Safety, pharmacokinetics and target engagement of AX-0810 a first-in-class RNA editing therapy designed to modulate bile acid transport for cholestatic disease

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Introduction

Cholestatic liver disease, such as primary sclerosing cholangitis (PSC) and biliary atresia, involve toxic intrahepatic bile acid (BA) accumulation leading to hepatocellular injury, inflammation, and fibrosis. There are no approved disease-modifying therapies for PSC and biliary atresia, and many patients require liver transplantation.[1,2]

Sodium taurocholate co-transporting polypeptide (NTCP; *SLC10A1*) is the dominant basolateral conjugated BAs transporter and a therapeutic target to reduce hepatocellular BA uptake. (**Fig. 1**)

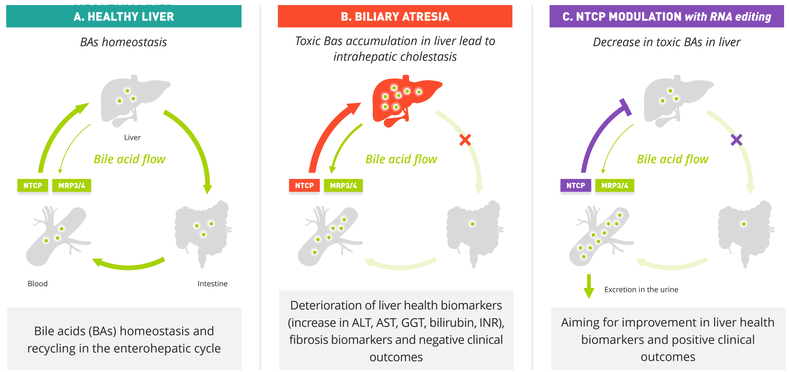


Figure 1. Enterohepatic cycle in (A) healthy individuals, (B) cholestatic disease, (C) following NTCP modulation with RNA editing

Evidences show that impacting NTCP BAs reuptake function can enhance liver function by reducing the levels of toxic BAs, improving liver damage markers and lowering inflammation biomarkers.[3] NTCP variants naturally occur in some people, changing the capacity to recycle BAs into the liver and increasing level of BAs in the plasma (hypercholanemia), without causing a phenotype or being associated with cholestasis nor pruritus.[4-7]

Axiomer™, an Adenosine Deaminase Acting on RNA (ADAR) based RNA editing platform, uses chemically modified editing oligonucleotides (EONs) to recruit and guide endogenous ADAR to perform Adenosine (A) to Inosine (I) editing on double stranded RNA with high specificity. (**Fig. 2**) The Inosine (I) is then translated as a Guanosine (G), changing an amino acid in the protein and impacting its function.

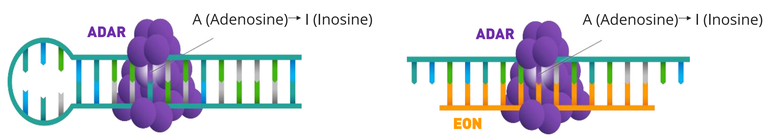


Figure 2. Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I).*

Editing oligonucleotides to target NTCP in cholestatic diseases as novel therapeutic strategy

AX-0810 is a novel modality and first-in-class GalNAc-conjugated RNA editing oligonucleotide, leveraging Axiomer platform, designed to induce a site-specific adenosine-to-inosine edit in *SLC10A1* mRNA, leading to NTCP Q68R variant aiming to reduce NTCP-mediated hepatocellular BA uptake.

NTCP Q68R is a variant located inside of a Na^+ binding pocket and can indirectly affect NTCP function by altering the precise geometry required for BAs binding.[8] (**Fig. 3**)

The Q68R variant solely affecting NTCP bile acid reuptake function, while preserving other hormones and drugs NTCP transport functions, making it a variant of interest for therapeutic application in cholestatic disease.[9]

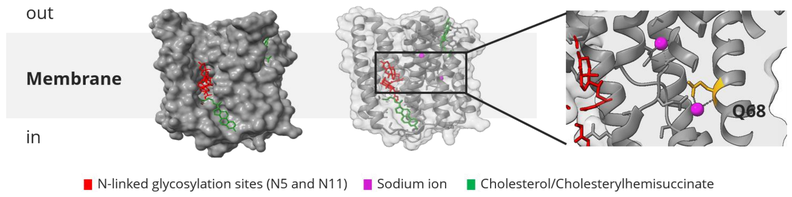


Figure 3. Structure of the human sodium/bile acid cotransporter (NTCP) and position of Q68 in the Na^+ binding pocket

Objectives

Assess AX-0810 in a first-in-human study combining single and multiple ascending dose features to evaluate safety, PK, and NTCP target engagement using linked biomarkers of NTCP activity. [EU CT number: 2025-521876-77-00]

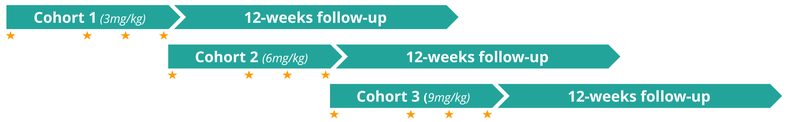
First-in-Human Evaluation of RNA editing-mediated NTCP modulation

The study was designed as a randomized, double-blinded, placebo-controlled, multiple-ascending-dose to evaluate subcutaneous AX-0810 in healthy adults (18–55 years) in 3 sequential dose cohorts (3, 6, and 9 mg/kg; total N=33), with safety and pharmacokinetics review before dose escalation.

Participants received an initial dose followed by a 2-week observation period, then 3 weekly doses with 12-week follow-up. (**Fig. 4**)

Study Design

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

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

Figure 4. AX-0810 FIH Phase 1 study

Primary endpoints are safety and tolerability. The secondary endpoint is to evaluate pharmacokinetics of AX-0810. Exploratory objectives evaluate pharmacodynamics with NTCP biomarker-based target engagement, using plasma total and conjugated BAs and a controlled oral tauro-ursodeoxycholic acid (TUDCA) challenge. BAs are measured after a standardized diet with calculated caloric and fat content at baseline and at multiple timepoints during dosing and follow-up.

- TUDCA was prespecified as a sensitive target-engagement biomarker due to its preferential NTCP-mediated hepatic uptake and controlled administration.
- Conjugated BAs are assessed as a translational biomarker relevant to cholestatic disease.
- Thyroid hormones, including free T4, are monitored to assess preservation of other NTCP-mediated transport functions.

Conclusions

- **AX-0810 is a potential novel hepatoprotective RNA-editing therapy to limit NTCP bile acid reuptake function in cholestatic liver disease.**
- **This study marks the first clinical evaluation of the Axiomer platform EONs and provides the first opportunity to establish clinical proof of concept for RNA editing-mediated NTCP modulation.**

References

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