Vutrisiran (Amvuttra)

Use of an Externally Controlled Trial and Confirmatory Evidence to Demonstrate Substantial Evidence of Effectiveness

Prior to reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. Please note this case study is not intended or designed to provide specific strategies for obtaining product approval. **Rare disease drug development is not one-size-fits-all.** The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

Introduction

This case study examines the use of a single adequate and well-controlled investigation, with an external control, and confirmatory evidence to demonstrate substantial evidence of effectiveness for an application submitted to the U.S. Food and Drug Administration (FDA) for the approval of vutrisiran (Amvuttra). For further details on this case study, please refer to the Integrated Review.

Before conducting the clinical trial, the Applicant provided evidence to support the use of an external control from their previously approved drug in the same pharmacological class in the assessment of the single adequate and well-controlled investigation. The Applicant's confirmatory evidence comprised strong mechanistic evidence for vutrisiran, along with the mechanistic data and scientific knowledge about the effectiveness of another drug in the same, well-characterized pharmacological class.

Vutrisiran is a synthetic, double-stranded small interfering ribonucleic acid (siRNA)-GalNAc conjugate that targets variant and normal (wild type) transthyretin (TTR) messenger RNA (mRNA). It is approved for the treatment of polyneuropathy (PN) caused by hereditary transthyretin-mediated amyloidosis in adults, which is hereafter referred to as hATTR-PN.

The Applicant engaged with the Agency early in planning for its new drug application (NDA) submission to discuss the design of its one adequate and well-controlled investigation and confirmatory evidence to satisfy statutory requirements (section 505(d) of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. § 355(d)) for demonstrating substantial evidence of effectiveness.

Although the topic of establishing safety is not discussed in this case study, please note that FDA approval is based not only on the demonstration of substantial evidence of effectiveness but also on a determination that a drug is safe for its intended use and that the benefits of the drug outweigh its risks.

FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of draft FDA guidance documents which, when final, will represent the Agency's current thinking on topics in the case study. For up-to-date guidance documents please search Guidance Documents for Rare Disease Drug Development | FDA

In this case study, the Applicant engaged with the FDA early in planning for their new drug application. Meeting with the FDA early in the drug development process is crucial so that potential issues may be addressed prior to pivotal clinical studies.

This guidance describes the types of meetings available to sponsors:

Draft guidance for industry: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry* (September 2023)

When a meeting is desired, a written request must be submitted to the FDA via the electronic gateway or, to CDER, via the CDER NextGen Portal, as applicable. Requests should be addressed to the appropriate center and review division or office and, if previously assigned, submitted to the relevant application (e.g., investigational new drug application [IND], new drug application [NDA], biologics license application [BLA]).

If necessary, noncommercial IND holders may also submit the meeting request via the appropriate center's document room.

For the single adequate and well-controlled investigation, the Applicant used the placebo arm from a study conducted for a previously approved drug in the same pharmacological class, patisiran, as an external control. Patisiran,[1] another siRNA developed by the same Applicant with the same mechanism of action as vutrisiran, was also approved for the treatment of hATTR-PN. In addition, the Applicant provided confirmatory evidence from data that supported the mechanism of action of vutrisiran, as well as mechanistic data and scientific knowledge about the effectiveness of patisiran.

Introduction to the Rare Condition

hATTR amyloidosis is a rare life-threatening autosomal dominant disorder caused by more than 120 known variants in the *TTR* gene. The normal (or wild type) TTR protein is primarily synthesized in the liver and secreted into the bloodstream. Normal TTR exists in a tetrameric form that acts as a carrier, transporting vitamin A (retinol) and a hormone called thyroxine throughout the body. Mutations in the *TTR* gene lead to misfolding of the TTR protein, resulting in protein aggregation and amyloid deposition in the peripheral and central nervous systems, heart, kidneys, eyes, bone, and gastrointestinal tract.

hATTR-PN is one of the three forms of hATTR amyloidosis, each defined by the organs where amyloid deposition occurs. hATTR-PN primarily affects the peripheral nervous system, resulting in progressive nerve damage and symptoms such as numbness, tingling, pain, and weakness. Focal nerve lesions (e.g., carpal tunnel syndrome) and autonomic dysfunction (e.g., orthostatic hypotension, gastrointestinal dysfunction) are also common among patients with hATTR-PN.

Symptoms of hATTR-PN typically begin between 20 and 70 years of age and most patients die within 5 to 12 years after onset, usually due to cardiac dysfunction, infection, or cachexia. While the exact incidence of hATTR amyloidosis is unknown and varies geographically, approximately 100 to 2500 individuals are estimated to have hATTR-PN in the United States.[2]

FDA Guidance Corner

Meeting with the FDA to discuss development plans is crucial so that potential issues may be addressed prior to pivotal clinical studies.

This guidance highlights important considerations in rare disease drug and biologics development:

Guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023)

FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses even within a condition. Further complexity is added depending on what is known about a disease's natural history and pathophysiology. As such, no one program will be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

Current Treatment Options

Before the approval of vutrisiran, patisiran and inotersen were the two drugs approved for the treatment of hATTR-PN in the U.S. patisiran is administered intravenously every three weeks and inotersen is administered subcutaneously once a week. Inotersen is only available through a restricted distribution program because of the risks of thrombocytopenia and glomerulonephritis. Since the approval of vutrisiran, eplontersen was approved in 2023 for the same indication and is administered once a month. Diflunisal and tafamidis are sometimes used off-label to treat hATTR-PN. Diflunisal is a non-steroidal anti-inflammatory drug, and tafamidis is approved for the treatment of the cardiomyopathy associated with hATTR amyloidosis in adults. Other treatment options for hATTR amyloidosis include liver transplant and medical management of associated symptoms.

[1] For more information about patisiran, please refer to the Integrated Review for patisiran.

[2] Schmidt, H, M Waddington-Cruz, M Botteman, J Carter, A Chopra, M Hopps, M Stewart, S Fallet, and L Amass, 2018, Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. Muscle Nerve, 57: 829-837.

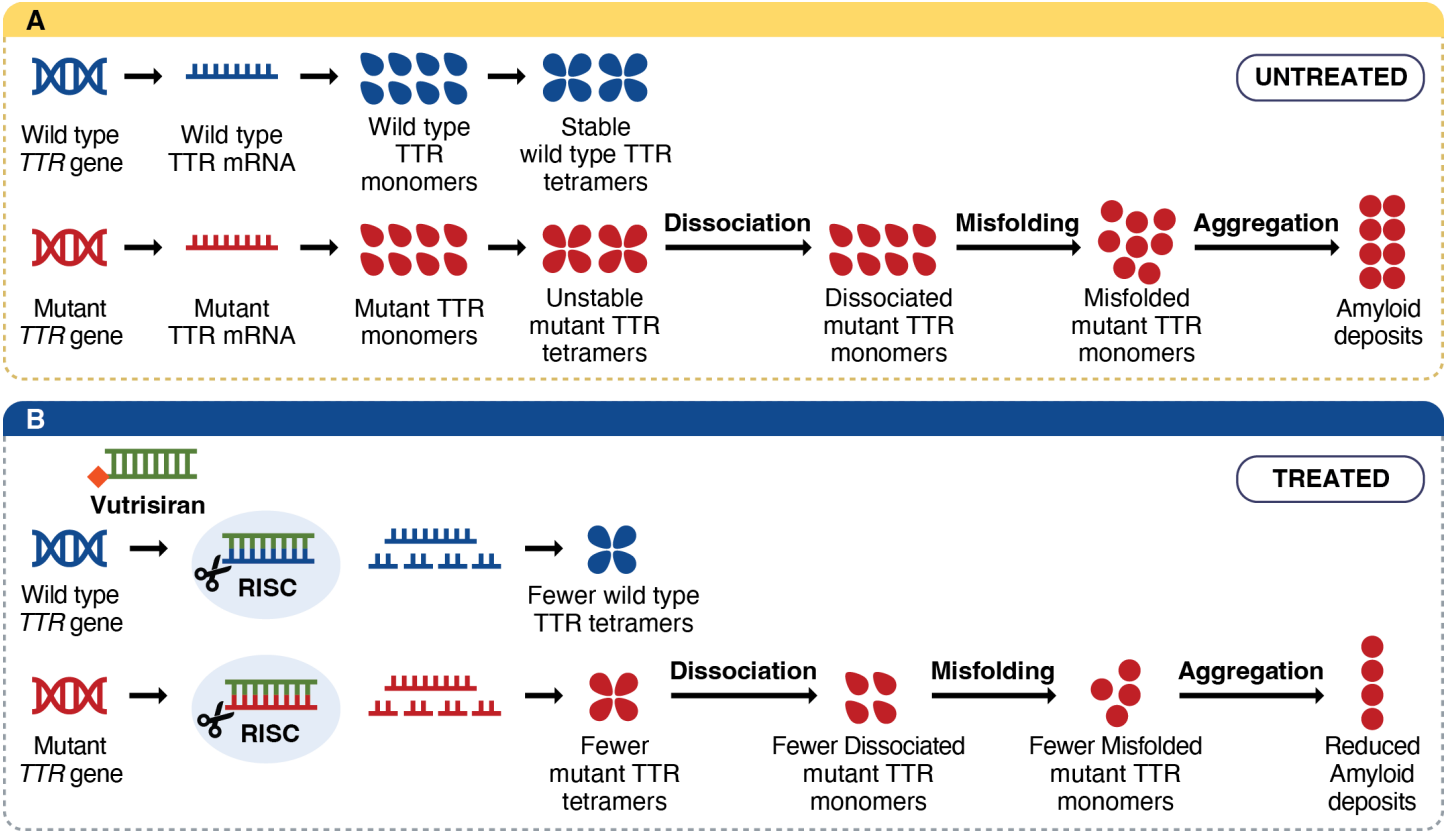
Vutrisiran Mechanism of Action

hATTR amyloidosis is caused by variants in the *TTR* gene leading to structural changes in the TTR protein. These changes cause the tetrameric TTR protein to break down into monomeric units which then misfold and aggregate into amyloid fibril deposits. Vutrisiran is an siRNA that targets and degrades TTR mRNA. The binding of vutrisiran to TTR mRNA triggers its degradation by the RNA-induced silencing complex (RISC) pathway, a cellular mechanism involved in RNA interference (Figure 1). By degrading the TTR mRNA, vutrisiran reduces the synthesis of TTR protein in the liver, reduces abnormal protein production and the formation and accumulation of amyloid deposits, and addresses the underlying cause of hATTR amyloidosis.

Both patisiran and inotersen also reduce TTR protein production by targeting and degrading TTR mRNA. However, patisiran and vutrisiran have a similar mechanism of action, reducing TTR protein production by degrading TTR mRNA via the RISC pathway. Inotersen is an antisense oligonucleotide that also binds TTR mRNA but utilizes a different mechanism of action.

Unlike patisiran, vutrisiran is synthetically modified (i.e., covalently linked to a ligand containing three N-acetylgalactosamine [GalNAc] residues) for greater metabolic stability, prolonged liver residence time, and less frequent dosing (every 3 months) compared to the dosing regimen for patisiran (every 3 weeks). Vutrisiran is administered subcutaneously every three months while patisiran is administered intravenously every three weeks.

Figure 1: A) *In the liver, the TTR gene is transcribed into TTR mRNA, which is then translated into correctly folded (wild type) TTR monomers. TTR monomers assemble into stable tetramers, which are secreted into bloodstream and facilitate transport of vitamin A and thyroxine throughout the body. Mutations in the TTR gene cause structural changes that lead to the dissociation of tetramers into monomers, which then misfold and aggregate into amyloid deposits in various parts of the body.* ***B)*** *Vutrisiran, a chemically modified siRNA, targets both wild type and mutant TTR mRNAs, leading to their degradation by RISC pathway. As a result, fewer misfolded TTR monomers are made, resulting in reduced amyloid deposits and fewer polyneuropathy symptoms.*



The Single Adequate and Well-Controlled Clinical Investigation (HELIOS-A)[3]

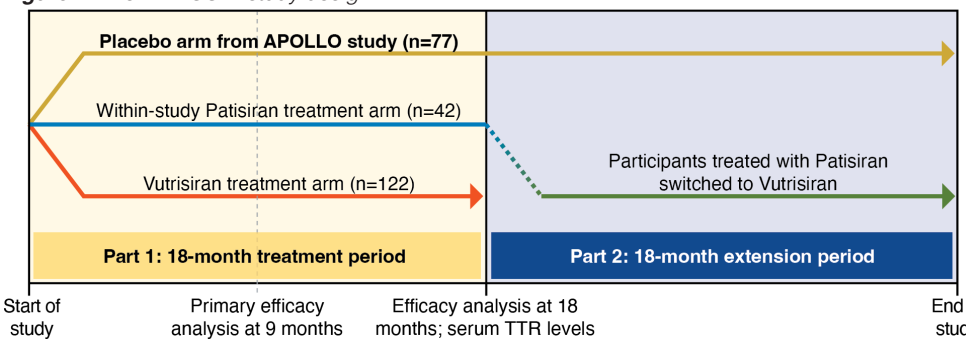
The Applicant met with FDA early in the development program to discuss trial design and efficacy endpoints. Evidence of effectiveness for vutrisiran came from a single adequate and well-controlled clinical investigation (i.e., HELIOS-A), which utilized an external control. The HELIOS-A study was a Phase 3, randomized, open-label trial that enrolled participants between 18 and 85 years of age who were diagnosed with hATTR amyloidosis with a documented mutation in the *TTR* gene. The Applicant enrolled 164 participants into two different treatment arms (122 vutrisiran-treated, and 42 patisiran-treated) and included 77 placebo-treated participants from a separate study (APOLLO)[4] for the external comparator group (**Figure 2**). The APOLLO study was previously conducted for the approval of patisiran for the treatment of hATTR-PN.

The Applicant proposed use of the APOLLO placebo group as an external control for their HELIOS-A study because:

- The enrollment criteria for the APOLLO and HELIOS-A studies were similar.
- In addition to enrolling similar patient populations, the two studies evaluated similar endpoints.[5]
- Given vutrisiran and patisiran were in the same pharmacological class, the Applicant expected a large magnitude of effect of vutrisiran that was comparable to the effects observed with patisiran.

Given the aforementioned considerations, FDA accepted the Applicant's proposal to use this external control for the HELIOS-A study. The HELIOS-A study also included an active control arm with patisiran, which was not powered for formal comparisons to vutrisiran on clinical outcomes but was intended to assess the relative efficacy and safety of vutrisiran compared with previously approved patisiran. The 42 participants treated with patisiran were switched to vutrisiran after the initial 18-month treatment period and were assessed using an exploratory endpoint.

Figure 2: *The HELIOS-A study design.*[6]



FDA Guidance Corner

In this case study, the Applicant used a suitable externally controlled trial design. This guidance provides insight into important considerations when designing an externally controlled trial:

Guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023)

In an externally controlled trial, outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people external to the trial who had not received the same treatment… Importantly, before choosing to conduct a clinical trial using an external control arm as a comparator, sponsors and investigators should consider the likelihood that such a trial design would be able to distinguish the effect of a drug from other factors that impact the outcome of interest and meet regulatory requirements.

Sponsors should finalize a study protocol before initiating the externally controlled trial, including selection of the external control arm and analytic approach, rather than selecting an external control arm after the completion of a single-arm trial. Specific design elements to prespecify in the protocol (i.e., before conducting an externally controlled trial) include suitable study data sources, baseline eligibility (inclusion and exclusion) criteria, appropriate exposure definitions and windows, well-defined and clinically meaningful endpoints, cogent analytic plans, and approaches to minimize missing data and sources of bias.

[3] For more information on trial design, please refer to pg. 26 of the Integrated Review.

[4] For more information about APOLLO, please refer to the Integrated Review for patisiran, NDA 210922.

[5] Participants enrolled in both trials had the same inclusion criteria in terms of age, hATTR-PN diagnosis (i.e., a documented mutation in the *TTR* gene), neuropathy impairment score (NIS), and polyneuropathy Disability (PND) score.

[6] Figure 2 was generated using information provided in the Integrated Review for vutrisiran (Amvuttra), NDA 215515 on pg. 27.

HELIOS-A: A Closer Look at the Study Population and Endpoints

Study Population

In addition to the inclusion criteria regarding age and diagnosis (see The Single Adequate and Well-Controlled Clinical Investigation section), to participate in the study, participants were also required to have:

- A neurological impairment score (NIS) of 5 to 130 (inclusive).
- A Polyneuropathy Disability (PND) score of ≤3b.

For more information on the NIS assessment and PND scale, please refer to the publicly available clinical review at Drugs@FDA.

Study Endpoints

The primary endpoint was the change from baseline to Month 9 on the Modified Neurological Impairment Score +7 (mNIS+7) in vutrisiran-treated participants compared to the external placebo control arm. As measured by the change in mNIS+7 score at 9 months, there was worsening of neurological impairment in the external placebo group and improvement in the vutrisiran group ($p<0.0001$). The Applicant had been advised to use a functional endpoint as the primary endpoint and that the mNIS+7 results would be considered in the context of results from the secondary endpoints, particularly the functional endpoint (i.e., the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score).

Only 9 months of efficacy data for the HELIOS-A study were included with the application. Therefore, only the first two secondary endpoints at Month 9 for the HELIOS-A study, the Norfolk QoL-DN and the 10-meter walk test (10-MWT), were statistically evaluated. The remaining pre-specified Month 18 secondary endpoints (modified Body Mass Index (mBMI), Rasch-built Overall Disability Scale (R-ODS)) were evaluated at Month 9 as exploratory endpoints.

The key secondary endpoint for the HELIOS-A study is the change in Norfolk QOL-DN score at 9 months. It is a clinically meaningful functional endpoint that is appropriate for use in this study. There was an improvement in the Norfolk QOL-DN score in the vutrisiran group, compared to a worsening in the external placebo group. The next secondary endpoint, the change from baseline at Month 9 in the 10-MWT, showed maintenance of gait speed in the vutrisiran group compared to mean worsening in the external placebo group at 9 months. Both Month 9 secondary efficacy endpoints for the HELIOS-A study had statistically significant results that support the efficacy of vutrisiran.

FDA Guidance Corner

In this case study, the Applicant performed one adequate and well-controlled investigation and provided confirmatory evidence which was generated from quality data derived from an appropriate source.

This guidance which, when final will represent the Agency's current thinking, provides important insights into single trial design, and considerations when determining the appropriateness of confirmatory evidence:

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Confirmatory Evidence: The quantity (e.g., number of sources) of confirmatory evidence necessary to support effectiveness may vary across development programs. Importantly, the quantity of confirmatory evidence needed in a development program will be impacted by the features of, and results from, the single adequate and well-controlled clinical investigation that the confirmatory evidence is intended to substantiate. It may be possible for a highly persuasive adequate and well-controlled clinical investigation to be supported by a lesser quantity of confirmatory evidence, whereas a less-persuasive adequate and well-controlled clinical investigation may require a greater quantity of compelling confirmatory evidence to allow for a conclusion of substantial evidence of effectiveness.

Mechanistic or Pharmacodynamic Evidence: Under certain circumstances, strong mechanistic evidence of the drug's treatment effect in a particular disease may be appropriate to use as confirmatory evidence. In such cases, (1) the pathophysiology of the disease should be well understood and (2) the drug's mechanism of action should be both clearly understood and shown to directly target the major driver or drivers of the disease pathophysiology.

The Confirmatory Evidence

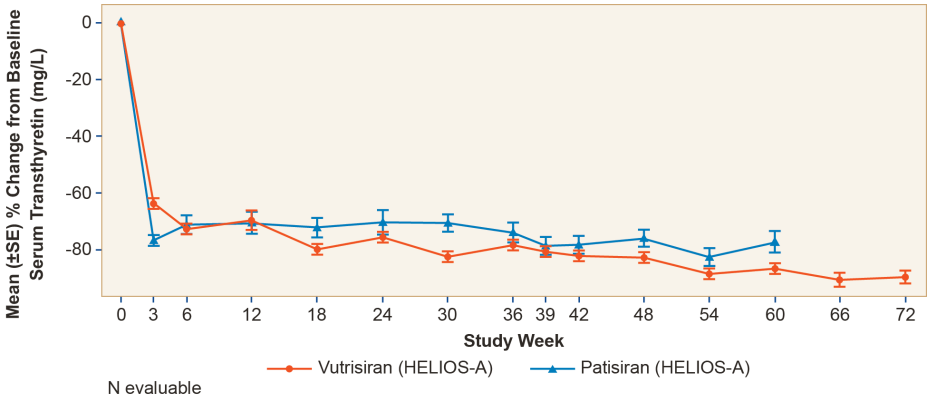
In the HELIOS-A study, the Applicant used a pharmacodynamic endpoint, serum TTR levels, in participants treated with vutrisiran and patisiran (see **Figure 2**) as confirmatory evidence.

Figure 3 illustrates the serum TTR change from baseline over time among participants from HELIOS-A treated with vutrisiran and patisiran.

These pharmacodynamic data show significant reductions in TTR levels over time for vutrisiran that align with the efficacy assessments and are consistent with vutrisiran's mechanism of action. These mechanistic insights are further substantiated by the similar results observed for patisiran which shares the same mechanism of action with vutrisiran.

These mechanistic data (i.e., reduction in serum TTR), in addition to the scientific knowledge of a similar drug in the same pharmacological class, supported the mechanism of action of vutrisiran and provided confirmatory evidence to demonstrate substantial evidence of effectiveness.

Figure 3: *Mean (±SE) TTR percent change from baseline over time during the HELIOS-A study.*[7]



N evaluable															
Vutrisiran	122	114	109	119	105	117	91	118	113	51	85	35	41	8	11
Patisiran	42	42	41	41	37	38	39	34	37	22	27	14	12		

Conclusion

Demonstrating substantial evidence of effectiveness is required for regulatory approval. The effectiveness of vutrisiran for treating hATTR-PN was established based on the positive results of a single adequate and well-controlled investigation and confirmatory evidence, which came from data that provided strong mechanistic support (i.e., reduction in serum TTR) in addition to scientific knowledge about the effectiveness of another drug in the same pharmacological class (i.e., patisiran for the treatment of hATTR-PN).

FDA Guidance Corner

In this case study, the Applicant was able to demonstrate substantial evidence of effectiveness through the use of one adequate and well-controlled investigation plus confirmatory evidence. This guidance which, when final, will represent the Agency's current thinking, provides important considerations for designing a drug development program that will result in the demonstration of substantial evidence of effectiveness:

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

The Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115) state[s] that the substantial evidence requirement for effectiveness, which had generally been interpreted as calling for two adequate and well-controlled trials, could also be met by a single trial plus confirmatory evidence.

FDA will consider a number of factors when determining whether reliance on a single adequate and well-controlled clinical investigation plus confirmatory evidence is appropriate. These factors may include the persuasiveness of the single trial; the robustness of the confirmatory evidence; the seriousness of the disease, particularly where there is an unmet medical need; the size of the patient population; and whether it is ethical and [practical] to conduct more than one adequate and well-controlled clinical investigation. Sponsors intending to establish substantial evidence of effectiveness using one adequate and well-controlled clinical investigation plus confirmatory evidence should consult FDA in advance to discuss the appropriateness of such an approach for their development program.

[7] Figure 3 was generated using information provided (Figure 6) from the Integrated Review for vutrisiran (Amvuttra), NDA 215515.

Vutrisiran (Amvuttra)

Highlights

- To demonstrate effectiveness of vutrisiran for treating hATTR-PN, the Applicant conducted a single adequate and well-controlled investigation that utilized an **external placebo control arm** from a previous study conducted for an already approved therapy that shares the same mechanism of action and was approved for the same indication.
- The Applicant used pharmacodynamic data comparing vutrisiran with the available therapy, patisiran, for hATTR-PN as confirmatory evidence.
- For drug developers contemplating use of confirmatory evidence to support an FDA application, FDA recommends discussion early in the drug development process. For information on how to interact with the FDA please see Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry* (September 2023) which, when final, will represent the Agency's current thinking.

For more information on confirmatory evidence please refer to the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) which, when final, will represent the Agency's current thinking.

Key Takeaways

The statutory requirement (section 505(d) of the FD&C Act (21 U.S.C. § 355(d)) for demonstrating substantial evidence of effectiveness was met with this single multicenter phase 3 investigation and confirmatory evidence for the following reasons:

- The study results provided statistically significant evidence of the efficacy of vutrisiran in treating hATTR-PN on a primary efficacy endpoint that evaluated the effect of vutrisiran on clinically meaningful aspects of neurologic impairment in participants treated with the drug relative to the external control group.
- Vutrisiran demonstrated statistically significant and clinically meaningful improvement in quality of life, a secondary endpoint, for vutrisiran-treated participants as compared to placebo arm from a prior trial (i.e., the external control group).
- Vutrisiran also demonstrated a statistically significant improvement on a separate secondary endpoint measuring gait speed (i.e., 10-meter walk test). Modified body mass index (mBMI) at month 9 was an exploratory endpoint in HELIOS-A. The mBMI is the product of BMI and the concentration of serum albumin. Although the mBMI measured at 9 months was an exploratory endpoint, its inclusion in product labeling was considered and ultimately accepted because of its clinical meaningfulness and large effect size.
- The inclusion of the within-study patisiran treatment arm demonstrated that vutrisiran's effect on clinical outcomes was comparable to the available therapy, patisiran.
- The Applicant compared patisiran and vutrisiran (i.e., within-study comparison) using a pharmacodynamic endpoint, serum TTR levels, in participants treated with vutrisiran and patisiran to generate pharmacodynamic/mechanistic data. These data supported the mechanism of action of vutrisiran and provided confirmatory evidence to support substantial evidence of effectiveness.

For different approaches to establish substantial evidence of effectiveness, please refer to draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) which, when final, will represent the Agency's current thinking.

Critical Thinking Questions for a Rare Disease Drug Development Program:
Will the Development Plan Establish Substantial Evidence of Effectiveness?

1. What is the development plan to demonstrate substantial evidence of effectiveness?

- If the plan does not include two adequate and well-controlled clinical investigations, what is the scientific justification for the proposed development approach?

2. If planning to use a one adequate and well-controlled clinical investigation plus confirmatory evidence approach, consider the following questions:

- What is the plan for designing a single adequate and well-controlled investigation?
- Is it possible, and appropriate, to use an external placebo control arm from a previous study that supported the approval of another drug?
- Is there measurement of a clinically meaningful endpoint(s)? How reliable and objective is/are the endpoint(s)?
- What is the anticipated treatment effect of the medical product?

Please note that the quantity of confirmatory evidence may be impacted by the design and results of the one adequate and well-controlled clinical investigation.

3. What is the confirmatory evidence? (Prior to initiating clinical trials, consider the following questions that pertain to confirmatory evidence):

- Is the mechanism of action of the proposed drug well understood? If so, is there a plan to use pharmacodynamic or mechanistic data as confirmatory evidence?
- Is it possible to draw on scientific knowledge (e.g., mechanism of action) of an already approved drug in the same pharmacological class to support confirmatory evidence?

We recommend speaking to the Agency to reach alignment regarding the design of the one adequate and well-controlled clinical investigation and related confirmatory evidence.

Case Study References by Order of Appearance

Page 1

- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download.
- See FDA Integrated Review document for vutrisiran (Amvuttra) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215515Orig1s000MedR.pdf.
- See the FDA Guidance Documents for Rare Disease Drug Development webpage available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) available at https://www.fda.gov/media/172311/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See Food, Drug and Cosmetic (FD&C) Act section 505(d) (21 U.S.C. § 355(d)) for statutory requirements for demonstrating substantial evidence of effectiveness available at https://www.govinfo.gov/content/pkg/USCODE-2023-title21/pdf/USCODE-2023-title21-chap9-subchapV-partA-sec355.pdf.

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- See FDA Integrated Review document for patisiran (Onpattro) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210922Orig1s000MultiR.pdf.
- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) for important considerations in rare disease drug and biologics development, available at https://www.fda.gov/media/119757/download.
- See Schmidt, H, M Waddington-Cruz, M Botteman, J Carter, A Chopra, M Hopps, M Stewart, S Fallet, and L Amass, 2018, Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. Muscle Nerve, 57: 829-837 available at https://doi.org/10.1002/mus.26034.

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- See draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023) available at https://www.fda.gov/media/164960/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See page 26 of the FDA Integrated Review for more information on the trial design for vutrisiran (Amvuttra) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215515Orig1s000MedR.pdf
- See the FDA Integrated Review for more information about the APOLLO study for patisiran (Onpattro) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210922Orig1s000MultiR.pdf.

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- See the Drugs@FDA database to search for patient information, labels, approval letters, reviews, and other information for FDA-Approved Drugs available at https://www.fda.gov/drugsatfda.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.

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- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/download. When final, this guidance will represent the Agency's current thinking on this topic.

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- See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) available at https://www.fda.gov/media/172311/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/download. When final, this guidance will represent the Agency's current thinking on this topic.