DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jennifer Backo
Sr. Director, Regulatory Affairs
Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, MA 02142

RE: NDA 215515
AMVUTTRA® (vutrisiran) injection, for subcutaneous use
MA 352

Dear Jennifer Backo:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, the "ATTR-CM[1]," webpage[2] (AMV-USA-01405) (webpage) on the AMVUTTRA Consumer Website, for AMVUTTRA® (vutrisiran) injection, for subcutaneous use (Amvuttra) submitted by Alnylam Pharmaceuticals, Inc. (Alnylam) under cover of Form FDA 2253. FDA also received complaints regarding other promotional communications with representations similar to those discussed in this letter. FDA has determined that the webpage is false or misleading. Thus, the webpage misbrands Amvuttra and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The top of the webpage includes the following prominent headline claim (emphasis original):

- "**Proven to help people with ATTR-CM live longer**"

Below the headline claim, the center of the page includes the following prominent claim (emphasis original):

- "**People lived longer with continued treatment**"

When a user clicks on the above claim, the following claims and presentations appear which include study results from the open-label extension portion of the HELIOS-B study for "Everyone in the study" (i.e., overall population) (in pertinent part, emphasis original):

- "Analyses done over 3½ years compared the original AMVUTTRA® (vutrisiran) and placebo groups from the beginning of the study. After 3 years, people taking placebo

[1] Cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis
[2] "ATTR-CM" webpage is accessed by clicking on the "People lived longer with continued treatment" icon on the website: https://www.amvuttra.com/results-with-amvuttra/how-amvuttra-may-help/attr-cm (last accessed April 23, 2026).

switched to AMVUTTRA so that everyone still in the study received AMVUTTRA for up to an additional 6 months."

- "**The risk of death was lower over 3½ years with AMVUTTRA**.*"
  - In conjunction with a prominent graphic stating "**36% Lower Risk** compared to placebo"

- "**Survival was estimated in a separate analysis at 3½ years.**"
  - In conjunction with a prominent graphic stating "**80% Survival Rate** for people taking AMVUTTRA at 3½ years compared to **72% for people taking placebo**"

- "*Most deaths were heart-related"

Users can also click on the tab titled, "A group in the study," to see the following claims and presentations regarding the monotherapy population (i.e., "people not taking a stabilizer at the start of the study") (in pertinent part, emphasis original):

- "**The risk of death was lower over 3½ years with AMVUTTRA**.*"
  - In conjunction with a prominent graphic stating "**35% Lower Risk** compared to placebo"

- "**Survival was estimated in a separate analysis at 3½ years.**"
  - In conjunction with a prominent graphic stating "**76% Survival Rate** for people taking AMVUTTRA at 3½ years compared to **67% for people taking placebo**"

- "*Most deaths were heart-related"

The totality of the claims and presentations above creates a misleading impression that treatment with Amvuttra has shown a definitive and quantified benefit, with specific established levels of efficacy, on mortality over 3½ years, when this is not the case. These conclusions are not supported by the results from the open-label extension portion of HELIOS-B study. This is especially concerning from a public health perspective because ATTR-CM is a progressively debilitating and life-threatening disease that has high morbidity and mortality.

HELIOS-B was a multicenter, randomized, double blind, placebo-controlled study that evaluated the effect of Amvuttra compared to placebo in adult patients with ATTR-CM. The primary efficacy endpoint was the composite outcome of all-cause mortality and recurrent CV events during the double-blind treatment period of up to 36 months, evaluated in the overall population and in the monotherapy population.

The claims and presentations above are based on the secondary endpoint of all-cause mortality evaluated at 3½ years, which included the double-blind period plus an additional 6 month *open-label* extension period. At the 3½ year timepoint, no true placebo comparator group remained because all placebo patients had been unblinded and switched to Amvuttra following the double-blind period. Given the open-label nature of the extension period which introduces bias and confounding, and the lack of a concurrent control, it is unclear whether events occurring during the short duration of the open-label extension were due to continued

effects of treatment, continued progression of the disease, or differences in patient populations that remained in the study and continued into the open-label extension, thereby limiting the interpretability of the results.

For these reasons, the open-label extension portion of the HELIOS-B study was inadequately designed to support conclusory representations about the impact of Amvuttra on all-cause mortality over 3½ years such as those in the claims and presentations above. We acknowledge that the webpage includes the following statement in conjunction with the survival rates at 3½ years:

- "This analysis was not included in the original study plan, and other factors could have influenced the results. Talk to your doctor about what this might mean for you."

However, including this statement in Amvuttra promotional communications, along with misleading representations about Amvuttra's efficacy, does not render the promotional communication nonmisleading in light of the issues with the open-label extension portion of the HELIOS-B study (explained above) that make the study incapable of supporting such conclusions.

Conclusion and Requested Action

For the reasons described above, the webpage misbrands Amvuttra and makes the distribution of the drug in violation of the FD&C Act.

This letter notifies you of our concerns and provides you with an opportunity to address them. FDA requests that Alnylam take immediate action to address any violations (including, for example, ceasing and desisting promotional communications that are misleading as described above).

Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Amvuttra that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Amvuttra.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 352 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a

subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6.

Additionally, the response submission should be coded as an Amendment to eCTD Sequence 434 under NDA 215515. Questions related to the submission of your response letter should be emailed to CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ankur Kalola, PharmD, RAC
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Sapna Shah, PharmD
Team Leader
Division of Advertising & Promotion Review 2
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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