Patisiran for ATTR Cardiomyopathy

FDA Presentation

Cardiovascular and Renal Drugs Advisory Committee Meeting
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Outline

- Is the extent of the observed effect of patisiran clinically relevant?
- Does patisiran have benefits in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) who are also taking standard-of-care tafamidis?

APOLLO-B Trial

- 12-month, randomized (1:1), double-blind, placebo-controlled trial
- Enrolled adults with ATTR-CM and stratified randomization by baseline tafamidis use, genotype, New York Heart Association (NYHA) functional class, and age
- Primary endpoint: Change from baseline at Month 12 in 6-Minute Walk Test (6MWT)
- Secondary endpoints:
  - Change from baseline at Month 12 in Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS)
  - Composite: All-cause mortality, frequency of cardiovascular (CV) events, and change from baseline in 6MWT
  - Composite: All-cause mortality, frequency of all-cause hospitalizations and urgent heart failure (HF) visits, in patients not on tafamidis at baseline
  - Composite: All-cause mortality, frequency of all-cause hospitalizations and urgent HF visits

Observations and Assessments on APOLLO-B Trial

- Well-conducted phase 3 trial
- Discontinuation of study drug balanced between patisiran and placebo groups
- < 10% missing data in each arm
- Safety results from APOLLO-B trial largely consistent with the safety data from the hereditary transthyretin-mediated amyloidosis (ATTRv) polyneuropathy population, and with the expected risks for patients with ATTR-CM

Observations and Assessments on APOLLO-B Trial

- APOLLO-B met two of its pre-specified efficacy endpoints
  - Primary Endpoint: Change from baseline at Month 12 in 6MWT
  - First Secondary Endpoint: Change from baseline at Month 12 in KCCQ-OSS

- Small treatment effect
  - Median difference in 6MWT of 14.7 meters at Month 12 (median baseline 6MWT 364 m)
  - Mean difference in KCCQ-OSS of 3.7 points (mean baseline KCCQ-OSS: 70 out of 100)

Using Clinical Outcome Assessment Endpoints to Establish Effectiveness

- Clinical benefit of a drug can be established based on an improvement in how patients feel or function

- This approach typically uses clinical outcome assessment (COA)-based endpoints
  - 6MWT is an example of an acceptable functional measure for ATTR-CM
  - KCCQ is an example of a measure for ATTR-CM that can generate acceptable COA-based endpoints

- To establish clinical benefit, a drug must be shown to have an effect in adequate and well-controlled trial(s) that is statistically persuasive and clinically meaningful

Pertinent Regulatory History

- Prior to initiation of APOLLO-B, the FDA and Sponsor aligned on endpoints appropriate for a cardiomyopathy claim
  - The study should demonstrate a meaningful improvement in a clinical outcome such as cardiovascular death and hospitalization for HF
  - Alternatively, meaningful improvements in functional testing or Health-Related Quality-of-Life (HR-QoL) measures could suffice if a predetermined level of harm with respect to death and hospitalization could be excluded
- FDA did not object to the Sponsor's proposal to limit the number of subjects on background tafamidis based on the rationale that access to the newly approved therapy would vary by region

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Key Patient Characteristics in APOLLO-B

Baseline Characteristics	Patisiran (N=181)	Placebo (N=178)
Age (years), mean ± SD	75 ± 7	74 ± 8
United States, n (%)	45 (25%)	52 (29%)
Male, n (%)	161 (89%)	160 (90%)
White, n (%)	138 (76%)	140 (79%)
Hispanic, n (%)	21 (12%)	20 (11%)
Baseline tafamidis use, n (%)	46 (25%)	45 (25%)
ATTR amyloidosis type wtATTR, n (%)	144 (80%)	144 (81%)
ATTR amyloidosis disease stage 1, n (%)	124 (69%)	120 (67%)
NYHA Class, n (%)		
Class I	10 (6%)	15 (8%)
Class II	156 (86%)	150 (84%)
Class III	15 (8%)	13 (7%)
NT-proBNP (ng/L), mean ± SD	2390 ± 1742	2289 ± 1841

Abbreviations: ATTR, transthyretin-mediated amyloidosis; hATTR, hereditary ATTR; N, number of subjects; n, number of subjects with specific characteristic; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; wtATTR, wild-type ATTR

Source: Reviewer generated

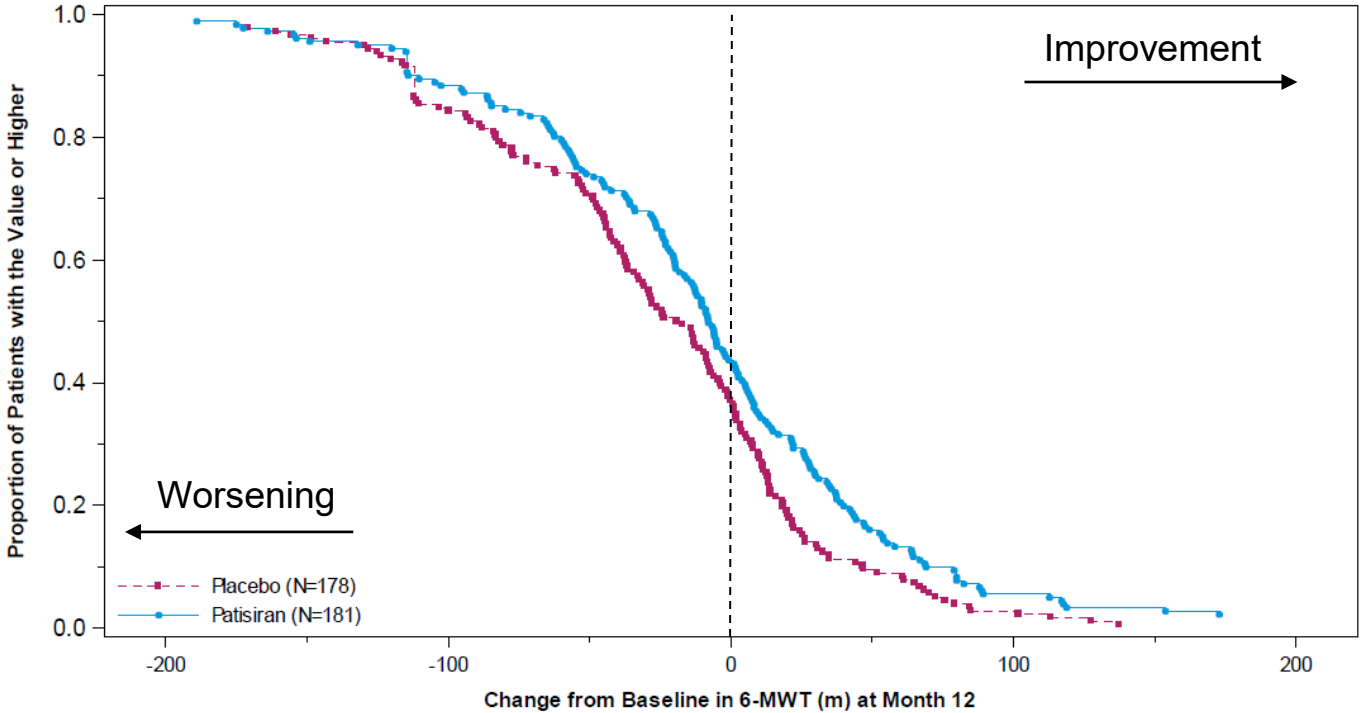
Primary Endpoint, 6MWT

Statistic	Patisiran (N=181)	Placebo (N=178)
Baseline (meters)		
Mean (SE)	360.5 (7.6)	374.6 (7.7)
Change from baseline at Month 12 with imputed values of missing data (meters)		
Mean (SE)	-13.0 (6.2)	-30.7 (5.5)
Median (Q1, Q3)	-8.1 (-54.7, 29.5)	-21.3 (-68.3, 12.8)
HL estimate of median difference (patisiran – placebo) (95% CI)	14.7 (0.7, 28.7)	

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; HL, Hodges-Lehmann; N, number of subjects; Q, quartile; SE, standard error

Source: Reviewer generated

Empirical Cumulative Distribution Function Plot of Change From Baseline at Month 12 in 6MWT



Source: Applicant's Figure 14.2.2.2 in Clinical Study Report ALN-TTR02-011, with arrows added by FDA to indicate direction of improvement and worsening in 6MWT
Abbreviation: 6MWT, 6-minute walk test

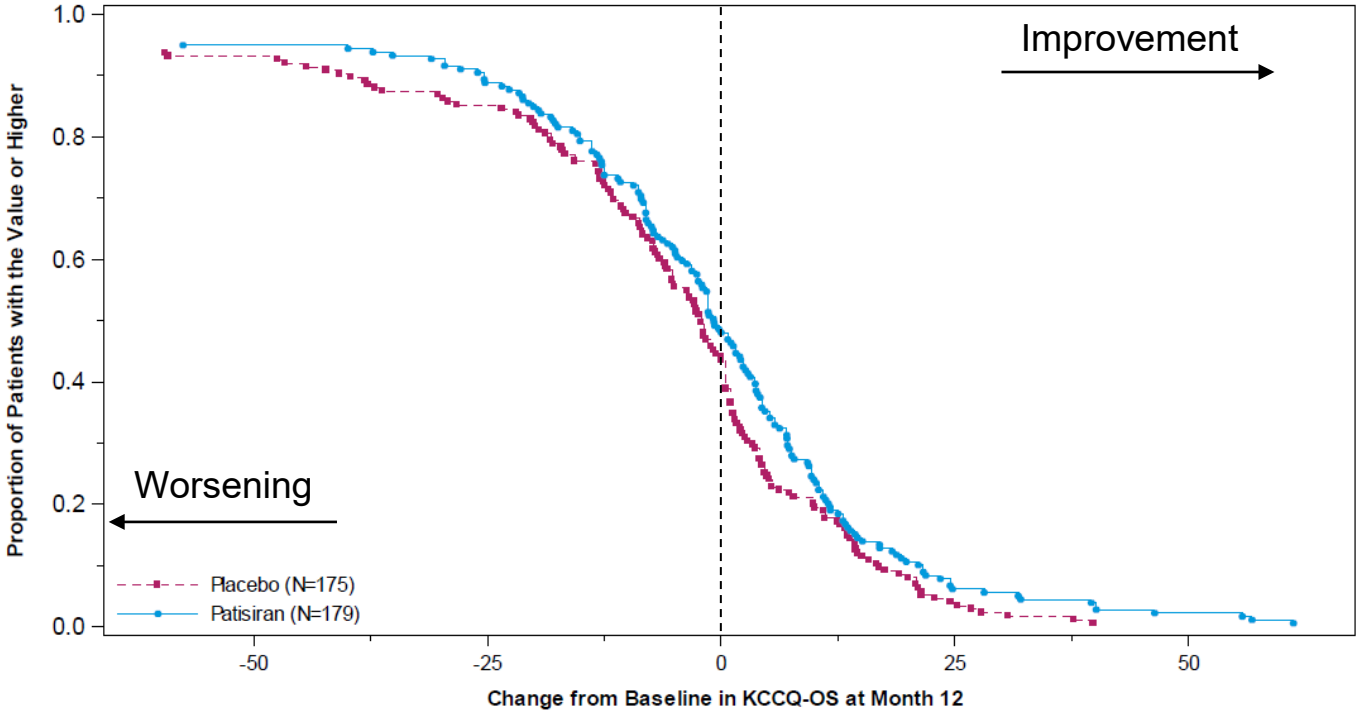
First Secondary Endpoint, KCCQ-OSS

Statistic	Patisiran (N=181)	Placebo (N=178)
Baseline (points)		
Mean (SE)	69.8 (1.6)	70.3 (1.6)
Change from baseline at Month 12 Estimated from MMRM model		
LS mean (SE)	0.3 (1.3)	-3.4 (1.3)
LS mean difference (95% CI)	3.7 (0.2, 7.2)	

Abbreviations: CI, confidence interval; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS, least square; MMRM, mixed effects model repeated measures; SE, standard error

Source: Reviewer generated

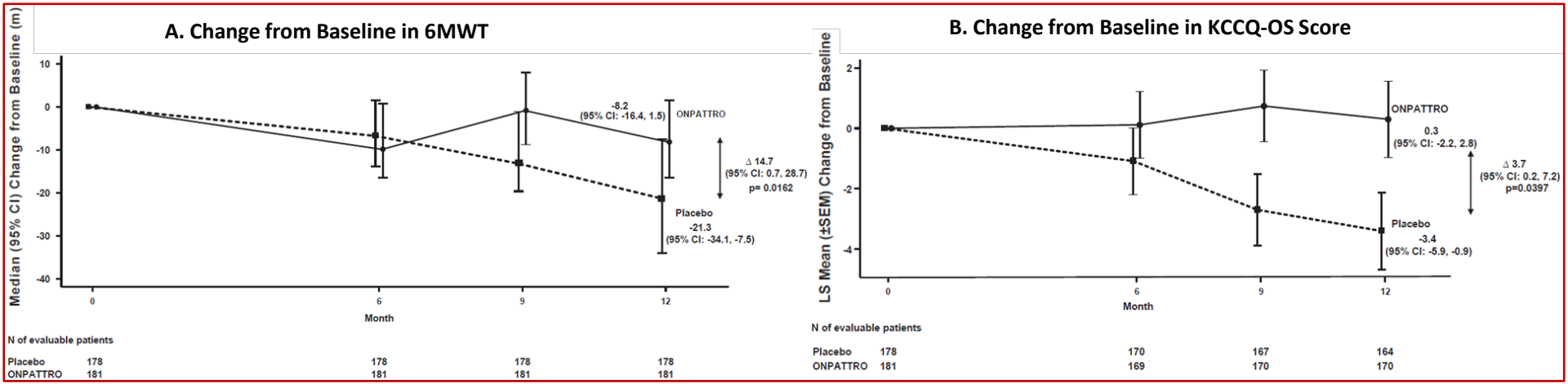
Empirical Cumulative Distribution Function Plot of Change From Baseline at Month 12 in KCCQ-OSS (0–100 Scoring)



Source: Applicant's Figure 14.2.2.8 in Clinical Study Report ALN-TTR02-011, with arrows added by FDA to indicate direction of improvement and worsening in KCCQ-OSS

Abbreviation: KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score

Patisiran's Treatment Effect on 6MWT and KCCQ-OSS



Source: Proposed patisiran USPI

Other Secondary Endpoints

Composite Endpoints (Assessed Over the 12-Month Double-Blind Period)		
	Stratified Win Ratio (95% CI)	**p-value**
All-cause Mortality, Frequency of CV Events, and Change From Baseline in 6MWT	1.27 (0.99, 1.61)	0.057
	Hazard Ratio (95% CI)	**p-value**
All-cause Mortality, Frequency of All-cause Hospitalizations, and Urgent HF Visits (Patients Not on Tafamidis at Baseline)	1.00 (0.62, 1.60)	0.99
All-cause Mortality, Frequency of All-cause Hospitalizations, and Urgent HF Visits (All Patients)	0.88 (0.58, 1.34)	0.56

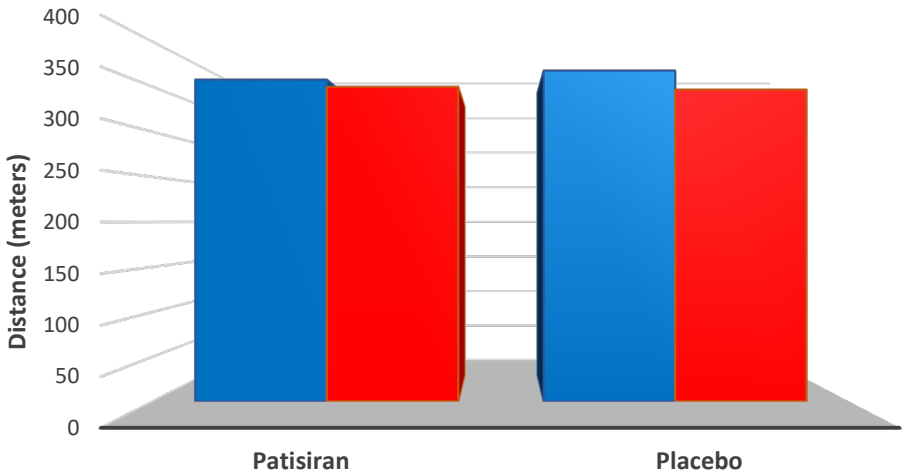
Abbreviations: 6MWT, 6-meter walk test; CI, confidence interval; CV, cardiovascular; HF, heart failure

Source: Reviewer generated

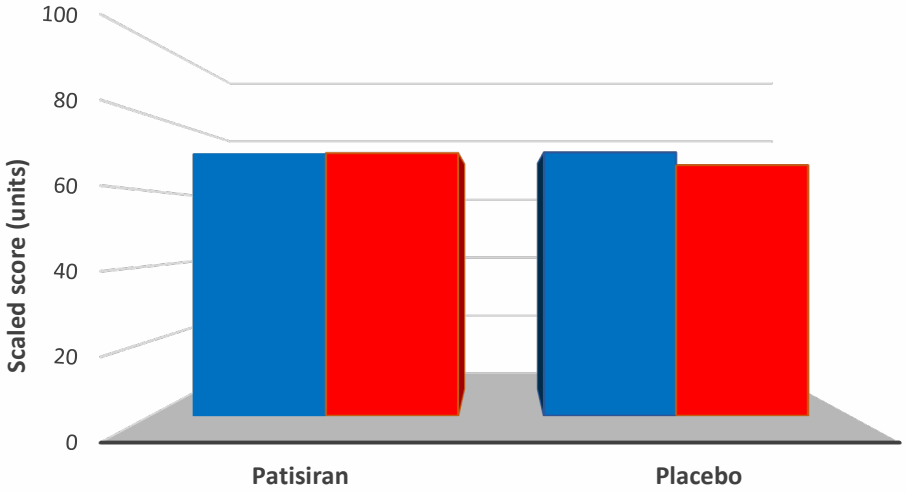
APOLLO-B Efficacy Findings: Summary

- Treatment effects for 6MWT and KCCQ-OSS statistically significant, but small
  - 14.7 meters (95% CI: 0.7, 28.7) for 6MWT (median baseline 364 meters)
    - Sensitivity analyses under varying assumptions yielded slightly smaller estimates
  - 3.7 points (95% CI: 0.2, 7.2) for KCCQ-OSS (range 0-100; mean baseline 70)
    - Sensitivity analyses yielded consistent treatment effects
- The trial did not show a treatment effect on any other secondary endpoints
- The trial did not show a benefit on mortality or irreversible morbidity
- Uninterpretable efficacy results from the open-label extension (months 12-24)
  - No control arm (all subjects received patisiran)
  - Potential for bias on efficacy endpoints due to knowledge of treatment assignment

Treatment Effect on 6MWT (Medians)



Treatment Effect on KCCQ-OSS (Means)



Source: Reviewer generated

FDA Guidance on Evaluating the Meaningfulness of Treatment Benefit for COA-Based Endpoints

- Anchor-based approach is a useful method for understanding what patients regard as clinically meaningful within-patient change (improvement or deterioration from the patient's perspective)
  - An anchor is an external variable (not derived from the COA, whose scores require interpretation) for which meaningful differences are directly interpretable or already known
- Other methods (e.g., qualitative exit interviews, surveys) could be used with or instead of anchor-based approaches (e.g., when appropriate anchors do not exist)
- Distribution-based approaches (e.g., effect sizes) do not directly consider patient voice; not recommended as a primary method to determine clinical meaningfulness

APOLLO-B Trial

- There were neither appropriate anchor scales administered, nor qualitative data collected to aid in the evaluation of the clinical meaningfulness of the treatment effects of 6MWT or KCCQ-OSS, from the perspective of patients
  - As a result, there was no evidence provided to show that the treatment effects on 6MWT or KCCQ-OSS are clinically meaningful to patients
- Applicant's analyses did not align with FDA guidance
  - 6MWT: Used KCCQ-OSS (key secondary endpoint) and KCCQ-Physical Limitation Score as anchors; both scores require interpretation of their own
  - KCCQ-OSS: Compared effect size with other products

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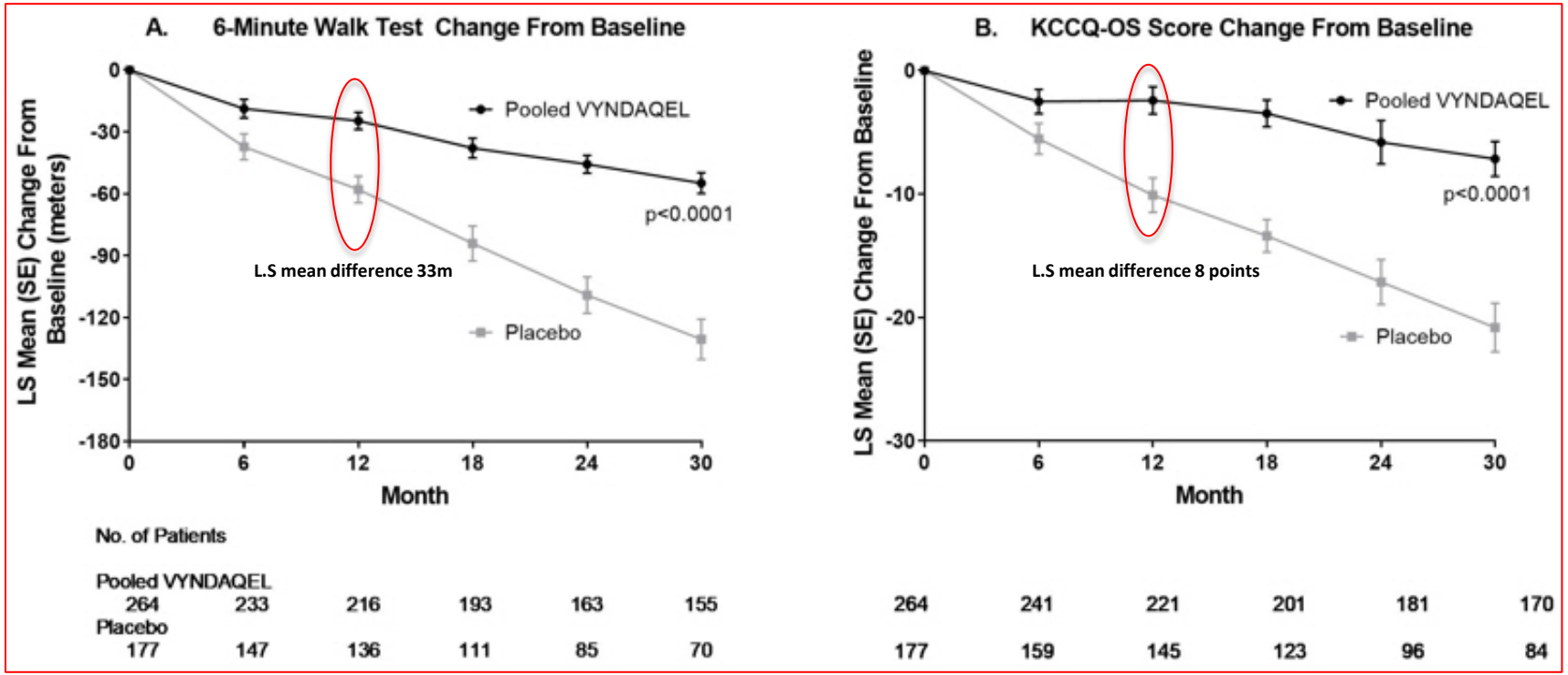
Available Treatment Options for ATTR-CM

- Tafamidis is the only FDA approved therapy for treatment of ATTR-CM
- Efficacy and safety for tafamidis is based on the ATTR-ACT trial
  - Primary endpoint: Hierarchical composite of all-cause mortality and frequency of CV-related hospitalization at Month 30
  - Secondary endpoint: Change from baseline at Month 30 in 6MWT and KCCQ-OSS
- American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure recommends tafamidis in patients with ATTR-CM and NYHA class I to III heart failure symptoms to reduce CV morbidity and mortality

Treatment Effect on the 6MWT and KCCQ-OSS (Tafamidis)



Source: Tafamidis USPI

Tafamidis Subgroup

- Tafamidis is now standard-of-care in ATTR-CM
- 96% of participants in Patisiran Expanded Access Program also receiving tafamidis
- In APOLLO-B, patients on background tafamidis showed neutral results
  - 91 (25%) of the 359 randomized patients received background tafamidis
  - Change from baseline at Month 12 for patisiran – placebo
    - 6MWT (median): -4.2 meters (95% CI: -29, 20.5)
    - KCCQ-OSS (LS mean): 2.1 points (95% CI: -4.9, 9.0)

Subgroup Findings

- Subgroup analyses are exploratory
  - Do not provide conclusive evidence for or against a treatment effect
  - Hypothesis-generating, explore effect of intervention across range of baseline factors
  - Risk of inflated Type 1 error with no multiplicity control

- Patisiran plus tafamidis subgroup in APOLLO-B
  - Biological plausibility for additive effects when patisiran is used with tafamidis (but neither addresses the effects of pre-existing end-organ involvement)
  - Small number of patients, wide confidence interval increases uncertainty
  - APOLLO-B was not designed or powered to provide definitive conclusions regarding the efficacy of patisiran in patients on tafamidis

Concluding Remarks

- Small treatment effect of patisiran on 6MWT and KCCQ-OSS with no evidence that these small effects are meaningful to patients

- All-cause mortality and CV events over the double-blind period were not significantly improved (study not powered for these endpoints)

- Unclear what to do in patients on background therapy with tafamidis

FDA Review Team

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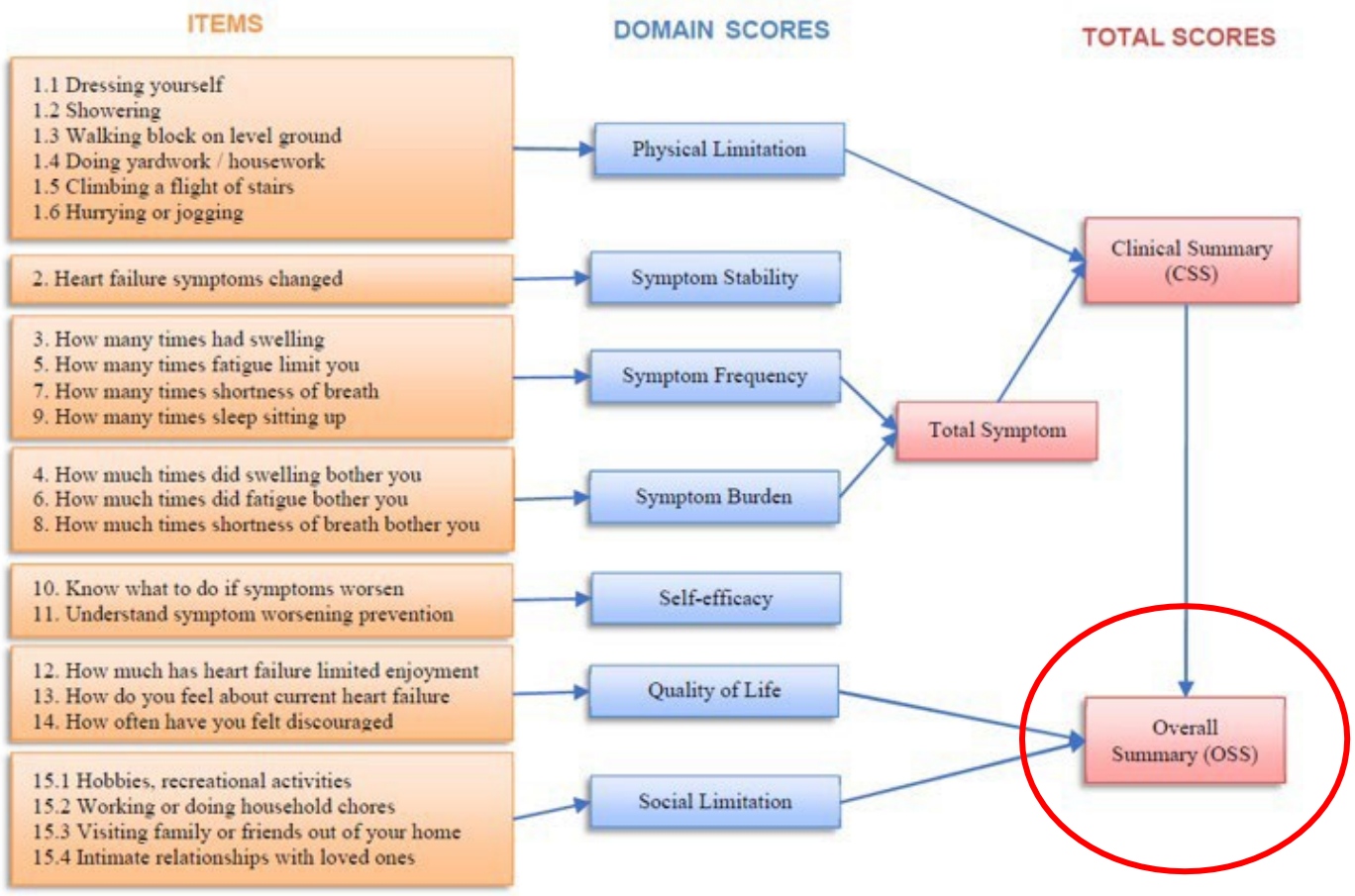
Back-up Slides

Change From Baseline in the 6MWT Using KCCQ-OSS as an Anchor



Abbreviations: CSS, Clinical Summary Score; KCCQ-23, Kansas City Cardiomyopathy Questionnaire, OSS, Overall Summary Score

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214998Orig1s000OtherR.pdf, with encircilation of KCCQ-OSS added by FDA