HELIOS-B:

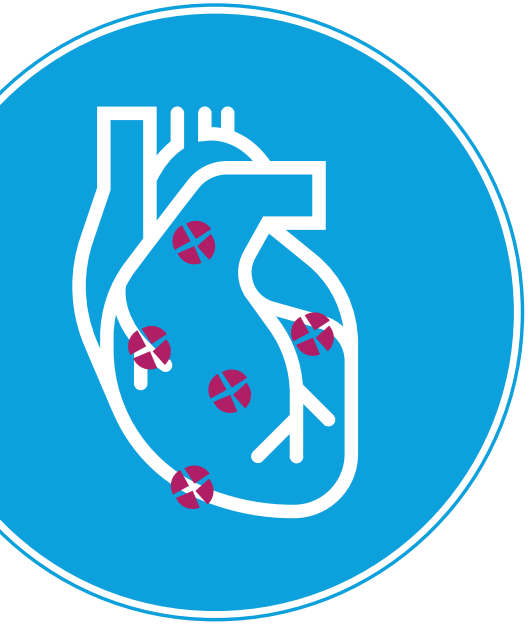
A PHASE 3 CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF VUTRISIRAN IN PATIENTS WITH TRANSTHYRETIN AMYLOIDOSIS WITH CARDIOMYOPATHY (NCT04153149)

This Plain Language Summary (PLS) is based on scientific literature reporting HELIOS-B study results.

Developed and funded by Alnylam Pharmaceuticals.
For healthcare professionals and patient advocacy group leaders only.

HELIOS-B:

A phase 3 clinical trial to evaluate the efficacy and safety of vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy[1]



WHAT WAS THIS TRIAL ABOUT?

Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a disease that affects the heart.[1] It occurs when a protein, transthyretin (TTR), clumps together forming amyloid deposits that build up in the heart, causing damage.[1] This means the heart cannot function as well, called heart failure, and leads to more frequent hospital visits and a greater risk of dying.[1]

Vutrisiran is a treatment for ATTR-CM in adults, and also for the polyneuropathy of hereditary ATTR amyloidosis in adults.[1] It is given as an injection 4 times per year and reduces the amount of TTR protein made by the liver.[1]

The HELIOS-B trial was a clinical study that investigated vutrisiran in patients with ATTR-CM to understand if the treatment was effective and assess any side effects.[1]

SUMMARY OF THE RESULTS

655 patients were enrolled into the trial:[1]

- **326 patients** randomly selected to receive vutrisiran
- **329 patients** randomly selected to receive placebo

In the overall trial population:[1,2]

- Patients who received vutrisiran were **28% less** likely to die or experience hospitalizations or urgent visits to hospital for heart problems than those who received placebo over 3 years.
- Those who received vutrisiran had a **36% lower** chance of dying of any cause than those who received placebo at 42 months.

The trial found that patients who had taken vutrisiran had less decline in physical function and quality of life compared with those who received placebo at 30 months.[1]

Vutrisiran was well tolerated by the patients who received it, and the type and number of side effects was similar to those who received placebo.[1]

The HELIOS-B study showed that vutrisiran reduced the risk of death and hospitalizations in patients with ATTR-CM, and led to less decline in physical function and quality of life, compared with placebo.[1]

GLOSSARY

6-MWT	A clinical test to see how far patients can walk in 6 minutes
Amyloid	A protein, like TTR, that changes shape and clumps together, and has the potential to build up in different parts of the body
ATTR amyloidosis	A disease caused by amyloid clumps building up in organs and tissues throughout the body
Cardiomyopathy	A disorder that affects the heart muscle and its ability to pump blood well
KCCQ-OS	A clinical score that measures patient-reported health status and health-related quality of life
Misfolded	A situation when a protein changes shape and so does not work the way it should in the body
NYHA	A clinical score that measures how much a patient's physical activity is impacted by heart problems
Placebo	A control medicine that has no therapeutic effect, and is used in clinical trials as a comparison when testing medicines
Primary endpoint	The main outcome in a clinical trial that is used to see how well a treatment works
RNA	A molecule present in all living cells that carries genetic information and makes proteins
RNA interference	A process that stops the RNA from producing a protein
Secondary endpoint	Additional outcome measured in a clinical trial that provides additional information on a treatment
Tafamidis	A medicine, given as oral capsules, that works by stabilizing the TTR protein
Transthyretin (TTR)	A protein mainly produced in the liver whose role is to transport vitamin A and other substances around the body
Vutrisiran	A medicine, given as an injection, that works by reducing the production of the TTR protein

WHAT IS ATTR-CM?

ATTR-CM is an underdiagnosed, progressive disease that affects the heart.[1,3] It is caused by problems with a protein in the body called transthyretin, or TTR, which misfolds, or changes shape, and starts to clump together to make deposits called amyloids.[1,3] These amyloid deposits can build up in the heart, causing damage to the heart muscle and stopping it from working normally.[1,3]

There are two main types of ATTR amyloidosis that can cause ATTR-CM: one is genetic and runs in families, hereditary ATTR amyloidosis (hATTR amyloidosis); the other, known as wild-type ATTR amyloidosis (wtATTR amyloidosis), occurs spontaneously and may be associated with aging.[3,4]

WHAT IS VUTRISIRAN?

Vutrisiran is a treatment for ATTR-CM in adults.[1] The medicine works by reducing the production of the TTR protein in the liver.[1] This means that there is less TTR protein available in the body to clump together, form amyloid deposits, and build up in organs like the heart.[1]

HOW WAS THE HELIOS-B TRIAL CONDUCTED?

The HELIOS-B trial was a phase 3 clinical trial that assessed vutrisiran in a large number of patients with ATTR-CM.[1]

In the HELIOS-B clinical trial, 655 patients with ATTR-CM were selected at random to receive either vutrisiran (25 mg) or a placebo.[1] Those receiving the placebo formed the control group.[1] Both vutrisiran and the placebo were given via a subcutaneous injection every 12 weeks for up to 36 months.[1] The characteristics of the patients in both groups were similar and representative of present-day patients, as they had relatively mild disease and some were receiving medications to manage their heart failure caused by ATTR-CM.[1]

WHAT TYPES OF PATIENTS WERE INCLUDED IN THE HELIOS-B TRIAL?

- Aged 18-85 years (the median age of patients in the study was 77 years)[1]
- Had a diagnosis of ATTR amyloidosis (hATTR or wtATTR)[1]
- Had a diagnosis of cardiomyopathy and a medical history of heart failure[1]
- Most were men[a] (92% of patients in the vutrisiran group and 93% of patients in the placebo group)[1]
- Some were already taking the medicine tafamidis for ATTR-CM (~40% in both groups)[1]
- Of those who were not taking tafamidis at the start of the study, ~20% in each group began taking it after the study started[1]

HOW WAS THE TRIAL DESIGNED?

HELIOS-B clinical trial[1]

655 patients with ATTR-CM

Day 1 (Baseline)

TREATMENT ASSIGNMENT

Vutrisiran
25 mg injection
(326 patients)

Placebo
Control injection
(329[b] patients)

Primary endpoint:

- How many patients died from any cause or experienced hospitalizations or urgent visits to hospital for heart problems up to 36 months?

Studied in:

- All trial patients (overall population)
- A subgroup of patients who were not receiving tafamidis at the start of the study (monotherapy population)

Secondary endpoint:

- How many patients died from any cause over 42 months of the trial?
- How was a patient's physical ability at Month 30 of the trial compared with at the start, as measured by the 6-MWT?
- How was a patient's quality of life at Month 30 of the trial compared with at the start, as measured by KCCQ-OS?
- How was a patient's physical activity impacted by their heart problems at Month 30 of the trial compared with at the start, as measured by NYHA?

Up to Month 36

Month 42
(Death from any cause was assessed up to this time point as a secondary endpoint)

[a]ATTR-CM is more common in men than in women.[5] Studies show that >85% of patients with wtATTR-CM are men, as are the majority of patients with hATTR-CM.[5]
[b]329 patients were randomized to placebo, but 1 patient withdrew from the study prior to receiving any dose.[1]

What were the results of the trial?

28%

PRIMARY ENDPOINT

In the overall population, it was found that those who received vutrisiran were 28% less likely to die of any cause or experience hospitalizations or urgent visits to hospital for heart problems than those who received placebo over 3 years.[1]

› A similar reduction was also observed in the patients receiving vutrisiran in the monotherapy population (those who were not receiving tafamidis at the start of the trial).[1]

SECONDARY ENDPOINTS

DEATH FROM ANY CAUSE UP TO MONTH 42 OF THE TRIAL

- In the overall population, those who received vutrisiran had a 36% lower chance of dying of any cause than those who received placebo.[1,2]
  - › Patients who received vutrisiran in the monotherapy population had a similar reduction in the risk of dying of any cause compared with those receiving placebo.[1,2]
- The benefits of vutrisiran here and in the primary endpoint were consistent across patient subgroups.[1]

MEASURES OF DISEASE PROGRESSION

- Patients receiving vutrisiran also experienced better outcomes than those receiving placebo in several assessments that measure disease progression.[1]
  - › 6-MWT: Patients in the vutrisiran group retained more physical ability from the start of the trial to Month 30 than patients in the placebo group, which was assessed by the 6-MWT.
  - › KCCQ-OS: Patients in the vutrisiran group reported less of a decline in quality of life from the start of the trial to Month 30 than patients in the placebo group, which was assessed by the KCCQ-OS score.
  - › NYHA: Fewer patients in the vutrisiran group experienced a decline in physical activity due to their heart problems from the start of the trial to Month 30 than patients in the placebo group, which was assessed by the NYHA class.

TTR PROTEIN LEVELS

Patients receiving vutrisiran experienced a rapid reduction in the levels of TTR protein in their body (from the level that they started the trial at) compared with those in the placebo group; this continued through the last time point measured at Month 30.[1]

SAFETY

Vutrisiran was well tolerated by the patients who received it, and the type and number of side effects was similar to those who received placebo.[1]

All patients took a daily vitamin A supplement because vutrisiran lowers levels of vitamin A in the blood.[1]

What do the results of the HELIOS-B trial mean?

- Patients with ATTR-CM who took vutrisiran were less likely to die from any cause or experience hospitalizations or urgent visits to hospital for heart problems than those receiving placebo.[1]
- Patients who received vutrisiran had less decline in physical function and quality of life, compared with those receiving placebo.[1]
- This trial helps answer questions doctors and other healthcare professionals may have about how this medicine works and which patients may benefit from it.

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ABBREVIATIONS

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; FDA, Food and Drug Administration; hATTR, hereditary transthyretin amyloidosis; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NYHA, New York Heart Association; RNA, ribonucleic acid; RNAi, ribonucleic acid interference; TTR, transthyretin; wtATTR, wild-type transthyretin amyloidosis; wtATTR-CM, wild-type transthyretin amyloidosis with cardiomyopathy.

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