Treatment with Transthyretin-Lowering RNA Interference Therapeutics Is Not Associated with Ocular or Other Clinical Events Due to Vitamin A Reduction: Pooled Analysis of Vutrisiran and Patisiran Data

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Conclusions

- Across >10,000 patients with ATTR receiving vutrisiran or patisiran, some followed for up to 7 years, with >25,000 patient-years of treatment exposure, no confirmed cases of clinical vitamin A deficiency were observed in the clinical development programmes or post-marketing experience.
  - In a pooled analysis of five clinical studies, no safety findings attributable to vitamin A deficiency were observed or led to study drug discontinuation upon TTR lowering with vutrisiran or patisiran. In these studies, patients were instructed to take daily vitamin A supplementation.
- The lack of observed safety findings attributable to vitamin A deficiency is likely due to other known transport pathways facilitating continued delivery of vitamin A to tissues.
- These findings further support the favourable safety profile of RNAi therapeutics in ATTR treatment.

Key takeaway

No confirmed cases of clinical vitamin A deficiency were observed in the clinical development programmes of RNAi therapeutics or post-marketing experience

Introduction

ATTR and RNAi Therapy

- ATTR is a rapidly progressive, debilitating and fatal condition caused by pathogenic TTR accumulating as amyloid fibrils in multiple tissues, resulting in a spectrum of clinical manifestations that can include cardiomyopathy, polyneuropathy, and musculoskeletal, GI, and ocular manifestations[1–4]
- RNAi therapeutics vutrisiran and patisiran decrease hepatic TTR synthesis and improve the clinical manifestations of ATTR,[5–9] and are approved for the treatment of hATTR-PN[10,11] and wild-type or hereditary ATTR-CM (vutrisiran only)[11]

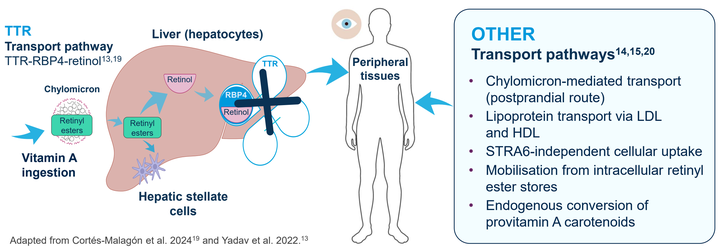
TTR Lowering and Vitamin A

- TTR has a role in transport of vitamin A (in the form of retinol) from the liver.[12] Vitamin A is essential for vision, immune function, reproduction, growth and cellular development[13]
  - Vitamin A is obtained from dietary sources, and hepatic stores of vitamin A are mobilised to be delivered via RBP4 as a complex with TTR, in cases of insufficient dietary uptake[13,14]
- While reduction in serum vitamin A is expected with TTR-lowering therapy,[10,11] multiple transport pathways can facilitate continued delivery of vitamin A to tissues (**Figure 1**)[14,15]
  - Patients receiving TTR-lowering RNAi therapeutics are advised to receive vitamin A supplementation at the recommended daily allowance, as a precautionary measure.[10,11] Serum vitamin A levels do not reflect the total amount of vitamin A available in the body and are not used to guide vitamin A supplementation beyond the recommended daily dose
- Vutrisiran and patisiran have demonstrated acceptable and well-tolerated safety profiles across phase 3 studies and in OLEs, with no AEs directly related to vitamin A deficiency reported.[5–8,16–18] The assessment of potential risk related to serum vitamin A reduction in cumulative clinical and real-world data has not been previously presented

Objective

- To assess whether TTR-lowering therapies vutrisiran and patisiran are associated with AEs attributable to vitamin A deficiency in patients with ATTR-CM or hATTR-PN

Figure 1. Vitamin A Transport Pathways



Adapted from Cortés-Malagón et al. 2024[19] and Yadav et al. 2022.[13]

OTHER
Transport pathways[14,15,20]

- Chylomicron-mediated transport (postprandial route)
- Lipoprotein transport via LDL and HDL
- STRA6-independent cellular uptake
- Mobilisation from intracellular retinyl ester stores
- Endogenous conversion of provitamin A carotenoids

Methods

- Pooled data from patients with ATTR who received ≥1 dose of vutrisiran, patisiran or placebo in **phase 3 studies** (**Figure 2**) were assessed for frequency and event rates of clinical and/or laboratory AEs:
  - High-level term "Visual impairment and blindness (excluding colour blindness)"
  - Preferred terms related to vitamin A deficiency
- Cumulative **post-marketing review** of Alnylam's global vutrisiran/patisiran safety database for safety concerns of ophthalmic or electroretinographic AEs or symptoms of vitamin A deficiency[21,22]

Figure 2. Clinical Studies of RNAi Therapeutics

ATTR-CM

HELIOS-B (NCT04153149)[5]

DB Period 33–36 months → OLE 24 months

Placebo n=328
Vutrisiran n=326

APOLLO-B (NCT03997383)[6]

DB Period 12 months → OLE 36 months

Placebo n=178
Patisiran n=181

hATTR-PN

HELIOS-A (NCT03759379)[7]

Treatment Period 18 months → RTE 42 months

Vutrisiran n=122
Patisiran[a] n=42

APOLLO and Patisiran OLE[b] (NCT01960348 / NCT02510261)[8,18]

DB Period 18 months → Global OLE 5 years[b]

Placebo n=77
Patisiran n=175

[a]No internal placebo arm. [b]Included patients from APOLLO and patisiran phase 2 study NCT01960348.

Results

- In the phase 3 clinical studies, all events categorised under the high-level term "Visual impairment and blindness" potentially attributable to vitamin A deficiency occurred at rates <1.0 event per 100 PY across treatment groups (**Table 1**)
- The most frequently reported ocular event was dry eye; there were no reports of visual AEs directly attributed to vitamin A deficiency (**Table 2**)
- There were no confirmed cases of clinical vitamin A deficiency, and therefore no such events led to study drug discontinuation
- Cumulative post-marketing review identified no safety concerns of ocular/electroretinographic AEs or vitamin A deficiency symptoms (**Figure 3**)

Table 1. "Visual Impairment and Blindness" High-Level Term Event Rates Were Low and Comparable across Groups

Preferred term, n events / EAER (per 100 PY)	Vutrisiran HELIOS-A, HELIOS-B N=709; PY=1915.1	Patisiran APOLLO, Patisiran OLE[a], APOLLO-B, HELIOS-A N=613; PY=1831.9	Placebo APOLLO, APOLLO-B, HELIOS-B N=583; PY=1098.5
Total high-level term[b] "Visual impairment and blindness (excluding colour blindness)"	20 / **1.0**	26 / **1.4**	12 / **1.1**
Amaurosis fugax	1 / **0.1**	0	0
Blindness	0	0	1 / **0.1**
Blindness unilateral	3 / **0.2**	0	0
Night blindness	2 / **0.1**	3 / **0.2**	2 / **0.2**
Visual acuity reduced	2 / **0.1**	8 / **0.4**	4 / **0.4**
Visual impairment	12 / **0.6**	15 / **0.8**	5 / **0.5**

[a]Includes patients with hATTR-PN from APOLLO and from the patisiran phase 2 OLE study. [b]Preferred terms within the high-level term with zero events are not presented.

Table 2. Event Rates for Preferred Terms Related to Vitamin A Deficiency Were Low across Groups, with No Symptomatic Vitamin A Deficiency

Preferred term, n events / EAER (per 100 PY)	Vutrisiran HELIOS-A, HELIOS-B N=709; PY=1915.1	Patisiran APOLLO, Patisiran OLE[a], APOLLO-B, HELIOS-A N=613; PY=1831.9	Placebo APOLLO, APOLLO-B, HELIOS-B N=583; PY=1098.5
Preferred term,[b] Clinical and / or Laboratory			
Dry eye	17 / **0.9**	24 / **1.3**	11 / **1.0**
Keratomalacia	0	0	0
Retinopathy	0	0	0
Vitamin A deficiency-related eye disorder	0	0	0
Vitamin A deficiency-related conjunctival disorder	0	0	0
Vitamin A deficiency-related corneal disorder	0	0	0
Xerophthalmia	1 / **0.1**	0	1 / **0.1**
Preferred term,[b] Laboratory only			
Vitamin A decreased	11 / **0.6**	2 / **0.1**	NR[c]
Vitamin A deficiency	2 / **0.1**	2 / **0.1**	NR[c]

[a]Includes patients with hATTR-PN from APOLLO and from the patisiran phase 2 OLE study. [b]List of preferred terms has been previously established to monitor for AEs related to vitamin A deficiency in post-marketing aggregate safety reports. [c]Laboratory vitamin A decrease or deficiency would not be reported for patients receiving placebo, as they were in the DB period of corresponding studies during which vitamin A measurements were prohibited due to the risk of unblinding.

Figure 3. Cumulative Experience Has Not Identified Signals of Clinical Vitamin A Deficiency

>10,000 patients received vutrisiran or patisiran[21,22]

>7 years of vutrisiran or patisiran treatment[18,21,22]

>25,000 PY of treatment exposure[17,21,22]

No confirmed cases of clinical vitamin A deficiency have been observed in the vutrisiran and patisiran clinical development programmes or post-marketing experience as of 19 November 2025

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If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.

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Abbreviations: AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; DB, double-blind; EAER, exposure-adjusted event rate; GI, gastrointestinal; hATTR-PN, hereditary ATTR with polyneuropathy; HCP, healthcare professional; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NR, not reported; OLE, open-label extension; PY, patient-years; RBP, retinol-binding protein; RNAi, RNA interference; RTE, randomised treatment extension; STRA6, stimulated by retinoic acid 6; TTR, transthyretin.