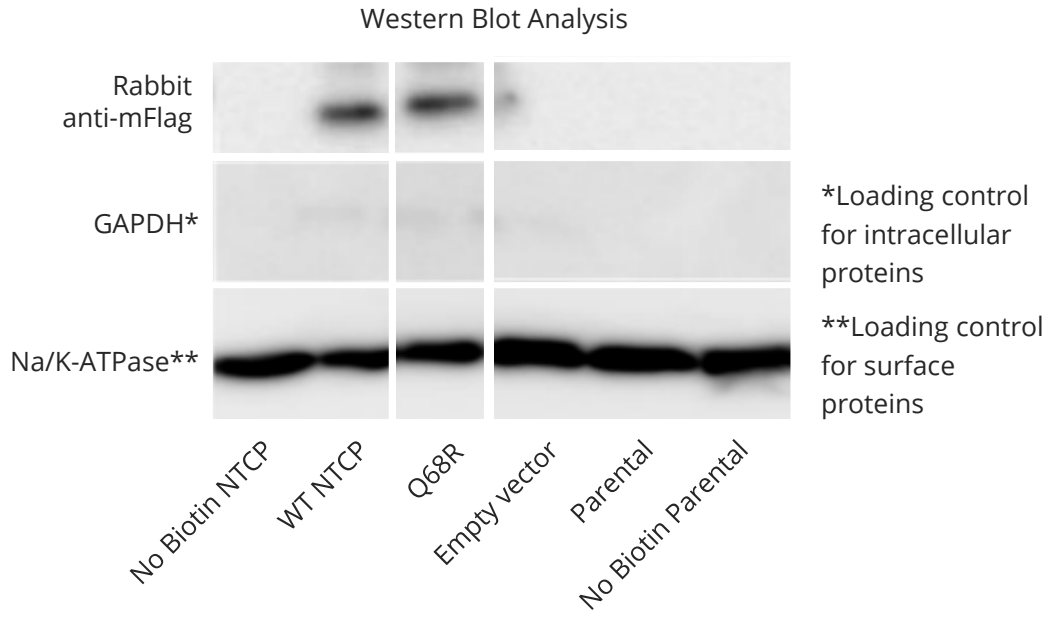
- The Q68R variant disrupts some hydrogen bonds and contacts in the Na^+ binding pocket.
- Clashes are inevitable since the Arg side chain is buried and likely to be found in one or another unfavorable rotamer state.

- Further assessment of Q68R variant in a BAs uptake assay showed a near complete inhibition of BAs (specifically Taurocholic Acid or TCA) uptake *in vitro*, confirming findings from the 3D modeling

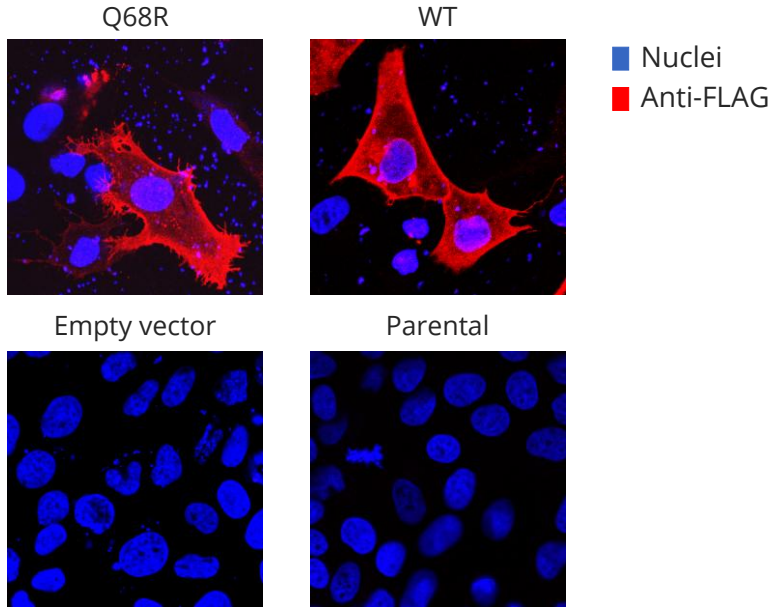
BAs: Bile acids, NTCP: Na-taurocholate cotransporting polypeptide, *transiently transfected U2OS cells.

The Q68R variant solely affects NTCP bile acids re-uptake function

NTCP protein expression was detected on western blot using the anti-FLAG antibody for all constructs



NTCP protein localization in vitro*



- No significant differences in NTCP RNA and protein levels were detected. The plasma membrane location of the Q68R variant was also unaffected.
- The Q68R variant solely affects NTCP bile acid reuptake function making it an approach of interest for Axiomer EON therapeutic application.

BAs: Bile acids, EON: editing oligonucleotide, NTCP: Na-taurocholate cotransporting polypeptide, *transiently transfected U2OS cells. *SLC10A1* is the gene that encodes for NTCP protein

Humanized mice model to assess therapeutic potential in cholestasis



HUMANIZED-LIVER MICE

Human hepatocytes in a mouse liver - enabling direct assessment of human NTCP editing in vivo



DDC CHOLESTASIS CHALLENGE

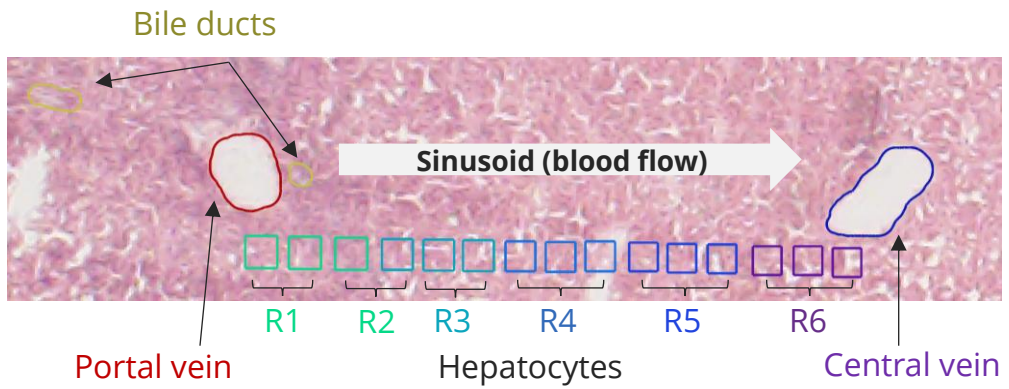
Diet induces bile-duct injury, inflammation and fibrosis



HUMANIZED MICE + DDC

A relevant model to assess therapeutic potential in cholestasis

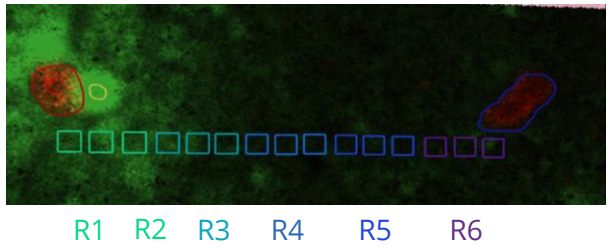
Editing of NTCP to the Q68R variant reduces hepatic toxic bile-acid uptake by ~80%

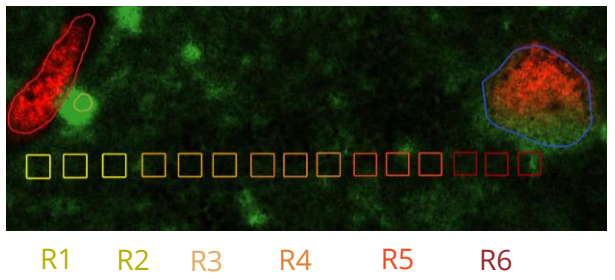


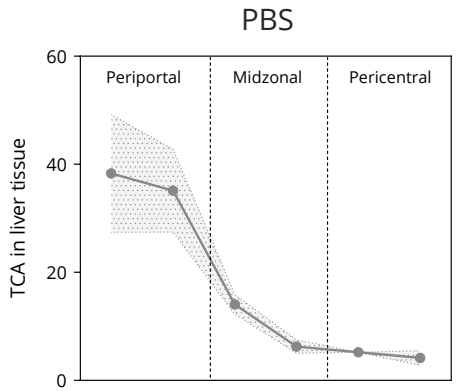
- MSI imaging maps NTCP-mediated TCA uptake across hepatic zones.
- Untreated mice show the expected periportal uptake gradient.
- AX-0811 editing to NTCP Q68R reduces hepatocyte uptake by up to 80%

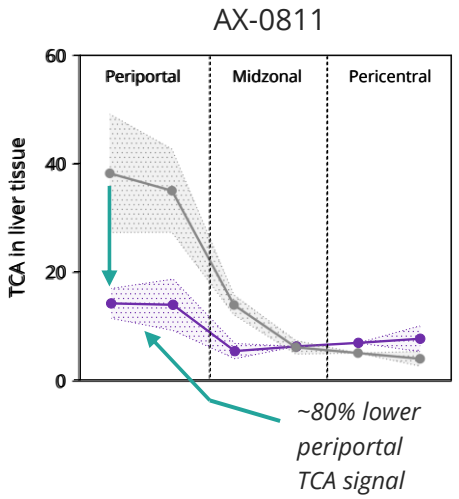
Taurocholic acid (TCA) is the major conjugated bile acid in mice, the primary substrate for NTCP uptake, enabling robust spatial measurements across the porto-central axis and serving as a functional readout of bile acid transport and liver zonation.
Treatment conditions: humanized mice, SC AX-0811 at 30 mg/kg, 10 doses, n=2, Maldi MS Imaging at 5um resolution, Mean, SEM

MSI TCA signal in hepatocytes / parenchyma



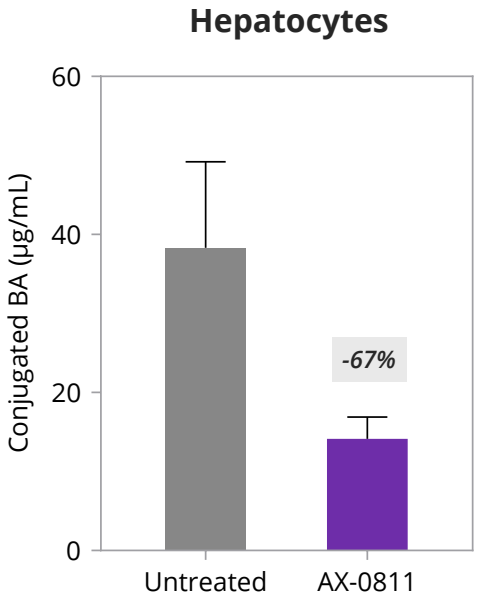


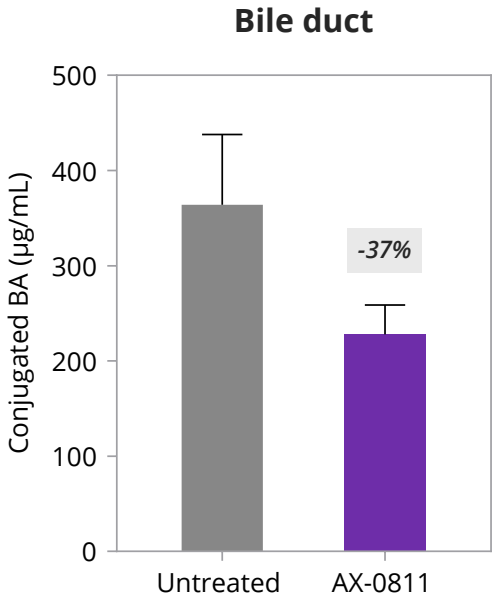


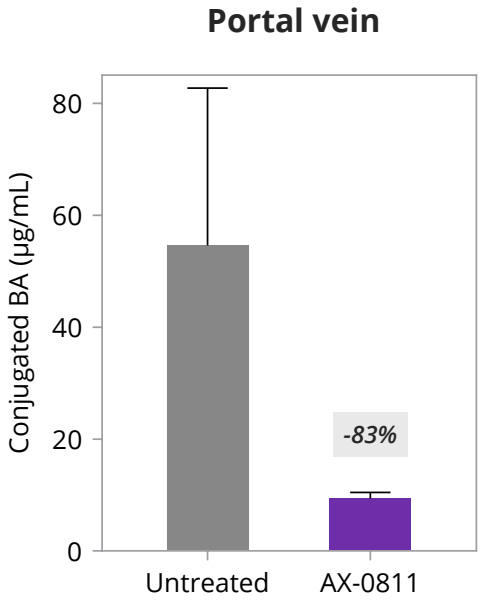


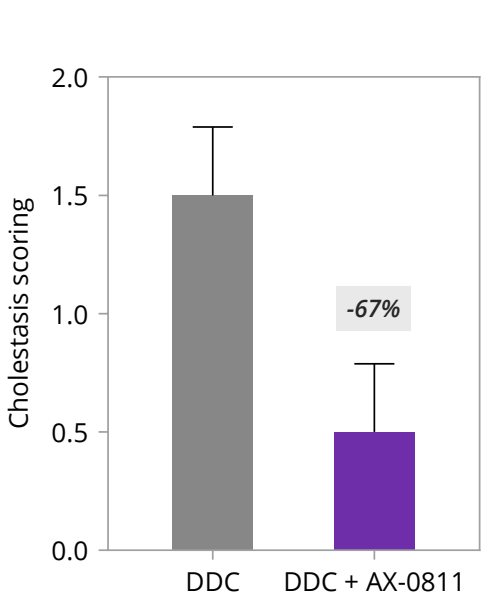
NTCP editing decreases toxic bile acids in the liver and improves cholestasis *in vivo*

REDUCED BILE ACID UPTAKE THAT DRIVES LIVER TOXICITY → **IMPROVED CHOLESTASIS**









67% decrease in hepatocytes bile acid levels

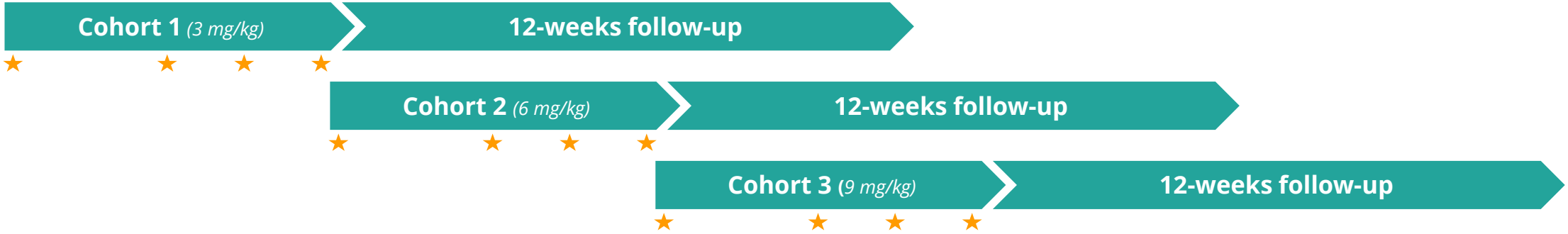
Lower intrahepatic load reduced downstream bile acid levels

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-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

Objectives

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

Key biomarkers of target engagement

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

Cohort 3 and 12-week follow-up full results in December 2026

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)

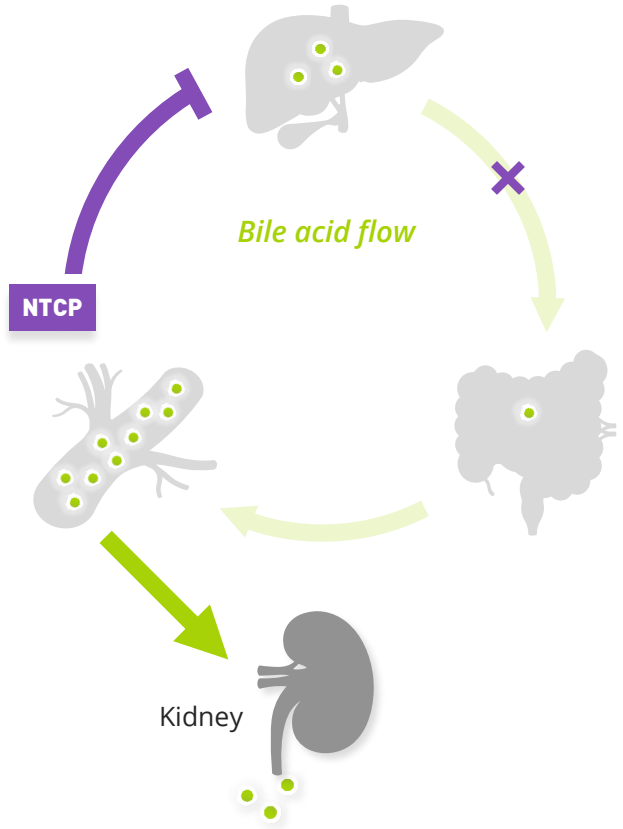
PK in line with expected profile

- 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)

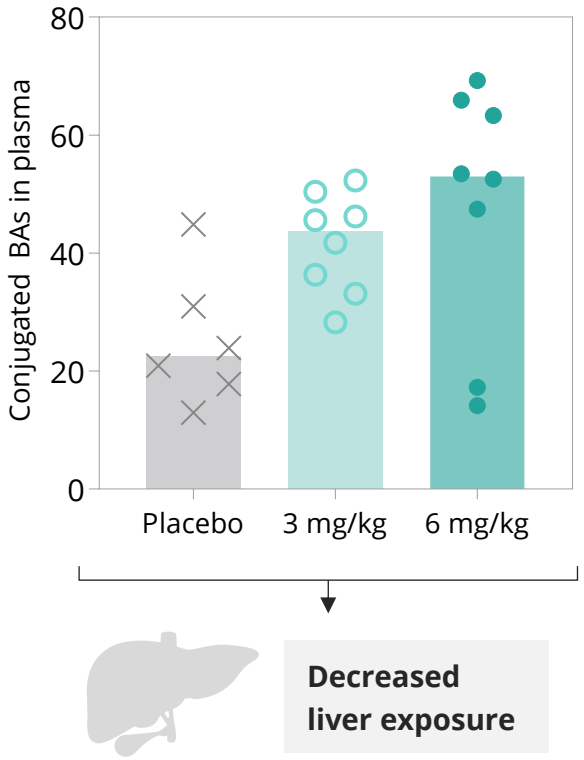
NTCP editing increases renal clearance of conjugated bile acids

NTCP MODULATION *with RNA editing*



Plasma conjugated BAs

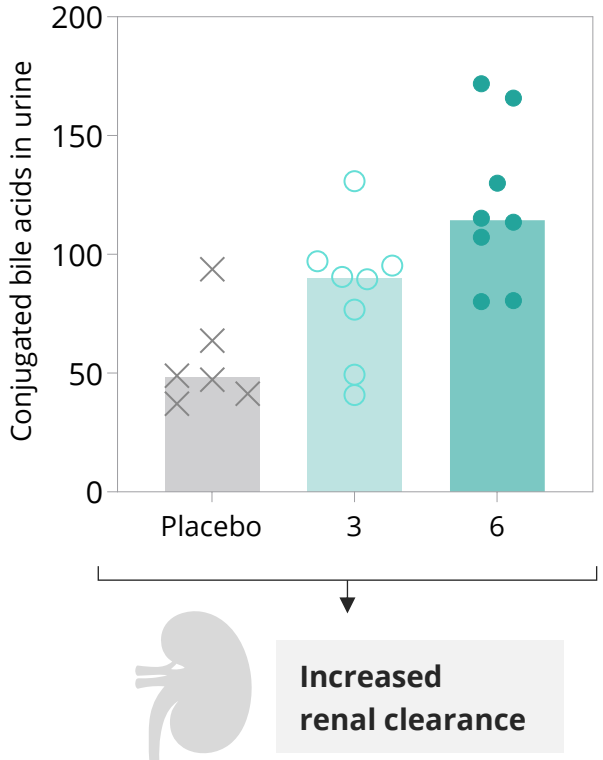
r= 0.53, p = 0.012



Decreased liver exposure

Urinary conjugated BAs

r= 0.68, p = 0.0004



Increased renal clearance

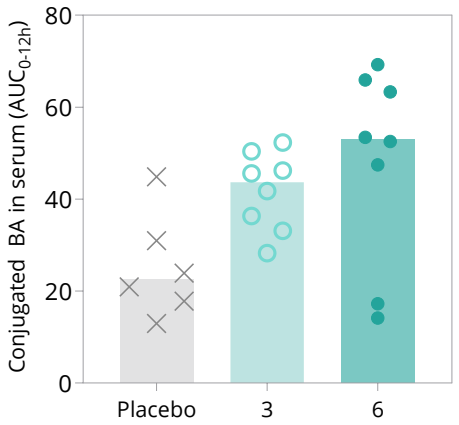
In serum, values represent each individual AUC (in serum from 0-12h) on Week 5 (µmol/L x h). In urine, represented total amount cleared 0-24h on week5 (nmol/L x h). Bars represent median mean with 95% CI. Post-hoc statistical analyses. N=22 (n=6 Placebo, crosses; n=8 Cohort 1 | 3mg/kg, circles; n=8 Cohort 2 | 6mg/kg, dots); 4 doses AX-0810; GalNac conjugation; Subcutaneous

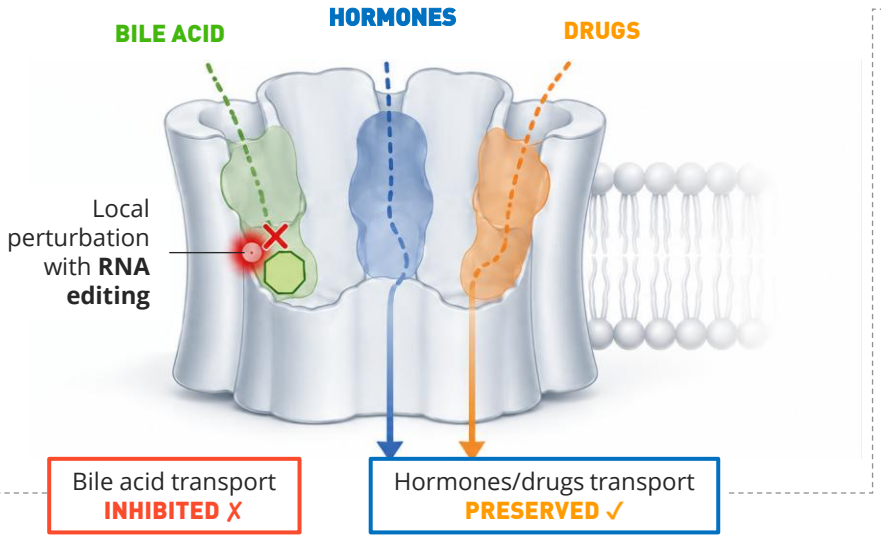
NTCP editing selectively modulates bile-acid transport

Conjugated bile acids increased

Serum conjugated BAs

r= 0.53, p = 0.012

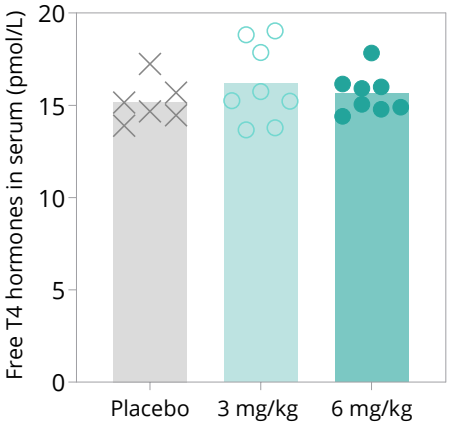




Hormone levels unchanged

Free T4 hormones

r= 0.15, p = NS



Selective NTCP modulation

- Bile acids and hormones use distinct NTCP pockets
- AX-0180 edits the bile-acid pocket, the hormone transport remains functional

Phase 1 supports functional selectivity

- Hormone levels unchanged
- Drug metabolism preserved
- Supports chronic use in cholestasis

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.

NTCP Editing confirms target engagement and potential to address cholestasis

AX-0810 Phase 1

- Met all PD objectives across 3 biomarkers
- Up to 8× increase in serum bile acids
- TUDCA and conjugated bile acids confirm NTCP specificity
- Favorable safety and tolerability to date
- Expected PK with an 8-week half-life
- Toxic bile acids redirected from the liver and cleared in urine

Translational proof

- Cholestasis score reduced in an animal disease model

Next milestone

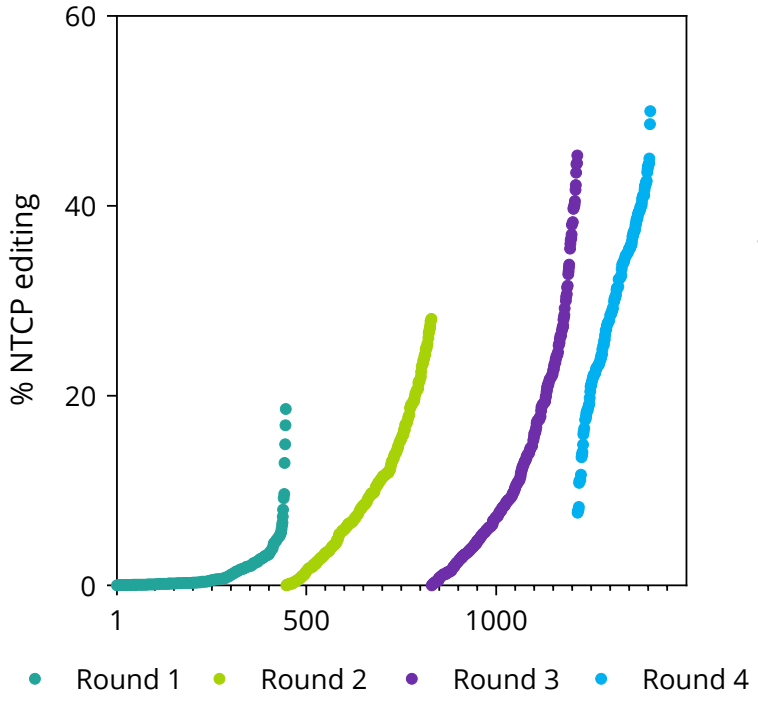
- AX-0810 Cohort 3 data and 12-week follow-up data expected in December 2026

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

Successful optimization of EON design across liver and CNS targets

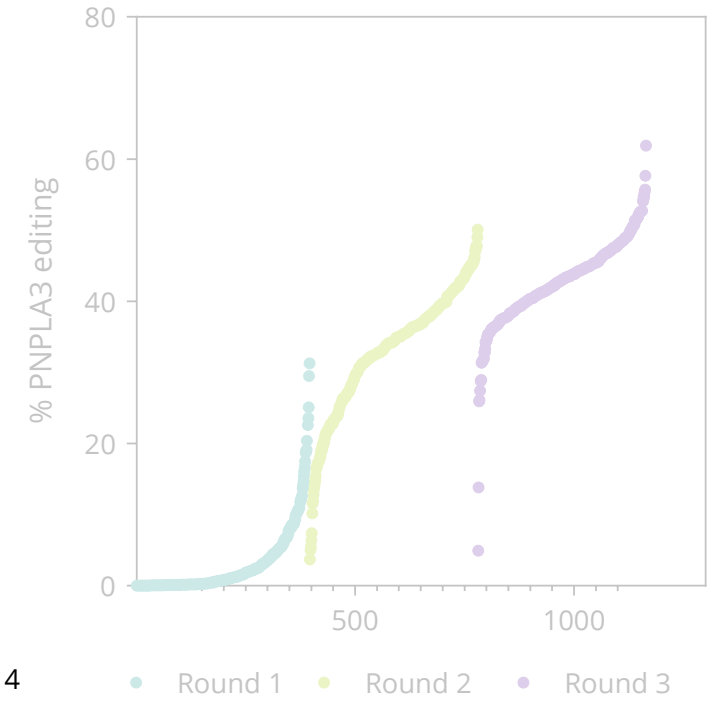
NTCP editing in PHH

Gymnosis, PHH, 5µM, 72h, N=2 biological, seed & treat, dPCR analysis (QiAcuity), AVG



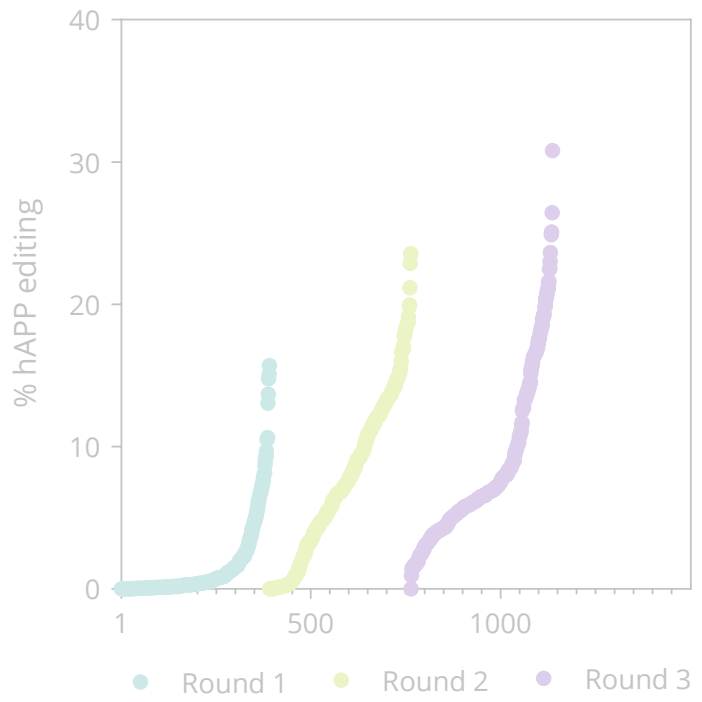
PNPLA3 editing in PHH

Gymnosis, PHH, 5µM, 72h, N=2 (biological, seed & treat, dPCR analysis (QiAcuity), AVG



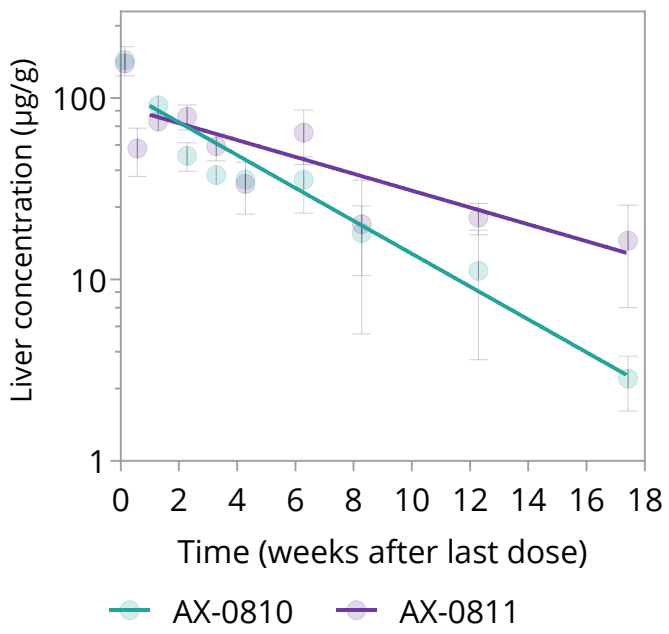
APP in forebrain neurons

Gymnosis, iPSC neurons, 5µM, 1-week washout, N=1, dPCR analysis (QiAcuity), AVG



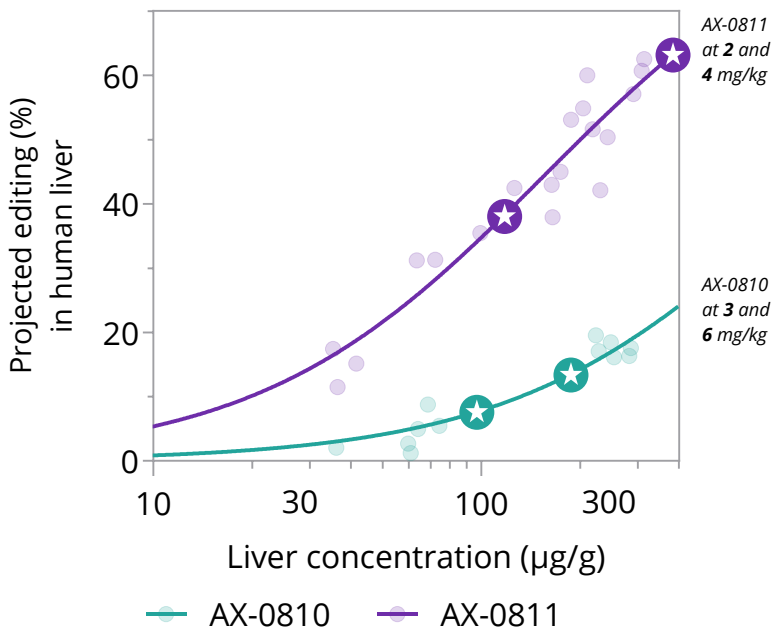
AX-0811 projected to achieve up to 65% editing

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



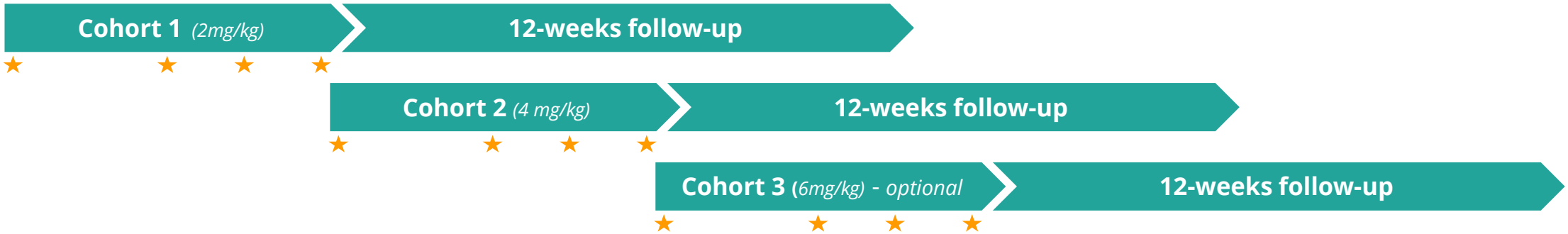
AX-0811 has >4x greater potency *in vivo*

- 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=18, 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 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

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

CTA enabling activities ongoing

- ✓ CTA filing in mid-2026
- Target engagement data expected from Cohorts 1 and 2 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



Multiple readouts

One exciting new technology

EDITING	TARGET ENGAGEMENT	DELIVERY TECHNOLOGY	DISEASE IMPACT	CLINICAL TRANSLATION
NTCP / CHOLESTATIC DISEASE			IDUA / MPS1	PNPLA3 / MASH
AX-0810 Ph 1 Cohort 3 and 12-week follow-up full results December 2026	*AX-0811 target engagement HV data Cohorts 1 & 2 expected by early Jan 2027*	*IIT initial data in biliary atresia patients H1 2027*	*Ph 2 development expected start mid 2027, with IA mid 2028*	*AX-0422 for MPS I Hurler syndrome initial human data H1 2027*	*AX-2911 for PNPLA3 IIT H1 2027*

Adike A, et al. Expert Rev Gastroenterol Hepatol. 2018 Oct;12(10):1025-1032; Verkade HJ, et al. J Hepatol. 2016 Sep;65(3):631-42; Sundaram SS, et al. Liver Transpl. 2017 Jan;23(1):96-109; Raghu VK, et al. Liver Transpl. 2021 May;27(5):711-718; NORD, 2019, Japanese Biliary Atresia Society. Japanese Biliary Atresia Registry (JBAR). https://jbas.net/en/national-registration/.

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