# Vutrisiran: Use in Patients with NYHA Class III and NAC Stage 3, or NYHA Class IV Heart Failure in HELIOS-B

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## SUMMARY

- 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.[1]
- Vutrisiran reduced the risk of the primary composite of all-cause mortality and recurrent CV events compared with placebo through the double-blind period in the overall population (HR 0.72; 95% CI 0.56, 0.93; P=0.01) and monotherapy population (HR 0.67; 95% CI 0.49, 0.93; P=0.02).[1]
- Patients were excluded from enrolling in the study if they had NYHA class IV or NYHA class III with NAC ATTR Stage 3 (defined as NT-proBNP > 3,000 ng/L and eGFR < 45 mL/min/1.73m$^2$) at screening.[1]
- A post hoc analysis was conducted to evaluate the proportion of patients in HELIOS-B who developed advanced disease (defined as NYHA class III HF and NAC stage 3, or NYHA class IV HF) during the double-blind period.[2]
    - In the overall population, 8.0% of patients in the vutrisiran group (26 out of 326 patients) developed advanced disease compared with 10.7% in the placebo group (35 out of 328 patients). In the monotherapy population, 8.2% of patients in the vutrisiran group (16 out of 196 patients) compared with 11.1% in the placebo group (22 out of 199 patients) developed advanced disease.[2]
    - In patients who developed advanced disease, treatment with vutrisiran compared with placebo resulted in a HR of 0.604 (95% CI 0.287, 1.274) in the overall population and a HR of 0.542 (95% CI 0.240, 1.223) in the monotherapy population for the primary outcome of all-cause mortality and recurrent CV events through the 33-36 month double-blind period.[2]
    - In the patients who developed advanced disease, treatment with vutrisiran compared with placebo resulted in a HR of 0.442 (95% CI 0.148, 1.323) in the overall population and a HR of 0.226 (95% CI 0.054, 0.940) in the monotherapy population for all-cause mortality though 42 months.[2]
    - The incidence of AEs was similar or fewer in the vutrisiran group compared with placebo after the development of advanced disease.[2]

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## STUDY DESIGN

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 outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) at the end of the double-blind period (up to Month 33–36) in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all remaining eligible patients were allowed to receive vutrisiran in an OLE.[1]

Select exclusion criteria at screening included[1]:

- NYHA Class IV HF
- NYHA Class III HF with NAC ATTR Stage 3

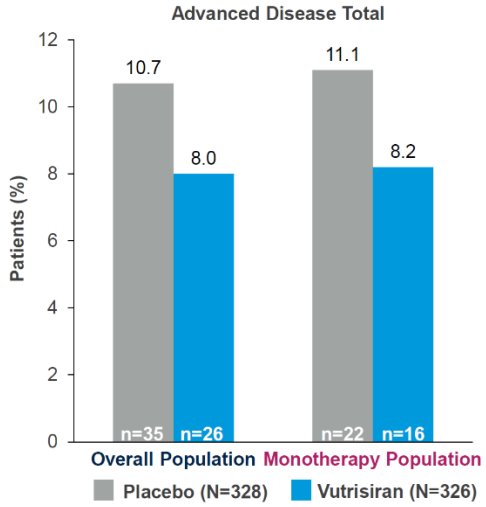
Post hoc analyses of patients in the HELIOS-B overall and monotherapy populations were conducted to compare the risk of developing advanced disease, defined as transition to NYHA class III HF and NAC stage 3 or NYHA class IV HF, in the vutrisiran group compared with the placebo group during the double-blind period. A subgroup analysis of the patients who developed advanced disease evaluated the effect of vutrisiran compared with placebo on clinical outcomes.[2]

Only events occurring after patients developed advanced disease were included in the analysis.

## PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

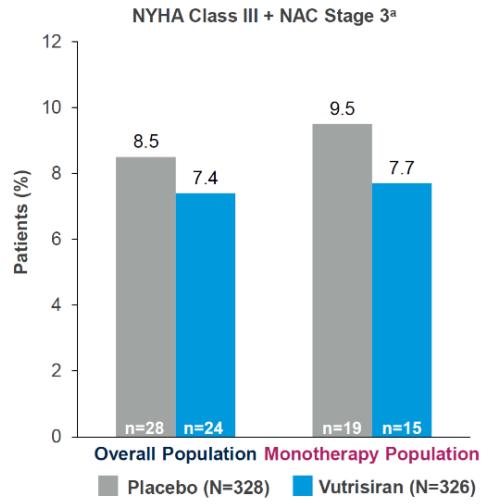
In the overall population, a total of 26 patients in the vutrisiran group and 35 patients in the placebo group developed advanced disease during the double-blind period of the study (**Figure 1**).The percentage of patients who transitioned to advanced disease are further categorized as those who transitioned to NYHA class III HF and NAC stage 3 (**Figure 2**) or those who transitioned to NYHA class IV HF (**Figure 3**).[2]

## Figure 1. Percentage of Patients Who Developed Advanced Disease.[2]



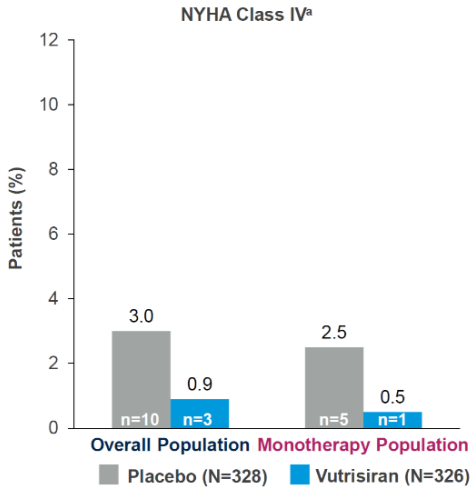

From Witteles et al.[2]

## Figure 2. Percentage of Patients Who Developed NYHA Class III HF and NAC Stage 3[a].[2]




Abbreviations: HF = heart failure; NAC = National Amyloidosis Centre; NYHA = New York Heart Association.
[a]Number of patients in these categories may add up to more than the number of patients with advanced disease in total, as some patients transitioned to NYHA class III HF and NAC stage 3 and then to NYHA class IV HF.
From Witteles et al.[2]

**Figure 3. Percentage of Patients who Developed NYHA Class IV[a] HF.**[2]




Abbreviations: HF = heart failure; NAC = National Amyloidosis Centre; NYHA = New York Heart Association.
[a]Number of patients in these categories may add up to more than the number of patients with advanced disease in total, as some patients transitioned to NYHA class III HF and NAC stage 3 and then to NYHA class IV HF.
From Witteles et al.[2]

In the patients who developed advanced disease, the clinical characteristics at baseline were similar between the vutrisiran and placebo groups, except that NT-proBNP, and troponin I levels were higher in the vutrisiran group than the placebo group, indicating more advanced disease at baseline (**Table 1**).[2]

**Table 1. Baseline Patient Demographics and Clinical Characteristics in Patients Who Developed Advanced Disease.**[2]

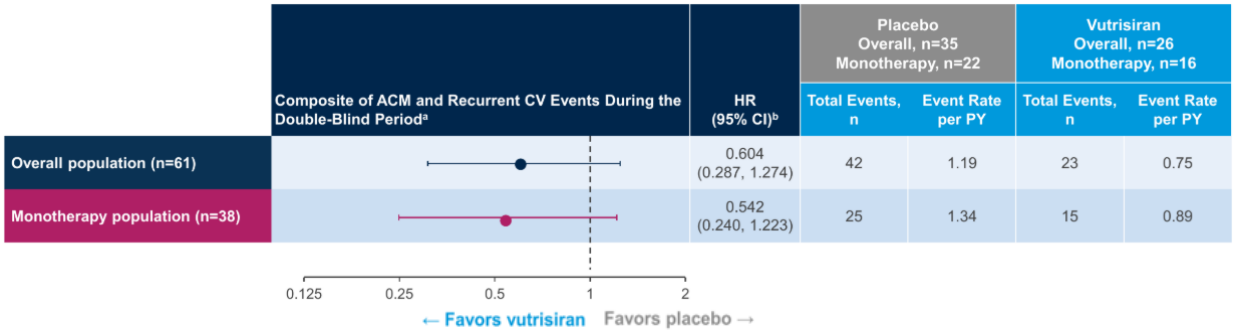
| Baseline Characteristics | Overall Population | | Monotherapy Population | |
|---|---|---|---|---|
| | Placebo (n=35) | Vutrisiran (n=26) | Placebo (n=22) | Vutrisiran (n=16) |
| Age at randomization, years, median (range) | 77.0 (64–85) | 77.5 (66–85) | 77.5 (64–84) | 79.0 (70–85) |
| Male sex, n (%) | 33 (94) | 26 (100) | 21 (95) | 16 (100) |
| hATTR, n (%) | 5 (14) | 1 (4) | 2 (9) | 1 (6) |
| NYHA Class, n (%) | | | | |
| I | 1 (3) | 0 | 1 (5) | 0 |
| II | 25 (71) | 19 (73) | 17 (77) | 14 (88) |
| III | 9 (26) | 7 (27) | 4 (18) | 2 (13) |
| Previous HF hospitalization | 12 (34) | 13 (50) | 8 (36) | 8 (50) |
| Laboratory parameters, median (IQR) | | | | |
| NT-proBNP, pg/mL | 3359.0 (2154.0–4548.0) | 3650.5 (2425.0 4677.0) | 2767.5 (1749.0–4674.0) | 4091.5 (2552.0 6992.5) |
| Troponin I level, pg/mL | 68.8 (51.0–122.0) | 87.7 (52.8 140.7) | 64.9 (52.1–123.1) | 99.0 (54.0 142.2) |

Abbreviations: hATTR = hereditary transthyretin amyloidosis; HF = heart failure; IQR = interquartile range; NT-proBNP = N terminal pro brain natriuretic peptide; NYHA = New York Heart Association.

## EFFICACY RESULTS

In the patients who developed advanced disease, treatment with vutrisiran compared with placebo resulted in a HR of 0.604 (95% CI 0.287, 1.274) in the overall population and a HR of 0.542 (95% CI 0.240, 1.223) in the monotherapy population for the primary outcome of all-cause mortality and recurrent CV events through the 33-36 month double-blind period (**Figure 4**).[2]

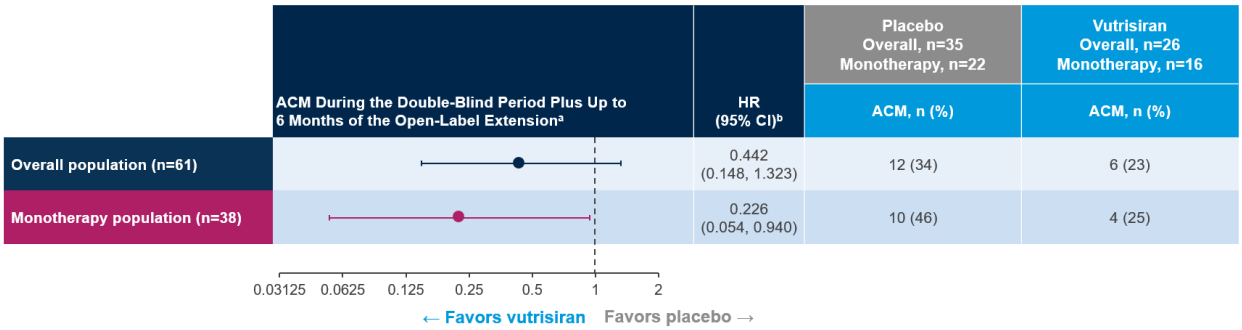
**Figure 4. Primary Composite of All-Cause Mortality and Recurrent CV Events in Patients Who Developed Advanced Disease.[2]**




Abbreviations: ACM = all-cause mortality; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; PY = patient-years
[a]ACM includes heart transplantation and LV assist device placement.
[b]Analysis based on the modified Anderson-Gill model.
From Witteles el al.[2]

Patients treated with vutrisiran compared with placebo resulted in a HR of 0.442 (95% CI 0.148, 1.323) in the overall population and a HR of 0.226 (95% CI 0.054, 0.940) in the monotherapy population for the outcome of all-cause mortality in the double-blind period and up to 6 months of the OLE (**Figure 5**).[2]

**Figure 5. All-Cause Mortality in Patients Who Developed Advanced Disease.[2]**




Abbreviations: ACM = all-cause mortality; CI = confidence interval; HR = hazard ratio.
[a]ACM includes heart transplantation and LV assist device placement.
[b]Derived from a Cox proportional hazards model.
From Witteles el al.[2]

## SAFETY RESULTS

In the patients who developed advanced disease, the proportion of patients with at least one AE and the incidence of SAEs and severe AEs was similar between treatment groups. A summary of the safety results are presented in **Table 2**.[2]

**Table 2. Safety Summary of the Patients Who Developed Advanced Disease.**[2]

| AE | Overall Population n (%) / Event Rates per 100 PY | |
|---|---|---|
| | Vutrisiran (n=26; PY=28.3) | Placebo (n=35; PY=33.7) |
| ≥1 AE | 24 (92) / 691.9 | 35 (100) / 946.9 |
| ≥1 SAE | 16 (62) / 165.9 | 21 (60) / 192.9 |
| ≥1 Severe AE | 15 (58) / 127.1 | 20 (57) / 160.3 |
| ≥1 AE leading to treatment interruption | 0 | 0 |
| ≥1 AE leading to treatment discontinuation | 2 (8) / 7.1 | 3 (9) / 17.8 |
| ≥1 AE leading to study withdrawal | 0 | 2 (6) / 14.8 |
| Deaths, n (%) | 4 (15) | 9 (26) |

Abbreviations: AE = adverse event; PY = patient-years; SAE = serious adverse event.

## ABBREVIATIONS

AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; HF = heart failure; HR = hazard ratio; IQR = interquartile range; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PY = patient-years; SAE = serious adverse event; wtATTR = wild-type transthyretin amyloidosis.

*Updated 30 March 2026*

## REFERENCES


1. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134
2. Witteles R, Gillmore JD, Tsujita K, et al. Vutrisiran reduces the risk of developing advanced disease and demonstrates benefit in patients who do develop advanced disease in ATTR-CM: Analysis from the HELIOS-B study. Presented at: American College of Cardiology (ACC) Annual Scientific Session; March 28-30, 2026; New Orleans, LA, USA.