First-in-person evidence of in vivo Axiomer RNA Editing of NTCP for the treatment of cholestasis: Proof of concept data from the AX-0810 Phase 1 Trial

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Introduction

Intrahepatic accumulation of toxic bile acids (BAs) is a key driver of cholestatic liver disease, and disease modifying treatment options remain limited.[1,2] Sodium taurocholate cotransporting polypeptide (NTCP; SLC10A1) mediates the majority of hepatic uptake of conjugated BAs and represents a novel therapeutic target. AX-0810 is a first-in-class GalNAc-conjugated Axiomer RNA editing oligonucleotide designed to selectively reduce NTCP-mediated BA uptake through site-specific editing of SLC10A1 mRNA while preserving other hormones and drugs NTCP transport functions. By reducing hepatic BA uptake, AX-0810 aims to lower the intrahepatic cholestatic BA toxicity.[3]

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 clinical evaluation of the Axiomer platform EONs and provides the first opportunity to establish clinical proof of concept for RNA editing-mediated NTCP modulation**

Multiple ascending dose (MAD) N=22 healthy volunteers *(16 on treatment, 6 on placebo)*



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

Objectives	Key biomarkers of target engagement
• Assess safety, tolerability, and PK of AX-0810	• TUDCA challenge
• Confirm target engagement as measured by biomarkers	• Bile acids profile
	• Change in bile acid levels

Figure 1. AX-0810 FIH Phase 1 *3 and 6 mg/kg cohorts study design*

In this randomized, double-blind, placebo-controlled, multiple-ascending-dose Phase 1 study, healthy participants received subcutaneous AX-0810 at 3 and 6 mg/kg, with four doses administered over 4 weeks and 12 weeks of follow-up. (**Fig. 1**) Objectives included safety, tolerability, pharmacokinetics, and pharmacodynamic evidence of NTCP target engagement. Target engagement was evaluated using plasma total and conjugated BAs and a controlled oral tauro-ursodeoxycholic acid (TUDCA) challenge. TUDCA was prespecified as a sensitive target-engagement biomarker due to its preferential NTCP-mediated hepatic uptake and controlled administration.

Conjugated BAs were assessed as a translational biomarker relevant to cholestatic disease. Thyroid hormones, including free T4, were monitored to assess preservation of other NTCP-mediated transport functions.

Results

haracteristics and safety

included 22 healthy participants (placebo, n=6; AX-0810 3 mg/kg, n=8; 6 mg/kg, n=8). (**Table 1**) AX-0810 was well tolerated, with no serious or severe adverse events, discontinuations, or clinically meaningful changes in liver function, bilirubin, thyroid hormones, (**Fig. 3C**) vitamin D, or pruritus. Treatment-related adverse events were limited to mild injection-site reactions. Pharmacokinetics were consistent with an estimated hepatic half-life of approximately 8 weeks. (**Table 2**)

Table 1. Baseline characteristics

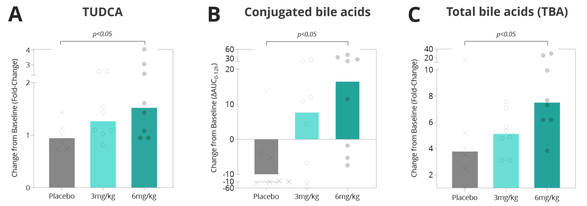
Characteristic	Placebo *(Cohort 1 + 2, n=6)*	3 mg/kg *(Cohort 1, n=8)*	6 mg/kg *(Cohort 2, n=8)*
Age, years (mean ± SD)	40.8 ± 8.98	40.9 ± 9.36	40.1 ± 11.4
Age, years (min–max)	27 – 50	26 – 55	27 – 54
Male, n (%)	*5* (83%)	8 (100%)	8 (100%)
Female, n (%)	*1* (17%)	0	0
Weight, kg (mean ± SD)	80.1 ± 10.4	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

Table 2. Overview of AX-0810 safety and tolerability profile in placebo, 3mg/kg and 6mg/kg cohorts

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

Pharmacodynamics : impact on NTCP target-engagement biomarkers

At week 5, AX-0810 produced concordant, dose-dependent changes across BA biomarkers, consistent with NTCP target engagement. Following challenge, plasma TUDCA (Cmax, µmol/L) increased by 34% and 61% from baseline at 3 and 6 mg/kg, respectively. Plasma conjugated BA exposure (AUC0-12h, µmol/L·h) increased by 95% and 136%, and total BA (Cmax, µmol/L) increased by 5- and 8-fold at 3 and 6 mg/kg, respectively. (**Fig. 2**)



Increased circulating TUDCA **confirmed NTCP specificity**

Selective increase in conjugated bile acids showed specific NTCP modulation

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

Figure 2. Change from baseline of (A) plasma TUDCA following oral challenge, (B) plasma conjugated bile acids, (C) plasma total bile acids. 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.*

Urinary conjugated BA excretion (AUC0-24h, nmol/L·h) increased by 87% and 138%, respectively, versus placebo, directionally aligned with plasma and indicating enhanced renal BA elimination. (**Fig. 3**)

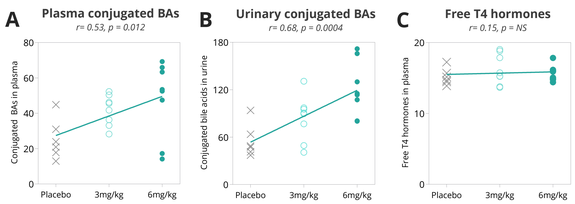


Figure 3. Change versus placebo of (A) plasma conjugated BAs, (B) urinary conjugated BAs, (C) plasma free T4 hormones. *Values represent each individual AUC (in plasma from 0-12h) on Week 5. In urine, represented total amount cleared 0-24h on Week 5. Pearson correlation calculated and significance indicated. Post-hoc statistical analyses*.

AX-0810 was also associated with dose dependent higher plasma level of Glycochenodeoxycholic acid (GCDCA, post-hoc Pearson correlation, r=0.56, p = 0.007) and Taurochenodeoxycholic acid (TCDCA, r=0.48, p = 0.024) associated with lower sulfated (r= -0.42, p = 0.052) and secondary BAs (r= -0.37, p = 0.086). (**Table 3 and Fig. 4**)

Table 3. Overview of change (%) in conjugated BAs in plasma in placebo, 3mg/kg and 6mg/kg cohorts

	Placebo *(Cohort 1 + 2, n=6)*	3 mg/kg *(Cohort 1, n=8)*	6 mg/kg *(Cohort 2, n=8)*
GCDCA (% median at week 5, t=0)	29.6	29.4	41.2
TCDCA (% median at week 5, t=0)	2.0	3.1	5.7
Sulfated BAs (% median at week 5, t=0)	30.2	26.0	14.3
Secondary BAs (% median at week 5, t=0)	20.4	23.5	11.3

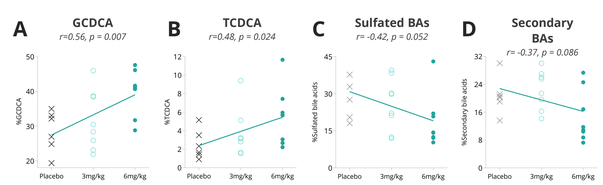


Figure 4. Change versus placebo of plasma level of (A) GCDCA, (B) TCDCA, (C) sulfated BAs and (D) secondary BAs. *Values represent the median of the % measured in serum from 0-12h on Week 5. Pearson correlation calculated and significance indicated. Post-hoc statistical analyses*

Conclusions

- **AX-0810 demonstrated favorable safety and pharmacokinetics together with concordant, dose-dependent pharmacodynamic evidence of NTCP target engagement.**
- **The observed changes in circulating and urinary conjugated BAs are consistent with reduced NTCP-mediated hepatic BA uptake and redistribution of BAs away from hepatocytes.**
- **These findings provide first reported clinical proof of concept for RNA editing-mediated NTCP modulation and support further evaluation in cholestatic liver disease to reduce intrahepatic cholestatic burden.**

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; 3.Cnubben NHP, et al. 2024 ASGCT