

# Consistent Efficacy of Vutrisiran Across Sexes in ATTR-CM

## HELIOS-B Trial – Prespecified Sex Analysis

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Monday May 11, 2026

# Why Study Sex Differences in ATTR-CM?



Women are **underrepresented** in **ATTR-CM trials + clinical registries (HELIOS-B: 7.5%)**



Evidence of a distinct baseline female phenotype in ATTR-CM



Limited sex-specific analyses: **potential heterogeneity motivating prespecified analysis**

**Sex-specific understanding is critical for interpreting trial outcomes**



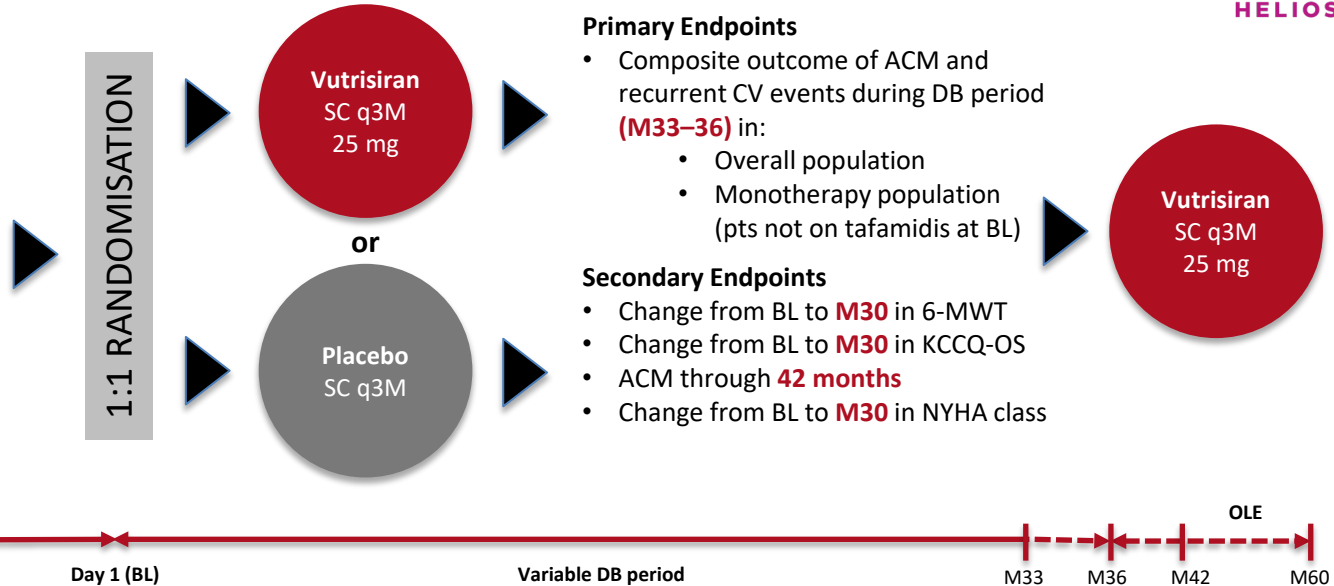
# HELIOS-B Trial Design: prespecified analysis by sex

## Patient Population (N=655)

- ATTR: wild-type or any TTR variant
- Confirmed cardiomyopathy and medical history of symptomatic HF
- NYHA Class ≤III; 6-MWT ≥150m; NT-proBNP limits at BL
- Approximately 40% of pts on tafamidis at BL

## Select Exclusion Criteria

- NYHA Class IV HF
- PND Score ≥III at screening visit
- Received prior TTR lowering treatment



## Primary Endpoints

- Composite outcome of ACM and recurrent CV events during DB period (**M33-36**) in:
  - Overall population
  - Monotherapy population (pts not on tafamidis at BL)

## Secondary Endpoints

- Change from BL to **M30** in 6-MWT
- Change from BL to **M30** in KCCQ-OS
- ACM through **42 months**
- Change from BL to **M30** in NYHA class

**WOMEN: n=49 (7.5%)**

**Small subgroup: limited statistical precision**

**↑ variant ATTR-CM (42.9% vs 9.1%, p<0.001)**

**Mean age 73.7 years vs 75.5 (p=0.07)**

# Females represented 7.5% of the cohort (n=49/654)



## DISTINCT FEMALE CLINICAL PHENOTYPE

- **Reduced functional capacity**
  - 6-MWD: **322** in women [259, 397] m vs **377** [316, 443] m  $P < 0.001$
- **Worse health status (KCCQ)**
  - CSS: **68.7 ± 22.8** vs **77.1 ± 18.4** ( $P = 0.003$ )
  - OSS: **66.3 ± 21.6** vs **73.1 ± 19.4** ( $P = 0.019$ )
  - TSS: **71.9 ± 22.6** vs **78.6 ± 19.3** ( $P = 0.021$ )
- **Lower myocardial injury marker**
  - Troponin I: **47.9 [25.0, 65.2]** ng/L vs **70.8 [44.8, 111.7]** ng/L.  $P < 0.001$
- **Less atrial arrhythmia**
  - AF: **42.9%** vs **61.5%** ( $P = 0.010$ )
  - Atrial flutter: **2.0%** vs **17.7%** ( $P = 0.005$ )

## COMPARABLE BASELINE DISEASE SEVERITY & TREATMENT EXPOSURE

- **NYHA class similar** ( $P = 0.15$ ): mostly Class II
- **NAC stage similar** ( $P = 0.80$ ): mostly NAC I
- **NT-proBNP comparable**: **1889 [865, 3136]** vs **1930 [1120, 3206]** ng/L ( $P = 0.35$ )
- **Haemodynamics and renal function similar**
  - SBP: **125.8 ± 17.5** vs **124.3 ± 16.5** mmHg ( $P = 0.54$ )
  - eGFR: **69.3 ± 25.8** vs **67.7 ± 20.6** ( $P = 0.60$ )
- **Tafamidis use**: **30.6%** vs **40.3%** ( $P = 0.18$ )
- **Tafamidis duration**: **14.3** vs **10.8** months ( $P = 0.76$ )
- **Heart failure therapies similar**
  - Loop diuretic: **77.6%** vs **79.7%** ( $P = 0.72$ )
  - Beta blocker: **42.9%** vs **44.1%** ( $P = 0.86$ )
  - ACEi/ARB: **38.8%** vs **46.9%** ( $P = 0.27$ )
  - MRA: **40.8%** vs **34.7%** ( $P = 0.39$ )

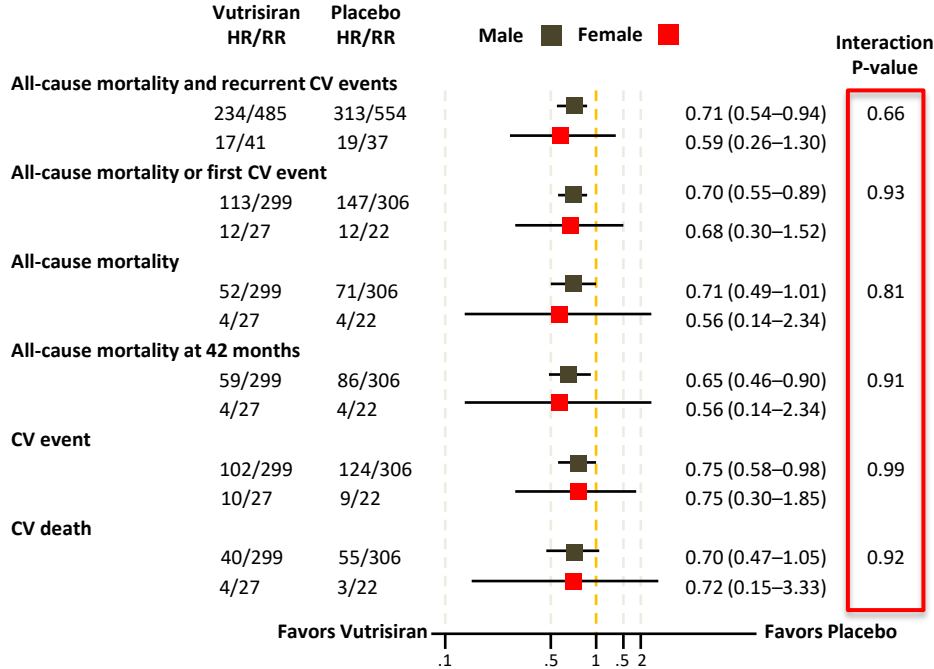
**Differences were not explained by baseline disease severity or treatment imbalance**

# Indexing alters interpretation of sex-based differences in cardiac structure

|                | LV Wall Thickness                                | LVEDD  | LV Mass                                      |
|----------------|--|--|--|
| Absolute       | ↓ women<br>1.76 vs 1.93<br><b>P&lt;0.001</b>     | ↓ women<br>3.86 vs 4.30<br><b>P&lt;0.001</b> | ↓ women<br>275 vs 358 g<br><b>P&lt;0.001</b> |
| BSA indexed    | ↑ women<br>1.05 vs 0.98<br><b>P=0.009</b>        | ↓ women<br>2.31 vs 2.18<br><b>P=0.006</b>    | ↓ women<br>166 vs 183 g<br><b>P=0.012</b>    |
| Height indexed | ≈ no difference<br>1.11 vs 1.11<br><b>P=0.97</b> | ↓ women<br>2.45 vs 2.48<br><b>P=0.52</b>     | ↓ women<br>174 vs 206 g<br><b>P&lt;0.001</b> |

Choice of indexing method influences sex-based differences

# Vutrisiran reduced the primary endpoint in both sexes



- Women showed a distinct baseline ATTR-CM phenotype
- Indexing method influences interpretation
- No statistically detectable heterogeneity of vutrisiran effect by sex
- Wide CI: limited precision from small subgroup size

Women remain underrepresented in ATTR-CM trials