ADVANCING AXIOMER™ ADAR RNA EDITING PLATFORM

Editing oligonucleotides optimization for therapeutic use

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Axiomer™ 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

ProQR's Axiomer ADAR journey since 2014

2014

ProQR invents oligo mediated RNA Editing recruiting endogenous ADAR

2014-2018+

ProQR secures broad key patent positions on ADAR-mediated RNA editing

2015-2021

ProQR optimizes the ADAR platform in stealth

2020-2023

Key ADAR patents get granted in EU and US

2021

ProQR and Eli Lilly enter into first 5 target partnership worth $1.25B

2022

ProQR pivots to solely focus on ADAR editing

2022

ProQR and Eli Lilly expand partnership to 10 targets worth ~$3.9B

2023-2024

ProQR's broad ADAR patents upheld in oppositions in several jurisdictions

2023

ProQR demonstrates >50% editing in CNS and liver in NHP and announces pipeline

2024

- ProQR first in the field to report a disease relevant biomarker effect using Axiomer in NHP. Initial indication of good safety profile.
- Initial clinical validation of ADAR editing

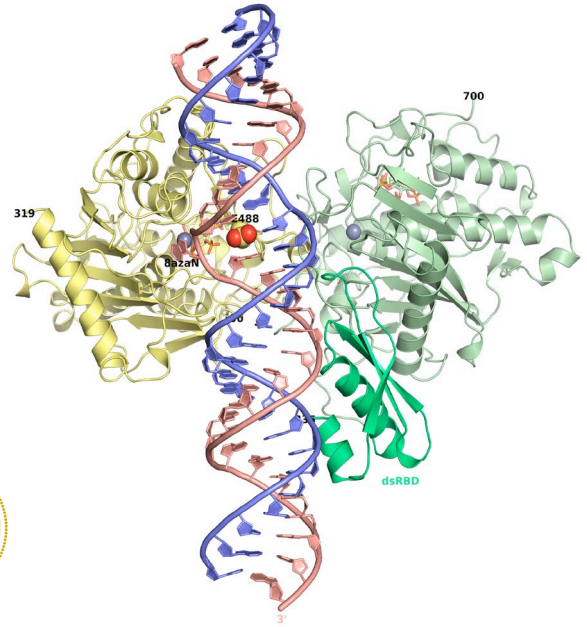
2025

- Advance AX-0810 NTCP program to clinical development
- Topline data Q4

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

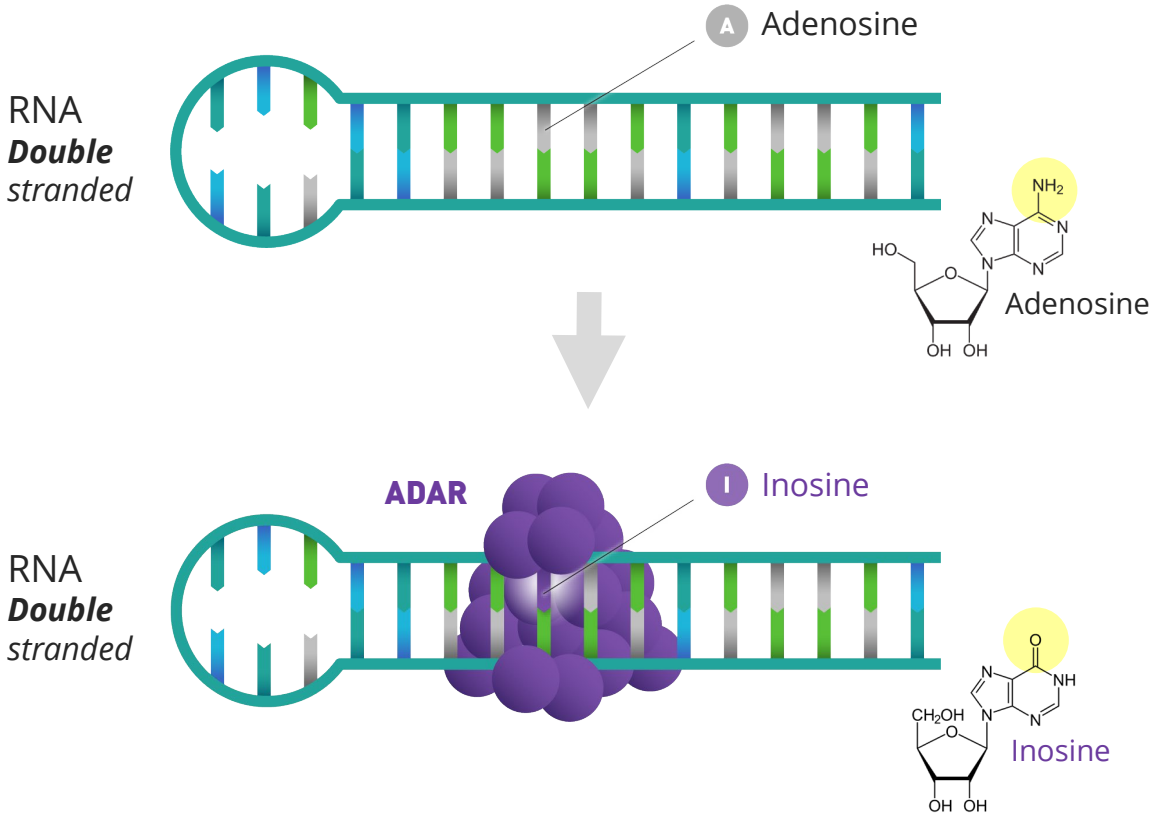
What is ADAR editing?

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)**

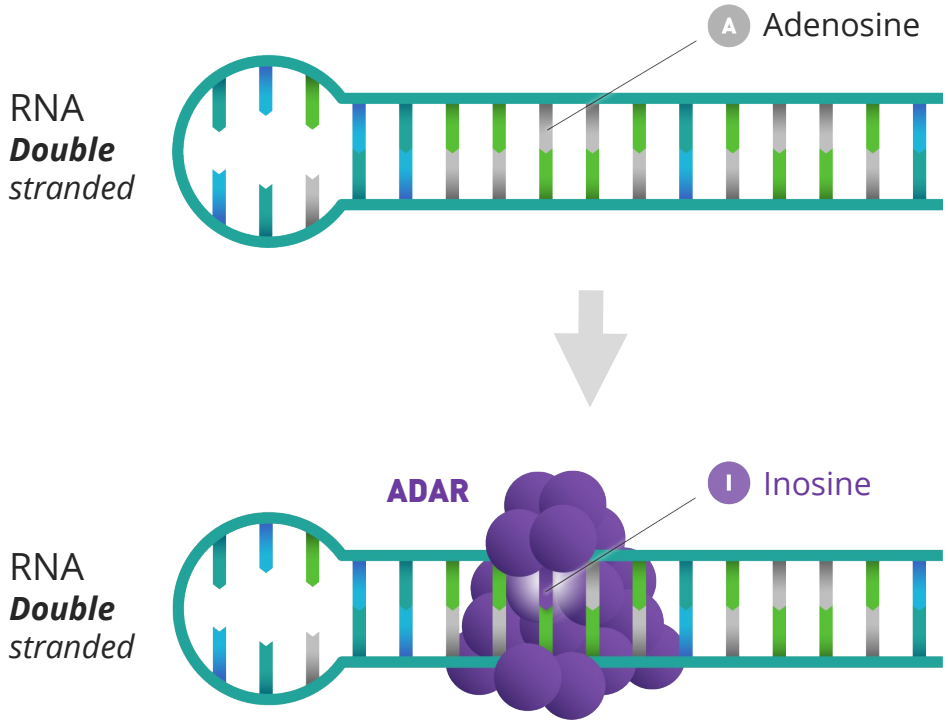
Natural ADAR editing *(A-to-I)*



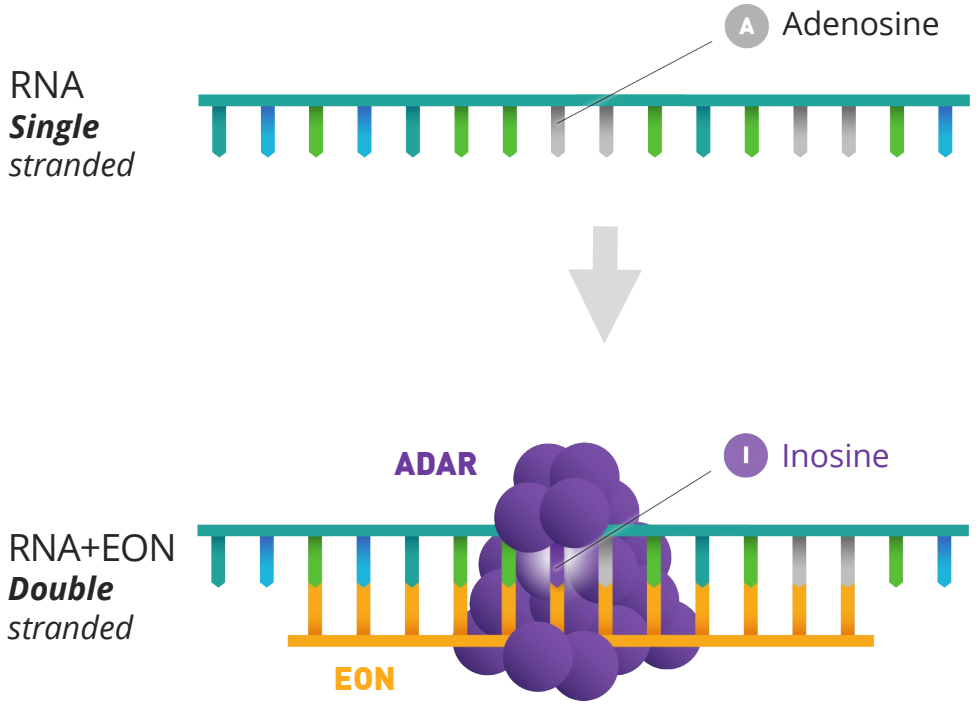
Axiomer EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

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

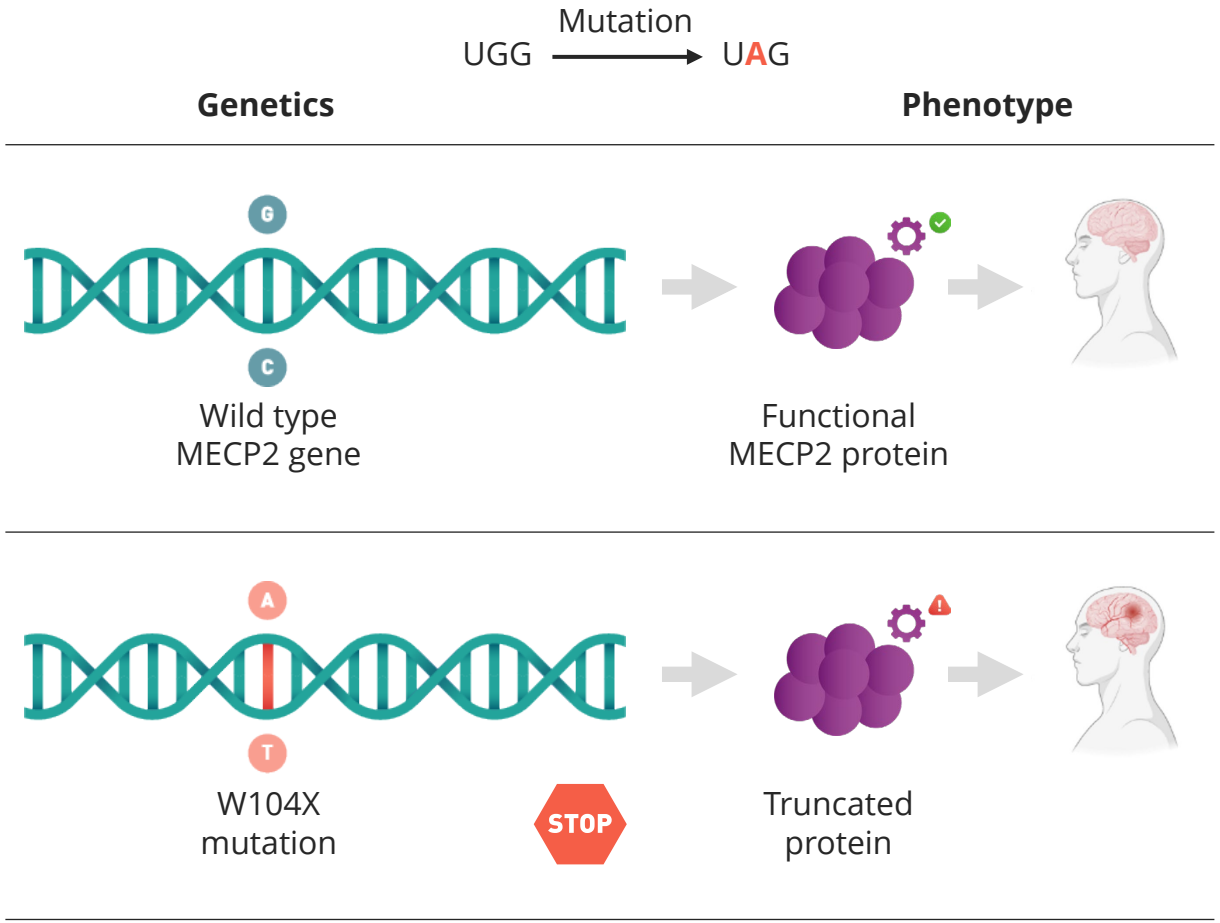


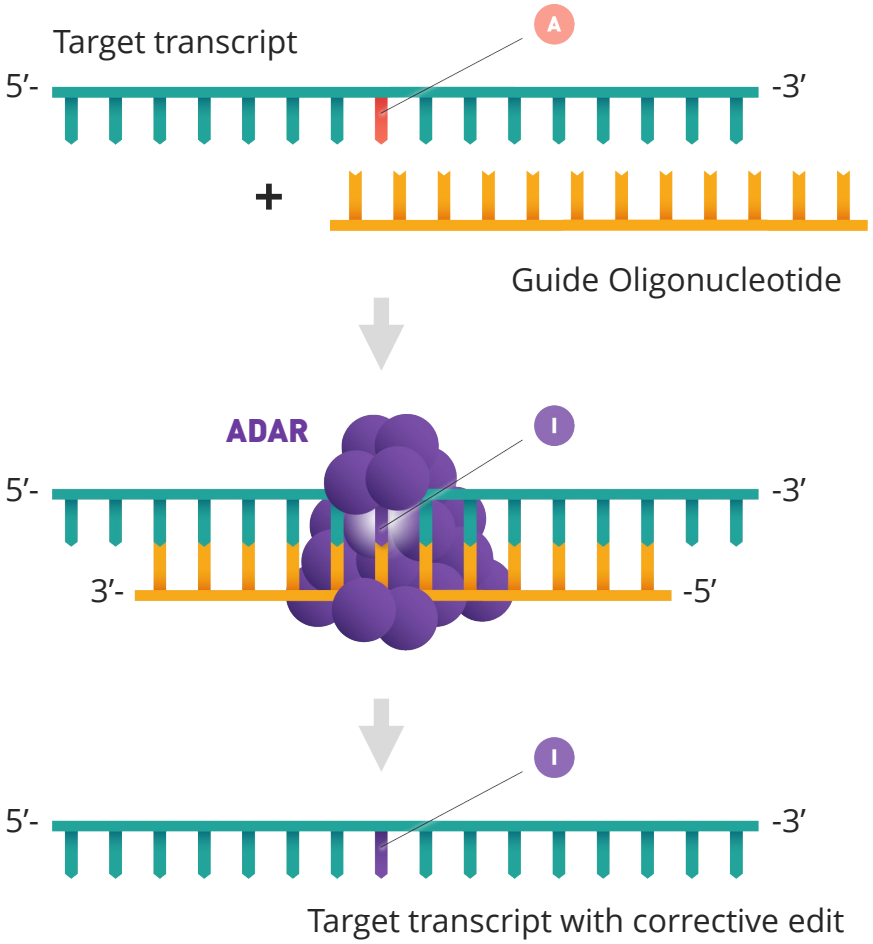
Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*



ADARs: Adenosine deaminases acting on RNA.

Oligonucleotide-directed RNA editing



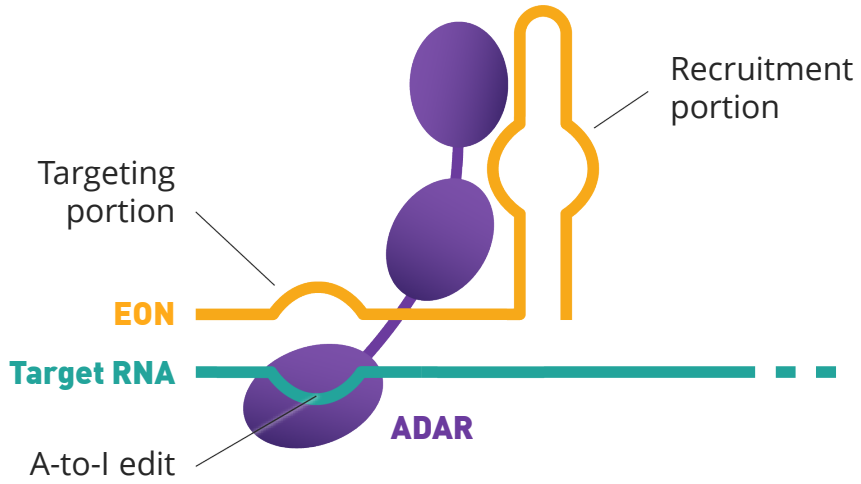


Reference: Doherty EE, Beal PA. Mol Ther. 2022 Jun 1;30(6):2117-2119.

Driving innovation in the RNA field with Axiomer editing oligonucleotides

1st Axiomer EONs generation

relate to (chemically modified) oligonucleotides that comprise

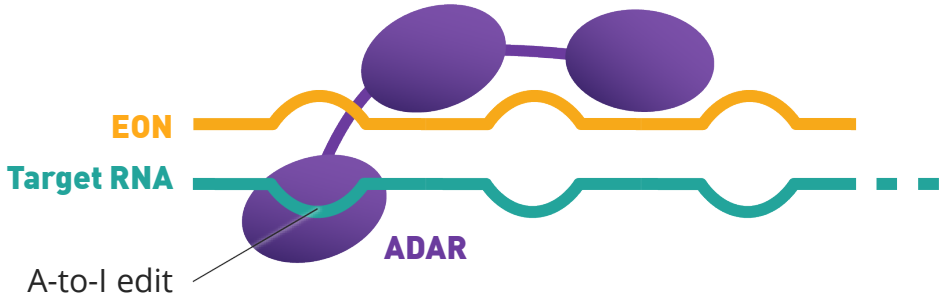


- **A targeting portion** for binding to a target RNA incl. target adenosine
- **A recruitment portion** (hairpin structure) for recruiting **endogenous** ADAR to edit the target adenosine

Patents: Granted appeal pending EP 3 234 134 B1; Granted US 10,676,737; Granted US 11,781,134

2nd Axiomer EONs generation

relate to oligonucleotides that comprise



- **No hairpin structure**
- One or more wobbles and/or mismatches, and chemical modifications in the base, ribose sugar and/or linkage to **increase activity as well as stability** and are still able to recruit **endogenous** ADAR to edit the target adenosine**.**

Patents: Granted US 10,941,402; Granted US 11,851,656; Allowed US 18/296,912

ProQR leading research to optimize editing oligonucleotides for therapeutic use

Modification of the orphan base

Zd in the Editing Enabling Region (EER) maximizes ADAR activity

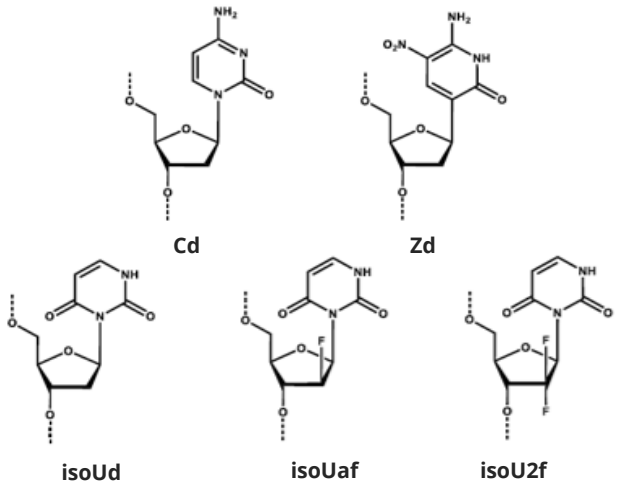
Modification of the base opposite to 5'G

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

Linkage modifications in the ADAR-binding region (ABR)

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

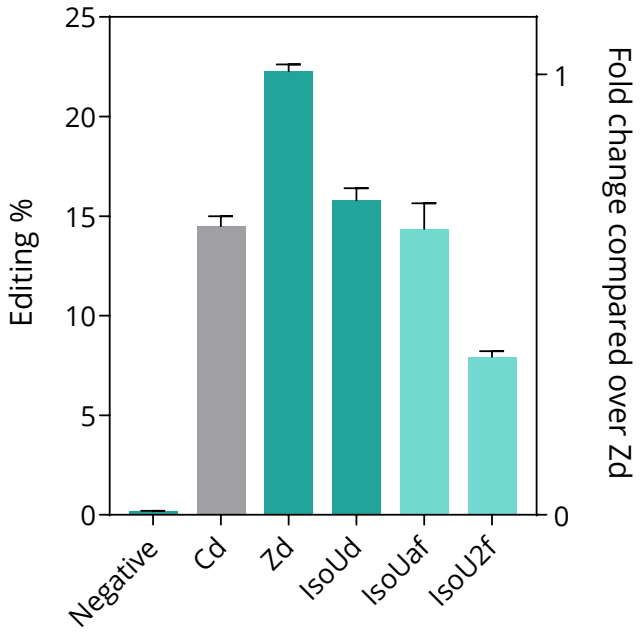
Zd in the Editing Enabling Region (EER) maximizes ADAR activity



With the same N3 H-bond mechanism **none of the tested base-modifications outperformed the editing efficiency of Zd**, indicating that the N3 hydrogen bonding ability of Zd is not the only key chemical component responsible for the high editing efficiency seen for Zd

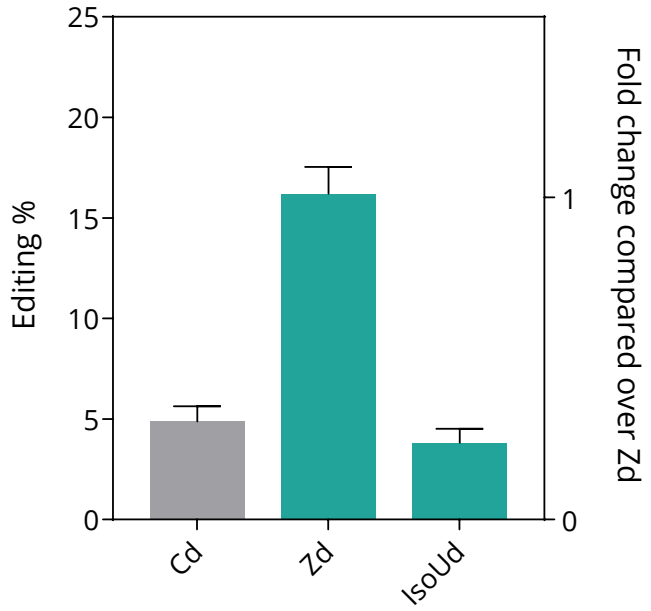
RNA editing of *ACTB* in PHH

Gymnosis, N=3-5, 0.1 µM, dPCR, mean, SEM



RNA editing of *Angptl3* in liver of C57BL/6JRj mice

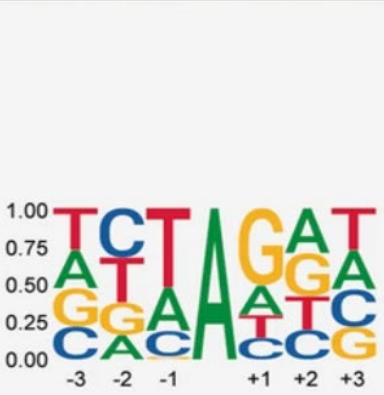
SC, 1 µmol/kg, 3x dose (D0, D2, D4), N=4, Necropsy D7, dPCR analysis, mean, SEM



ADAR knows few sequence constraints

With the exception of G upstream of target adenosine (5'-GA-3')

Location	ADAR1/ADAR2 common	ADAR1 specific*	ADAR2 specific*
	# sites (% WT/dHet sites)	# sites (% WT/dHet sites)	# sites (% WT/dHet sites)
Promoter/ 5' UTR	43 (57.33%)	13 (17.33%)	14 (18.66%)
Exon	225 (51.84%)	80 (18.43%)	92 (21.20%)
Intron	2239 (45.37%)	960 (19.45%)	1286 (26.06%)
3'UTR	142 (50.90%)	43 (15.41%)	66 (23.66%)
Intergenic	200 (65.36%)	47 (15.36%)	62 (20.26%)
Total	**2849 (47.25%)**	**1143 (18.96%)**	**1520 (25.21%)**

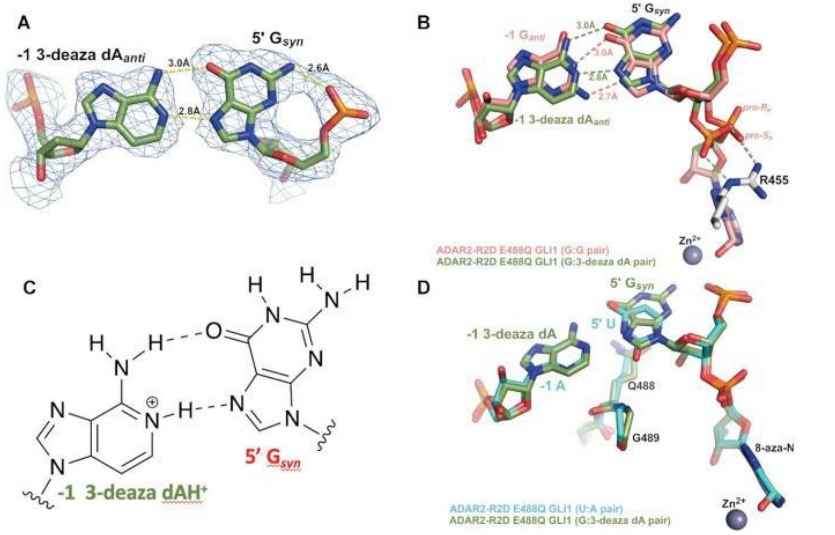


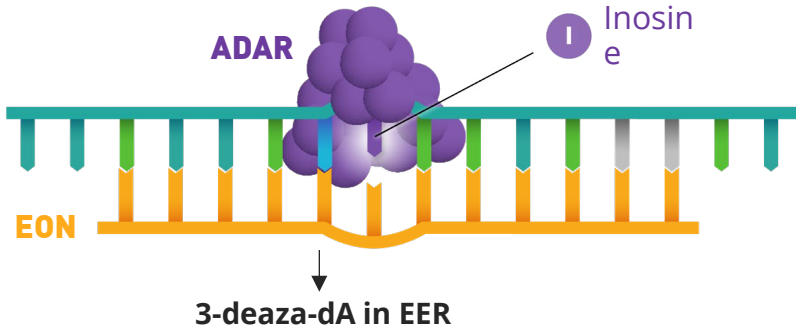
This has wide implications for the applicability of targeted RNA editing – guide RNAs with Watson-Crick complementarity are enough to recruit ADAR and induce targeted editing

Adapted from Eggington et al. Predicting sites of ADAR editing in double-stranded RNA. Nat Commun. 2011;2:319

A single base change opposite the target 5'G greatly enhances editing

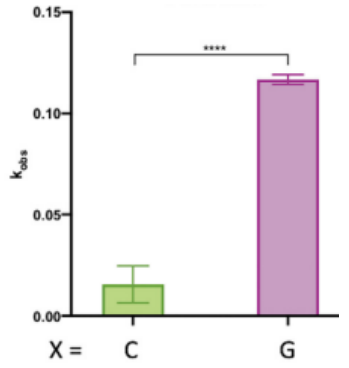
PROQR – UC DAVIS COLLABORATION

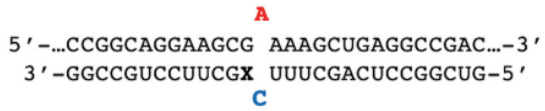




In vitro deamination kinetics for ADAR2 and duplex RNAs derived from WT _hMECP2_

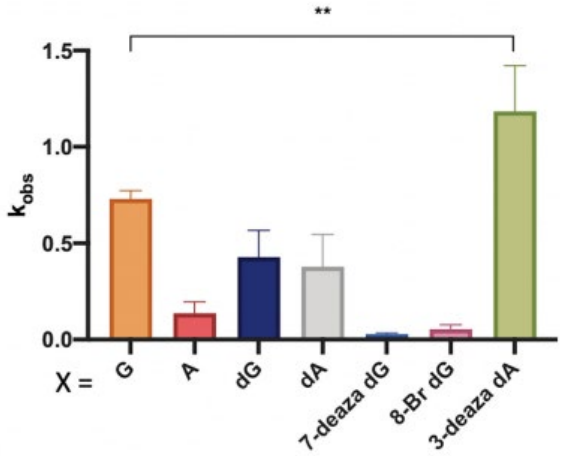
100 nM ADAR2, 3 technical replicates, mean, SD





In vitro deamination kinetics for ADAR2 and duplex RNAs derived from _hMECP2_ R255X

100nM ADAR2, 3 technical replicates, mean, SD



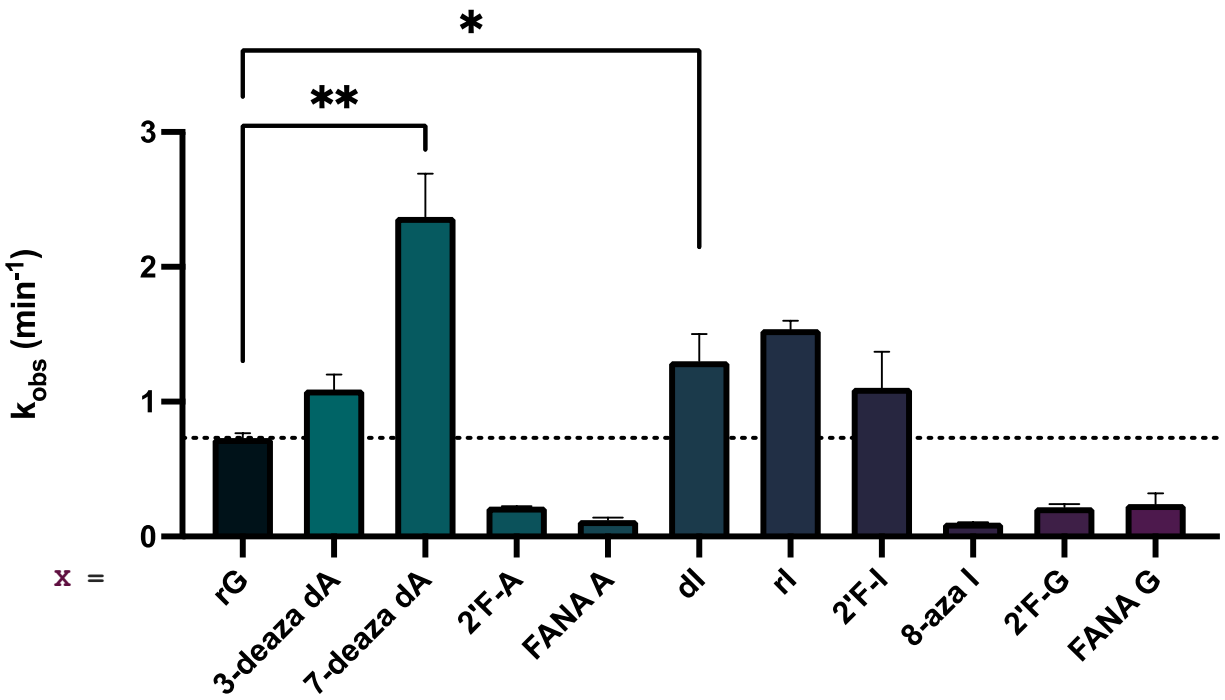
*Adapted from Doherty EE, et al. Nucleic Acids Res. 2022;50(19):10857-10868; Statistical significance between groups was determined using one-way ANOVA with Tukey's multiple comparisons test or an unpaired t-test with Welch's correction; **P < 0.01; ***P < 0.001; ****P < 0.0001.*

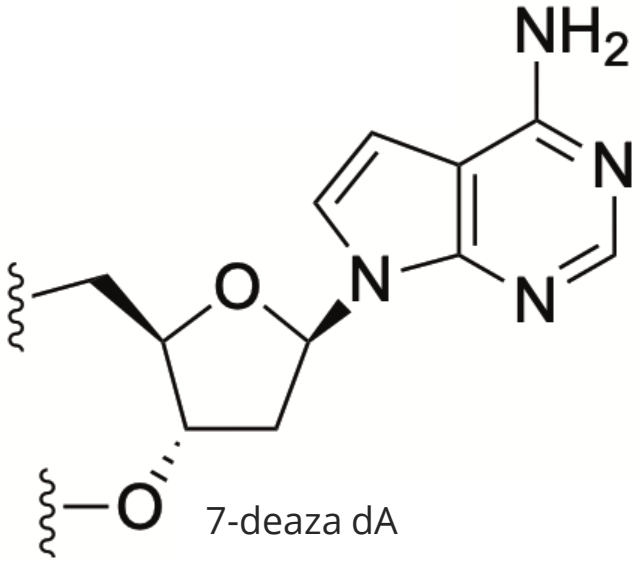
Effect of other purine analogs on editing at 5’ GA site

PROQR – UC DAVIS COLLABORATION

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*





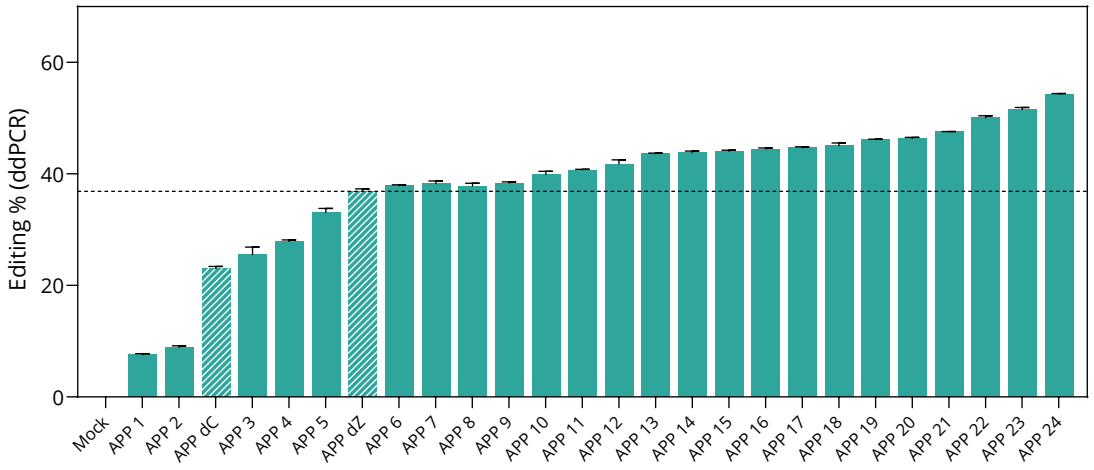
7-deaza dA

Adapted from: Manjunath, A. et al. Biomolecules 2024, 14, 10, 1229.

PN linkages in the ABR increase editing efficiency

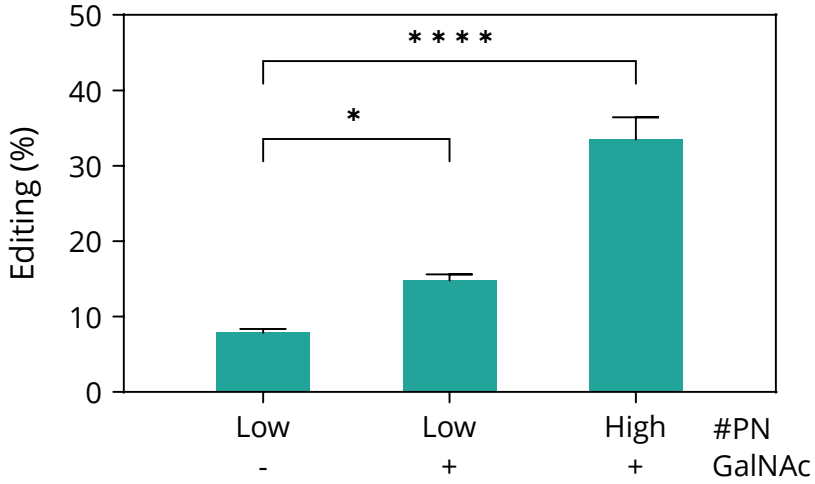
RNA editing of WT *APP* in human ARPE-19

Transfection, N=2, 2 days, 100nM, ddPCR, Mean, SD



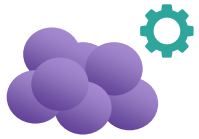
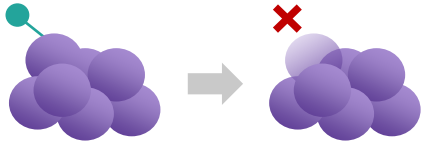
RNA editing of *ActB* in liver

C57Bl/6J mice, 7d, 3x10mg/kg, SC, N=4, dPCR, mean, SEM



- The sequences contain a mix of 2'-*O*-Me, DNA, PMe, PS, 2'-F, 2'-MOE
- The changing factor is +/- dZ in EER and +/- PN (N) with systematic change in location
- PN increases EON editing up to 2x and, in some positions, have negative effect on editing
- *In vivo* high PN content in combination with GalNAc delivery led to 2x increase in editing efficiency in liver of mice

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

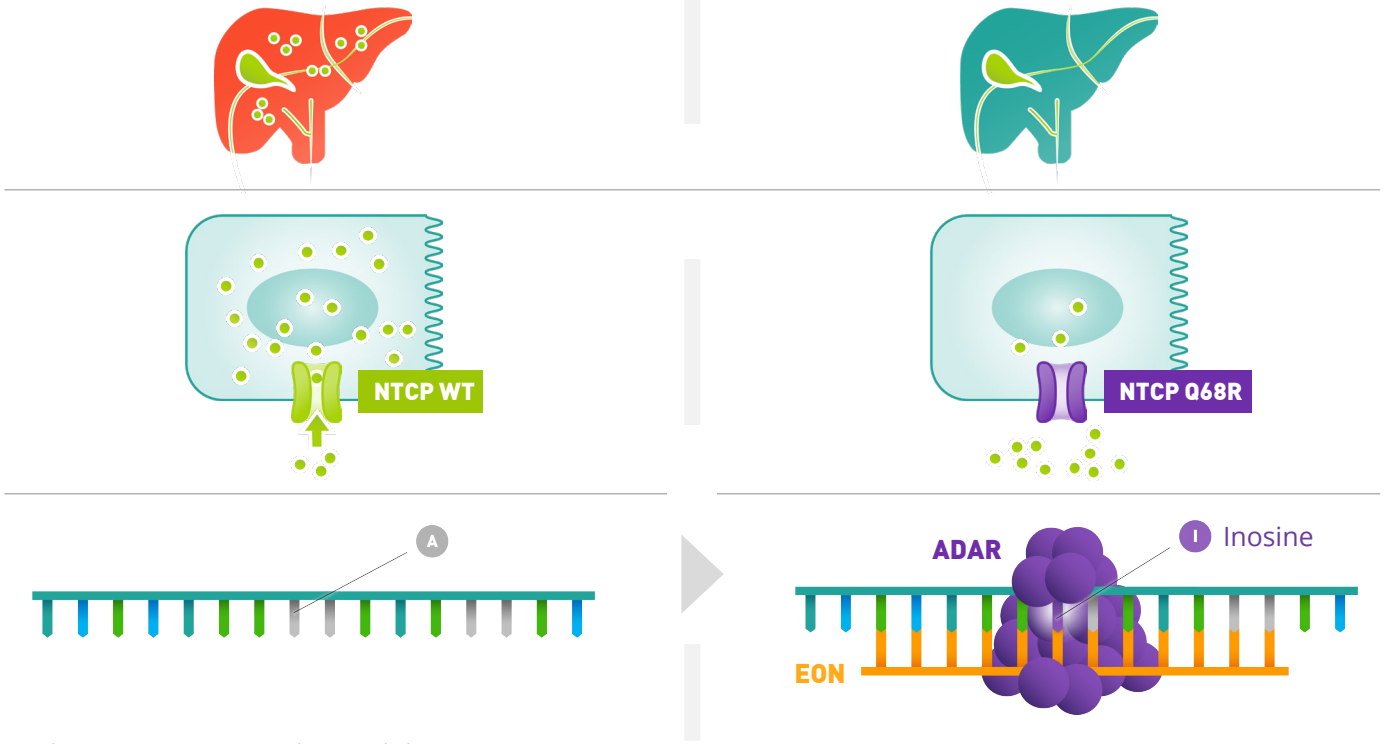
AX-0810 RNA editing therapy targeting NTCP for cholestatic diseases

LIVER WITH CHOLESTATIC DISEASE

High concentration of bile acids in hepatocytes

AX-0810 STRATEGY FOR DISEASED LIVER

AX-0810 modifies the NTCP channel to limit bile acids uptake while preserving all other functions of the channel



BA, Biliary atresia; PSC, Primary Sclerosing Cholangitis

- The AX-0810 program introduces a variant in individuals with cholestatic disease to lower bile acids concentration in hepatocytes by a single A-to-I change
- The AX-0810 program is designed to be a disease modifying treatment
  - To alleviate symptoms in PSC and BA
  - To limit inflammation and fibrosis linked to bile acid toxicity
  - To prevent or delay the development of cirrhosis, organ failure and need for transplant

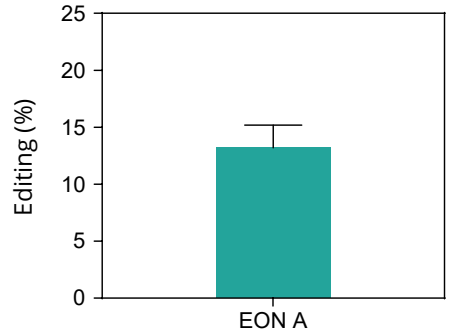
EON mediated editing demonstrates consistent editing of NTCP and impact on biomarker *in vivo*

MICE *in vivo*

EDITING EFFICIENCY

NTCP RNA Editing in Humanized Mice

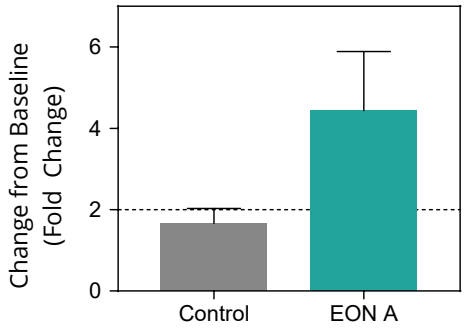
(N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25, ddPCR)



PLASMA TOTAL BILE ACIDS

Plasma TBA in Humanized Mice

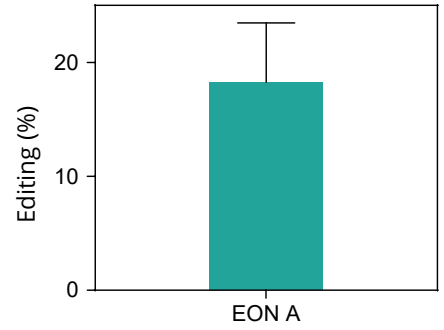
(N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25)



NHP *in vivo*

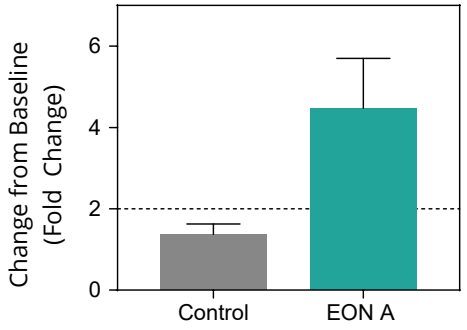
NTCP RNA Editing in NHP

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



Plasma TBA in NHP

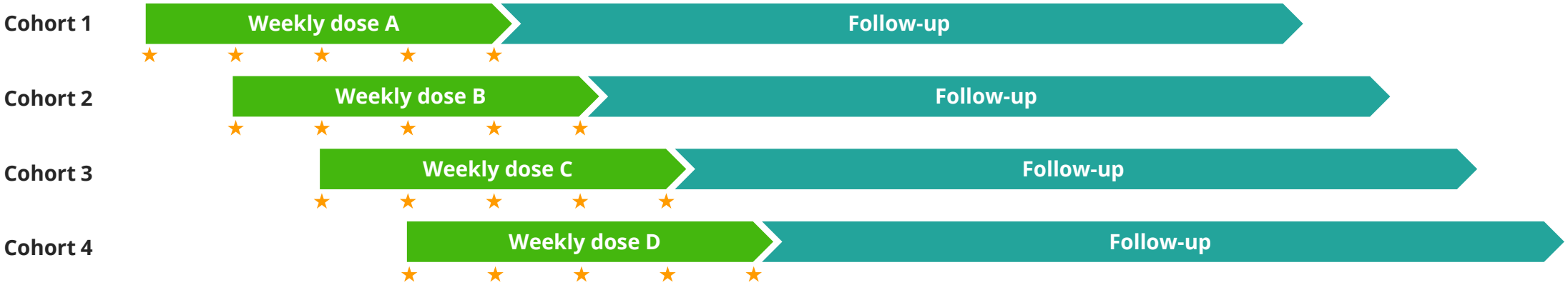
(N=1, 1-4mg/kg, 4 doses, LNP formulation IV, up to D39)



- 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

First in human trial of AX-0810 to establish target engagement

Integrated single/multiple ascending dose study design



Treatment

AX-0810 GalNAc conjugated editing oligo-nucleotide

Objectives

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

Trial design

- Combined single and multiple ascending dose
- ≥60 heathy volunteers, 4 weeks dosing phase followed by 12 safety weeks follow-up
- 5 weekly subcutaneous injections
- Baseline and placebo-controlled design
- Standardized conditions for assessment of bile acids at multiple timepoints
- DMC safety reviews before proceeding to next dose and dose escalation

Key endpoints

- Change in bile acids levels and profile in plasma and urine, liver biomarkers
- Circulating RNA as exploratory endpoint

CTA submission in Q2 2025

Top-line data in Q4 2025

Axiomer RNA editing science translating toward therapeutic applications

Science

- Harnessing advanced knowledge of ADAR and oligonucleotide science
- Pioneering the optimization of editing oligonucleotides (EONs) to achieve best-in-class therapeutic solutions

Versatile applicability

- Demonstrating proven success in correcting genetic mutations and enabling diverse protein modulation strategies
- Platform with potential to address diverse conditions rooted in human genetics

Leadership position

- Driving innovation in the ADAR RNA editing science with Axiomer EONs since 2014
- Dominant IP position to drive ADAR-mediated RNA editing platform innovation

ProQR®

IT'S IN OUR RNA

Forward-looking statements

This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "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 strategy and future operations, statements regarding the potential of and our plans with respect to our technologies and platforms (including Axiomer™), our preclinical model data, our pipeline targets, our other programs and business operations, our current and planned partnerships and collaborators and the intended benefits thereof, including the collaboration with Lilly and the intended benefits thereof, including the upfront payment, equity investment, and milestone and royalty payments from commercial product sales, if any, from the products covered by the collaboration, as well as the potential of our technologies and product candidates; our updated strategic plans and the intended benefits thereof, our plans to seek strategic partnerships for our ophthalmology assets, and our financial position and cash runway. 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 anticipated in 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 annual report filed on Form 20-F. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies 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 and logistics on the global market; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; 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. 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.