# Vutrisiran: Immunogenicity

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## SUMMARY


- In the Phase 1 study of vutrisiran, 1 of the 80 (1.3%) patients, who received vutrisiran 25 mg, was confirmed ADA positive on Day 29 with a low titer (50). All subsequent samples tested negative.[1,2]
- In the HELIOS-A study, a total of 3 (2.5%) vutrisiran-treated patients developed ADAs at Month 9 and 4 (3.3%) vutrisiran-treated patients developed ADAs at Month 18. ADA titers were low and transient with no evidence of an effect on clinical efficacy, safety, or PD parameters of vutrisiran.[3–5]
- In the HELIOS-B study, 1 (0.3%) vutrisiran-treated patient developed transient, low titer ADAs with no evidence of an effect on clinical efficacy, safety, PK, or PD parameters of vutrisiran.[6]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety concerns regarding ADAs.[7]
- ADA testing for vutrisiran is not commercially available.


## INDEX



## RELEVANT INFORMATION

### Vutrisiran Formulation

Vutrisiran utilizes GalNAc conjugate technology as the method of drug delivery which allows for subcutaneous injection.[3] GalNAc conjugation facilitates siRNA delivery into the liver via the ASGPR expressed on hepatocytes. Vutrisiran uses second generation ESC, which includes a combination of additional phosphorothioate linkages, as well as 2′-O-methyl and 2′-fluoro nucleotide modifications, that provide improved molecular and metabolic stability.[8]

### ADA Testing Availability

ADA testing for vutrisiran is not commercially available.

## CLINICAL DATA

### Phase 1 Study

A phase 1, randomized, single-blind, placebo-controlled, single ascending dose study was conducted to evaluate the safety, tolerability, PK, and PD of a single dose of vutrisiran in healthy subjects (N=80). The subjects were scheduled to receive a single dose of either subcutaneous vutrisiran (n=60) or placebo (n=20). Study subjects were enrolled in cohorts to receive 25 mg (n=6), 50 mg (n=6), 100 mg (n=6), 200 mg (n=6), or 300 mg (n=6) of vutrisiran. Following the enrollment of these cohorts, five additional cohorts were enrolled: a 5 mg cohort (n=6); two additional cohorts of 25 mg (n=6) and 50 mg (n=6) to better characterize these doses; and two cohorts of Japanese subjects, for whom dosing was initiated at a level shown to be tolerable in a prior cohort (25 mg [n=6] and 50 mg [n=6]).[2]

ADAs

In the Phase 1 study, blood samples were collected prior to dosing (Day -1) and on Days 29 and 90 post-dose for the detection of ADA. One of the 80 (1.3%) patients, who received vutrisiran 25 mg, was confirmed ADA positive on Day 29 with a low titer (50). The ADA did not affect the patient's PK or PD parameters, and all subsequent samples for ADA tested negative. Prior to dosing, 2 (3.3%) patients tested ADA positive. Of these patients, 1 tested ADA negative at all time points post-dose, and the other had a transient positive titer on Day 90.[1,2]

### HELIOS-A Study

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[3]

ADAs

The presence of ADAs to vutrisiran was assessed as an exploratory endpoint of the HELIOS-A study. Blood samples for ADA testing were collected at specified time points (Day 1 pre-dose; Week 3, 12, 24, 36, 48, 72, 79-80) during the study and assessed using a validated ELISA method.[9]

In the HELIOS-A study, a total of 3 (2.5%) vutrisiran-treated patients developed ADAs at Month 9 and 4 (3.3%) vutrisiran-treated patients developed ADAs at Month 18. ADA titers were low and transient with no evidence of an effect on clinical efficacy, safety, or PD parameters of vutrisiran.[3–5]

### HELIOS-B Study

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an OLE.[10]

ADAs

The presence of ADAs to vutrisiran was assessed as a PD endpoint of the HELIOS-B study. Blood samples for ADA testing were collected at specified time points (Week 1, 12, 24, 36, 48, and 108 during the double-blind treatment period; the pre-tafamidis drop-in visit; and every 12 weeks during the follow-up period) and assessed using a validated ELISA method.[11]

In the HELIOS-B study, 1 (0.3%) vutrisiran-treated patient developed transient, low titer ADAs. The available data are limited to make definitive conclusions regarding the effect of ADAs on PK or PD of vutrisiran.[6]

## GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify new safety concerns regarding ADAs.[7]

## AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following section(s) of the AMVUTTRA Prescribing Information[6]:

- CLINICAL PHARMACOLOGY Section 12.2 Pharmacodynamics: Cardiomyopathy of Wild-type (wt) or Hereditary Transthyretin-mediated Amyloidosis (hATTR)
- CLINICAL PHARMACOLOGY Section 12.6 Immunogenicity

## ABBREVIATIONS

ADA = antidrug antibody; ASGPR = asialoglycoprotein receptor; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; ELISA = enzyme-linked immunosorbent assay; ESC = enhanced stabilization chemistry; GalNAc = N-acetyl galactosamine; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; siRNA = small interfering ribonucleic acid; wtATTR = wild-type transthyretin amyloidosis.

*Updated 21 March 2025*

## REFERENCES


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