



Vutrisiran Phase 3 HELIOS-B Study

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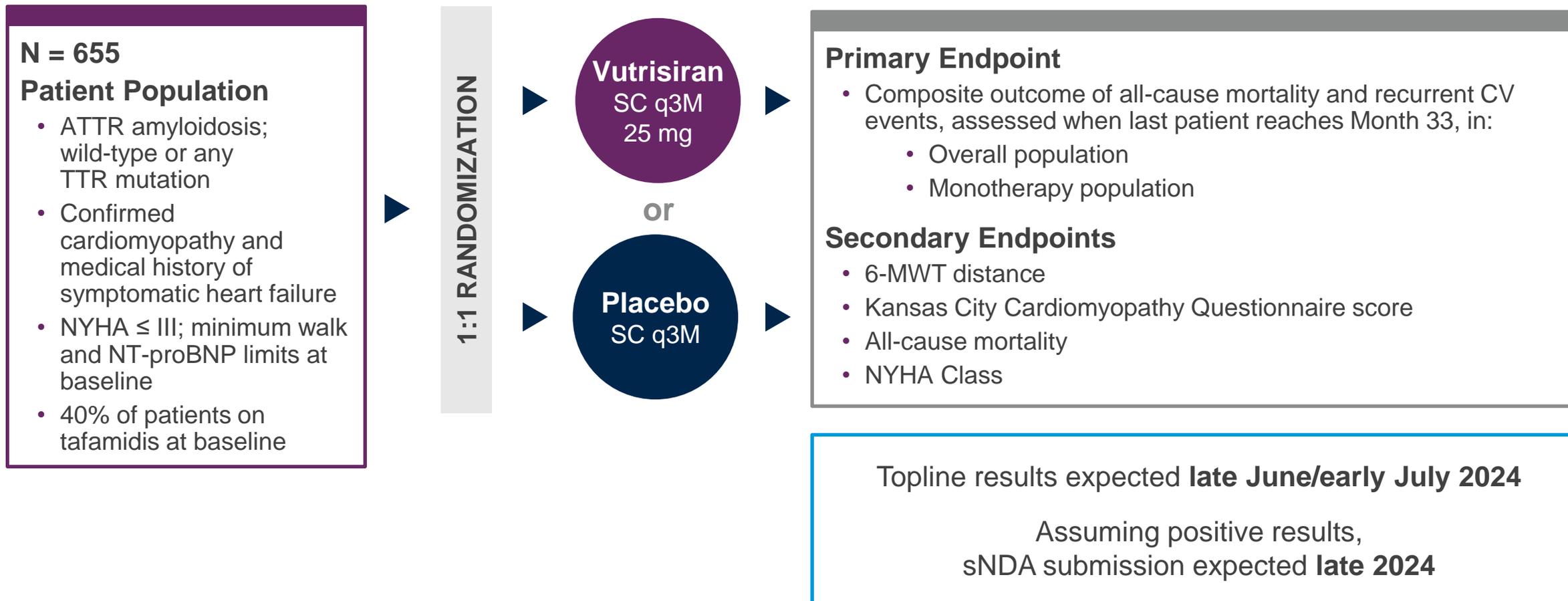


Phase 3 HELIOS-B Study

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Vutrisiran HELIOS·B Phase 3 Study

Randomized, Double-Blind Outcomes Study in ATTR Amyloidosis with Cardiomyopathy



Select Inclusion and Exclusion Criteria

Select Inclusion Criteria

- ATTR amyloidosis; wild-type or any TTR mutation
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA \leq III; minimum walk and NT-proBNP limits at baseline
- 40% of patients on tafamidis at baseline

Select Exclusion Criteria

- Known primary amyloidosis or leptomeningeal amyloidosis
- New York Heart Association (NYHA) Class IV heart failure
- NYHA Class III heart failure and at high risk based on pre-specified criteria
- A polyneuropathy disability (PND) Score IIIa, IIIb, or IV at the screening visit
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m²
- Received prior TTR lowering treatment
- Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease

HELIOS-B Statistical Analysis Methodology^{1,2}

Study Duration

Original

Study Duration

- Double-blind period up to 36 months
- Primary analysis conducted when last patient reaches Month 30



Updated

Study Duration

- Double-blind period up to 36 months
- Primary analysis conducted when last patient reaches **Month 33**

- Three additional months of event collection for patients enrolled later in study, enhancing statistical power
- ~60% of patients remaining on study will have greater follow-up; ~20% more patients will have follow-up to full 36 months
- Longest double-blind follow-up in any ATTR-CM study to date

HELIOS-B Statistical Analysis Methodology (cont.)^{1,2}

Primary Endpoint

Original

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV events in overall population



Updated

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV events, analyzed in:
 - Overall population
 - Monotherapy population (patients not on tafamidis at baseline)

- Hospitalization and mortality outcomes; will be analyzed in:
 - Overall population (100%)
 - Monotherapy group (60%)
- Primary endpoint tested in parallel; **study positive if:**
 - ***Both*** analyses $p \leq 0.05$, **OR**
 - ***Either*** analysis $p \leq 0.025$

HELIOS-B Statistical Analysis Methodology (cont.)^{1,2}

Secondary Endpoints

Original

Select Secondary Endpoints

- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ-OS) score
- Echocardiographic parameters
- All-cause mortality & recurrent all-cause hospitalizations & urgent HF visits
- All-cause mortality
- Recurrent CV events
- NT-proBNP



Updated

Secondary Endpoints

- 6-MWT distance
- KCCQ-OS
- All-cause mortality
- NYHA Class

- Secondary endpoints streamlined to clinically relevant endpoints
- Prioritized to show potential disease stabilization
- Other prior secondaries will still be analyzed