Vutrisiran: Immunogenicity

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SUMMARY

- In vutrisiran clinical studies, 1 (1.3%) vutrisiran-treated patient in the phase 1 study, 4 (3.3% by Month 18) in HELIOS-A, and 1 (0.3%) in HELIOS-B, developed transient, low-titer ADAs with no evidence of an effect on PK or PD parameters of vutrisiran.[1–6]
- A pooled safety analysis including data from 707 patients who received at least one dose of vutrisiran at any time during the HELIOS-A and HELIOS-B studies was conducted to evaluate the safety of vutrisiran in patients with ATTR who received treatment for up to 58 months.[7]
  - Of the patients with baseline and postbaseline ADA results, 1.5% developed treatment emergent, transient, low-titer ADAs with no pattern of AEs to suggest an impact on the safety profile of vutrisiran.[7]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify safety concerns regarding ADAs.[8]
- ADA testing for vutrisiran is not commercially available.

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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.[9]

ADA Testing Availability

ADA testing for vutrisiran is not commercially available.

CLINICAL DATA

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.[10]

In the HELIOS-A study, 3 (2.5%) vutrisiran-treated patients developed ADAs by Month 9, with a total of 4 (3.3%) patients by 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.[11]

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.[12]

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]

Pooled Safety Analysis of HELIOS-A and HELIOS-B

A pooled safety analysis including data from 707 patients who received at least one dose of vutrisiran at any time during the HELIOS-A and HELIOS-B studies was conducted to evaluate the safety of vutrisiran in patients with ATTR who received treatment for up to 58 months.[7]

The HELIOS-A vutrisiran group consisted of 160 patients who received at least one dose of vutrisiran in the initial 18-month treatment period (n=122) or initially received patisiran in the treatment period and were re-randomized to receive vutrisiran during the RTE (n=38). The HELIOS-B vutrisiran group

consisted of 547 patients who received at least one dose of vutrisiran during the double-blind treatment period (n=326) or initially received placebo during the double-blind period and transitioned to vutrisiran in the OLE (n=221).[7]

ADAs

Incidence of ADAs was low with vutrisiran treatment up to 58 months. In the combined vutrisiran group, 64.9% of patients had baseline and postbaseline ADA results. Treatment emergent ADAs developed in 1.5% of these patients. ADA titers were low and transient, with no pattern of AEs in patients with ADAs to suggest an impact of ADAs on the safety profile of vutrisiran.[7]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify safety concerns regarding ADAs.[8]

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; AE = adverse event; ASGPR = asialoglycoprotein receptor; ATTR = transthyretin amyloidosis; 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; RTE = randomized treatment extension; siRNA = small interfering ribonucleic acid; wtATTR = wild-type transthyretin amyloidosis.

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