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Sunday Plenary Session: Late Breaking Clinical Research Session I
9:00 AM – 10:30 AM ET

Efficacy Of Semaglutide In Patients With Obesity And HFpEF According To Frailty Status: A Pooled Analysis From The STEP-HFpEF Program

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Background: Frailty is common in patients with HFpEF and associated with poor functional status. In the STEP-HFpEF program, semaglutide improved HF-related health status and exercise function, and reduced body weight (BW) in participants with obesity-related HFpEF. Whether the efficacy and safety of semaglutide in this group vary by frailty status is unknown.
Methods: We performed a prespecified participant-level analysis of the STEP-HFpEF program that included two international double-blind trials in participants with obesity-related HFpEF both with (STEP-HFpEF DM) or without type 2 diabetes (STEP-HFpEF). In both trials, participants were randomized to once-weekly semaglutide 2.4 mg or placebo for 52 weeks. Dual primary endpoints were changes in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and BW from baseline to 52 weeks. Confirmatory secondary endpoints included change in 6-minute walk distance (6MWD) and a hierarchical composite endpoint (death, HF events, and changes in KCCQ-CSS and 6MWD). Baseline frailty was estimated using a cumulative deficit-derived frailty index (FI) using 34 variables across multiple domains. Efficacy and safety of semaglutide were tested in participants across three frailty strata: non-frail (FI ≤0.210), more frail (FI 0.211-0.310), and most frail (FI >0.310).
Results: Of the 1145 participants, 9.6% were non-frail, 30.0% more frail, and 60.4% most frail. Semaglutide-mediated weight loss was similar across frailty strata (p-int 0.38, Table). However, the effects of semaglutide on KCCQ-CSS varied based on frailty status; participants who were most frail had the greatest improvement at 52 weeks (p-int <0.001). The odds of KCCQ-CSS

improvement by ≥5 and ≥10 points with semaglutide were also greater in participants with higher frailty burden (p-int <0.001). A similar pattern was seen for other KCCQ domains (Table). For confirmatory secondary endpoints, semaglutide led to a greater improvement in the hierarchical composite endpoint (p-int 0.002) and numerically larger increase in 6MWD in participants with higher frailty burden. Although the number of serious adverse events (SAEs) seemed to increase with frailty burden, semaglutide (vs placebo) resulted in fewer SAEs across frailty strata (Table).

Conclusion: The frailty burden was high in participants with obesity-related HFpEF in the STEP-HFpEF program. Across increasing frailty strata, semaglutide resulted in a similar reduction in BW but greater improvements in HF-related symptoms, physical limitations, and the hierarchical composite endpoint in participants with the highest frailty burden. Semaglutide resulted in fewer SAEs than placebo across frailty strata.

Table 1: Treatment Effect of Semaglutide 2.4 mg (vs Placebo) on Key Outcomes and Safety Across Frailty Strata

Outcome	Non-frail (FI ≤0.210) n=110		More frail (FI 0.211–0.310) n=343		Most frail (FI >0.310) n=692		p-int
Adjusted mean difference, 95% CI (Sema 2.4 mg vs placebo)							
Change in body weight at 52 weeks (%)	−6.9 (−9.7, −4.2)		−8.0 (−9.5, −6.4)		−8.8 (−9.9, −7.7)		0.38
Change in KCCQ-CSS at 52 weeks (points)	−1.5 (−8.4, 5.4)		3.7 (−0.2, 7.6)		11.0 (8.1, 13.8)		<0.001
Change in 6MWD at 52 weeks (m)	−4.2 (−28.8, 20.4)		14.1 (0.2, 28.0)		21.7 (11.6, 31.8)		0.14
Odds ratio, 95% CI (Sema 2.4 mg vs placebo)							
KCCQ-CSS improvement by ≥5 points	0.88 (0.40, 1.91)		1.88 (1.18, 3.01)		2.71 (1.89, 3.89)		0.03
KCCQ-CSS improvement by ≥10 points	0.88 (0.34, 2.25)		1.59 (1.02, 2.49)		2.69 (1.92, 3.78)		0.03
Win ratio, 95% CI (Sema 2.4 mg vs placebo)							
Hierarchical composite endpoint	1.02 (0.64, 1.64)		1.38 (1.05, 1.81)		2.00 (1.65, 2.43)		0.002
Safety							
	Sema 2.4 mg	Placebo	Sema 2.4 mg	Placebo	Sema 2.4 mg	Placebo	–
SAEs, n (%)	10 (16.9)	15 (29.4)	19 (11.0)	27 (15.8)	61 (17.8)	117 (33.4)	–

6MWD, 6-minute walk distance; CI, confidence interval; FI, frailty index; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; SAE, serious adverse event; Sema, semaglutide.

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Effects Of Semaglutide In Patients With Obesity-related Heart Failure With Preserved Ejection Fraction According To The Exercise Function At Baseline: Insights From The STEP-HFpEF Program

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Abstract:
Introduction: Patients with obesity-related HFpEF experience severe functional impairment. The STEP-HFpEF program showed that once-weekly semaglutide 2.4 mg vs placebo reduced HF-related symptoms, physical limitations, body weight (BW), and inflammation, while improving exercise function measured by 6-minute walk distance (6MWD). This prespecified analysis aimed to investigate the effects of semaglutide on primary and key secondary endpoints across the range of exercise impairment measured by 6MWD at baseline.
Methods: STEP-HFpEF and STEP-HFpEF DM randomized 1145 participants with symptomatic HF, LVEF ≥45%, and BMI ≥30 kg/m2 to onceweekly semaglutide 2.4 mg or placebo for 52 weeks. Primary endpoints were changes from baseline in KCCQ-Clinical Summary Score (KCCQ-CSS) and BW. Confirmatory secondary endpoints included change in 6MWD, hierarchical composite endpoint assessed by the win ratio (death, HF events, and change in KCCQ-CSS and 6MWD), and change in CRP; NT-proBNP was an exploratory endpoint. Participants were separated into sex-stratified tertiles based on baseline 6MWD. Effects of semaglutide on the dual primary, confirmatory secondary, and select exploratory endpoints were examined according to baseline 6MWD.
Results: Participants with the lowest baseline 6MWD were older and had more severe obesity (higher BMI and waist circumference), greater symptom severity (lower KCCQ-CSS and higher NYHA class), more systemic inflammation (higher CRP), and more severe congestion (higher NT-proBNP and greater diuretic use; Table 1). Compared with placebo, treatment with semaglutide

improved KCCQ-CSS and reduced BW, improved 6MWD, and decreased CRP and NT-proBNP across the spectrum of baseline 6MWD, with no significant interaction across the overall population of trial participants (Table 1). In sex-stratified analyses, women in the lowest baseline 6MWD tertile (vs middle and highest tertiles) had greater improvement in KCCQ-CSS with semaglutide vs placebo (mean difference [95% CI], 13.2 points [8.0, 18.5] vs 4.6 points [−0.6, 9.8] vs 4.6 points [−0.4, 9.7], respectively; interaction p=0.028), whereas there was no significant treatment heterogeneity in men (mean difference [95% CI], 6.7 points [1.2, 12.2] vs 8.2 points [2.7, 13.7] vs 8.1 points [2.6, 13.6], respectively; interaction p=0.914).
Conclusions: In patients with obesity-related HFpEF, semaglutide led to improvements in HF-related symptoms, physical limitations, and exercise function, and reductions in inflammation, congestion, and BW, regardless of baseline 6MWD. Women with the most severe impairment in exercise function appear to derive the greatest benefit.

Table 1: Baseline Characteristics and Treatment Effect by Baseline 6-Minute Walk Distance (6MWD) in the STEP-HFpEF Program

Parameter	6MWD tertile 1 n=381	6MWD tertile 2 n=382	6MWD tertile 3 n=382	p value
6MWD (m), median (IQR)	192 (158, 220)	295 (270, 323)	395 (368, 440)	NA*
Female, n (%)	190 (49.9)	189 (49.5)	191 (50.0)	NA*
Age, n (%) <65 years 65–79 years ≥80 years	 91 (23.9) 228 (59.8) 62 (16.3)	 118 (30.9) 229 (59.9) 35 (9.2)	 159 (41.6) 209 (54.7) 14 (3.7)	<0.001
BMI (kg/m²), median (IQR)	39.8 (35.3, 44.4)	37.6 (34.5, 42.4)	37.0 (34.0, 40.7)	<0.001
Waist circumference (cm), median (IQR)	123 (114, 134)	119 (111, 129)	117 (110, 127)	<0.001
NYHA class III/IV, n (%)	170 (44.6)	109 (28.5)	81 (21.2)	<0.001
LVEF(%), median (IQR)	57 (50, 60)	56 (51, 60)	57 (50, 60)	0.92
KCCQ-CSS, median (IQR)	47 (33, 63)	61 (45, 73)	66 (54, 77)	<0.001
CRP (mg/L), median (IQR)	4.4 (2.0, 9.9)	3.5 (1.8, 7.4)	3.0 (1.7, 6.6)	<0.001
NT-proBNP, median (IQR)	639 (270, 1231)	462 (240, 1010)	379 (209, 830)	<0.001
Hypertension, n (%)	315 (82.7)	334 (87.4)	310 (81.2)	0.57
Atrial fibrillation, n (%)	177 (46.5)	163 (42.7)	178 (46.6)	0.97
Coronary artery disease, n (%)	159 (41.7)	163 (42.7)	131 (34.3)	0.035
Chronic diuretic use, n (%)	330 (86.6)	313 (81.9)	282 (73.8)	<0.001
Treatment effect, mean difference or treatment ratio vs placebo (95% CI)	**6MWD tertile 1 n=381**	**6MWD tertile 2 n=382**	**6MWD tertile 3 n=382**	**Interaction p value**
KCCQ-CSS (points)	10.3 (6.4, 14.1)	6.3 (2.5, 10.1)	6.3 (2.6, 10.1)	0.25
Body weight (% change from baseline)	−8.3 (−9.8, −6.7)	−7.3 (−8.8, −5.8)	−9.5 (−11.0, −8.1)	0.10
6MWD (m)	14.3 (0.5, 28.0)	22.1 (8.6, 35.7)	15.2 (1.9, 28.5)	0.68
CRP ratio	0.62 (0.50, 0.77)	0.71 (0.58, 0.88)	0.59 (0.48, 0.72)	0.44
Win ratio	1.8 (1.4, 2.3)	1.4 (1.1, 1.8)	1.8 (1.4, 2.4)	0.14
NT-proBNP ratio	0.80 (0.66, 0.95)	0.89 (0.74, 1.06)	0.78 (0.65, 0.93)	0.54

*NA, not an applicable comparison as groups were defined by 6MWD; †NA, not an applicable comparison as men/women were separated by sex into tertiles for analysis.
6MWD, 6-minute walk distance; BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, left ventricle ejection fraction; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

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Efficacy And Safety Of Finerenone In Patients With Heart Failure And Mildly Reduced Or Preserved Ejection Fraction And A Recent Worsening Heart Failure Event: The FINEARTS-HF Trial

Author Block: Akshay Desai[1], John Mcmurray[2], Scott Solomon[3]. [1]Brigham and Women's Hospital, Boston, MA; [2]University of Glasgow, Glasgow, United Kingdom; [3]Brigham and Women's Hospital

Abstract:
Introduction: Treatment guidelines for heart failure with reduced ejection fraction (HFrEF) now support in-hospital and early-post discharge optimization of guideline-directed medical therapies. Whether this strategy is safe and effective in patients with HF and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) who have had a recent worsening HF event remains uncertain. Previous trials of steroidal mineralocorticoid receptor antagonists (MRAs) in HFmrEF/HFpEF have principally enrolled patients in stable ambulatory care, but have suggested greater benefit in those with recent HF hospitalization.
Hypothesis: In this prespecified analysis of the FINEARTS-HF trial, we hypothesized that the safety and efficacy of finerenone would be comparable in patients with a recent HF event compared to those without a recent HF event.
Methods: FINEARTS-HF was a randomized, double-blind, placebo-controlled trial of finerenone in patients with HF and left ventricular EF (LVEF) ≥ 40%. Enrollment was permitted in hospital, after a recent hospitalization, or as an outpatient. Additional inclusion criteria included elevation in natriuretic peptides, evidence of structural heart disease, serum potassium of 5.0 mmol/L or lower, and eGFR of 25 ml/min/1.73 m^2 or greater. The primary outcome was a composite of total (first and repeat) worsening heart failure events and cardiovascular death. Secondary endpoints include total heart failure events, changes in NYHA class and KCCQ-TSS, a composite renal endpoint, and all-cause mortality. We will assess the safety and efficacy of finerenone in comparison with placebo, relative to the recency of a heart failure event.
Results: Overall, 6001 patients were validly randomized to finerenone or placebo between September 2020 and January 2023, of whom 1219 (20.3%) were randomized within 7 days 2028 (33.8%) between 7 days and 3 months, and 2754 (45.9%) more than three months from a worsening HF event. The mean age for the overall population was 72 ± SD 10 years, 46% were women and the majority were in New York Heart Association functional class II (69%). The mean LVEF was 53 ± 8% (range 34 - 84%) and the median N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 1041 (IQR 449 - 1946) pg/ml. Concomitant medications included beta-blockers (85%), ACEi or ARBs (79%), ARNIs (9%), loop diuretics (87%) and SGLT2 inhibitors (14%). We will present data regarding the safety and efficacy of finerenone compared with placebo in relation to the proximity to a worsening HF event.
Conclusion: The FINEARTS-HF trial will determine the efficacy and safety of the non-steroidal MRA finerenone in a broad population of hospitalized and ambulatory patients with

HFmrEF/HFpEF. As more than half of the study population was enrolled within 3 months of a HF event, this analysis will determine the balance of efficacy and safety of finerenone in patients with a recent HF event. Data will be presented at the HFSA.

Clinical Trial Registration: ClinicalTrials.gov NCT04435626, EudraCT 2020-000306-29

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Efficacy And Safety Of Finerenone Across The Ejection Fraction Spectrum In Heart Failure With Mildly Reduced And Preserved Ejection Fraction: The FINEARTS-HF Trial:

Author Block: John Mcmurray[1], Pardeep Jhund[1], Scott Solomon[2]. [1]University of Glasgow, Glasgow, United Kingdom; [2]Brigham and Womens Hospital

Abstract:
Background: The treatment effect of several neurohormonal agents have been previously shown to be modified by left ventricular ejection fraction (LVEF), with patients with higher LVEF experiencing less treatment benefit. FINEARTS-HF tested the non-steroidal mineralocorticoid receptor antagonist finerenone in patients with heart failure and mildly reduced or preserved ejection fraction. Hypothesis: In a pre-specified analysis, we hypothesized that the the safety and efficacy of finerenone would be similar across the spectrum of LVEF.
Methods: FINEARTS-HF was a randomized, double-blind, placebo-controlled trial comparing finerenone to placebo in patients with heart failure and left ventricular ejection fraction (LVEF) ≥ 40%. Patients were enrolled in hospital, after a recent hospitalization, or as outpatients. Additional inclusion criteria included elevation in natriuretic peptides, evidence of structural heart disease, serum potassium of 5.0 mmol/L or lower, and eGFR of 25 ml/min/1.73 m2 or greater. The primary outcome was a composite of total (first and repeat) worsening heart failure events and cardiovascular death. Secondary endpoints include total heart failure events, changes in NYHA class and KCCQ-TSS, a composite renal endpoint, and all-cause mortality (Figure).
Results: Overall, 6001 patients were validly randomized to finerenone or placebo between September 2020 and January 2023. The mean age was 72 ± SD 10 years, 46% were women and the majority were in New York Heart Association functional class II (69%). The mean LVEF was 53 ± 8% (range 34 - 84%) and the median N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 1041 (interquartile range 449 - 1946) pg/ml. A total of 1219 (20%) patients were enrolled during or within 7 days of a worsening HF event, and 3247 (54%) patients within 3 months of a worsening HF event. Concomitant medications included beta-blockers (85%), ACEi or ARBs (79%), ARNIs (9%), loop diuretics (87%) and SGLT2 inhibitors (14%). We will assess the safety and efficacy of finerenone, in comparison with placebo, in patients across the spectrum of ejection fraction within the trial.
Conclusion: The FINEARTS-HF trial will determine the efficacy and safety of the non-steroidal MRA finerenone in a broad population of hospitalized and ambulatory patients with HFmrEF/HFpEF and we will assess for evidence of effect modification by ejection fraction. Data will be presented at the HFSA.
Clinical Trial Registration: ClinicalTrials.gov NCT04435626, EudraCT 2020-000306-29

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Exploratory Biomarker Analyses From HELIOS-B, A Phase 3 Study Of Vutrisiran In Patients With Transthyretin Amyloidosis With Cardiomyopathy

Author Block: Mathew Maurer[1], John Berk[2], Thibaud Damy[3], Farooq H. Sheikh[4], José González-Costello[5], Caroline Morbach[6], Diego Delgado[7], Antoine Bondue[8], Olga Azevedo[9], Steen H. Poulsen[10], Ewa A. Jankowska[11], Lili L. Yang[12], Satish Eraly[12], John Vest[12], Marianna Fontana[13]. [1]Columbia University Irving Medical Center, New City, NY; [2]Boston University School of Medicine, Boston, MA; [3]Referral Centre for Cardiac Amyloidosis, Hôspital Henri Mondor, Creteil, France; [4]MedStar Heart and Vascular Institute, MedStar Health/Georgetown University School of Medicine, Washington, DC; [5]Hospital Universitari de Bellvitge, Barcelona, Spain; [6]University Hospital Würzburg, Würzburg, Germany; [7]Peter Munk Cardiac Center, University Health Network, Toronto, ON, Canada; [8]Hôpital universitaire de Bruxelles, Hôpital Erasme, Université libre de Bruxelles, Brussels, Belgium; [9]Hospital da Senhora da Oliveira, Guimarães, Portugal; [10]Aarhus University Hospital, Aarhus N, 82, Denmark; [11]Institute of Heart Diseases, Wroclaw Medical University; [12]Alnylam Pharmaceuticals, Cambridge, MA; [13]National Amyloidosis Centre, University College London, London, United Kingdom

Introduc)on: TransthyreVn amyloidosis with cardiomyopathy (ATTR-CM) caused by deposiVon of transthyreVn (TTR) amyloid fibrils in the heart is an increasingly recognized cause of heart failure associated with high mortality. In HELIOS-B, vutrisiran, an RNA interference therapeuVc, inhibited hepaVc producVon of TTR, decreased rates of cardiovascular (CV) events and all-cause mortality (ACM) among paVents (pts) with ATTR-CM, and preserved funcVonal capacity and quality of life. Here we present the effects of vutrisiran on exploratory measures of cardiac funcVon in HELIOS-B.
Hypothesis: Rapid knockdown of TTR by vutrisiran provides benefit on cardiac biomarkers in pts with ATTR-CM.
Methods: HELIOS-B randomized pts with ATTR-CM 1:1 to vutrisiran (25mg) or placebo. Prespecified exploratory analyses included change from baseline (BL) in NT-proBNP and troponin I. AddiVonal prespecified analyses assessed the risk of CV outcomes and mortality, based on BL levels of cardiac biomarkers.
Results: HELIOS-B enrolled 655 pts (vutrisiran, n=326; placebo, n=329); on tafamidis at BL, 40%. At BL NT-proBNP and troponin I levels were associated with increased risks of later CV events and mortality in the overall population. At Month 30, in the overall population, vutrisiran led to a 32% relative reduction in geometric mean fold change from BL in NT-proBNP and a 32% reduction in geometric mean fold change from BL in troponin I vs placebo (geometric fold-change ratio from BL [95% CI] in NT-proBNP and troponin I was 0.68 [0.61, 0.76], p<0.00001 and 0.68 [0.62, 0.75], p<0.00001). Vutrisiran maintained relative stability in both biomarkers compared with increases with placebo over 30 months. The effect of vutrisiran on NT-proBNP and troponin I was consistent across all prespecified subgroups. Similar consistent effects were observed in the monotherapy population (pts not on tafamidis at BL) and in the baseline

tafamidis subgroup. Median changes from BL at Month 30 for vutrisiran vs placebo in NT-proBNP and troponin I were 118 vs 753 ng/L and –5.8 vs 9.7 ng/L for the overall population, 203 vs 1713 ng/L and –3.0 vs 27.7 ng/L in the monotherapy population, and 15 vs 278 ng/L and –8.4 vs –3.2 ng/L in the baseline tafamidis subgroup.
Conclusions: Vutrisiran has the potenVal to improve the cardiomyopathy associated with ATTR. These exploratory results indicate that vutrisiran treatment atenuates the rise in cardiac biomarkers vs placebo, and maintains long-term stability of both NT-proBNP and troponin I. The effects of vutrisiran on cardiac biomarkers are consistent with the benefits on CV events and ACM.

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Effects of Vutrisiran on Echocardiographic Cardiac Structure and Function: The HELIOS-B Trial

Karola Jering[1], Marianna Fontana[2], Hicham Skali[1], Bernard Bulwer[1], Olivier Lairez[3], Simone Longhi[4], Olga Azevedo[5], Shaun Bender[6], Patrick Jay[6], John Vest[6], Scott Solomon[1]
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Introduction: Transthyretin cardiomyopathy (ATTR-CM) is caused by extracellular deposition of amyloid fibrils in the heart and is an increasingly recognized cause of heart failure associated with high morbidity and mortality. Vutrisiran, an RNA interference therapeutic agent, inhibits hepatic production of transthyretin. In HELIOS-B, vutrisiran decreased rates of cardiovascular events and all-cause death among patients with ATTR-CM and preserved functional capacity and quality of life. The effects of vutrisiran on echocardiographic measures of cardiac structure and function have not been well defined in this population.
Hypothesis: Vutrisiran attenuates decline in left ventricular (LV) systolic function, preserves LV diastolic function, and attenuates increases in LV mass and LV wall thickness over time in patients with ATTR-CM compared with placebo.
Methods: HELIOS-B randomized 655 patients with ATTR-CM to vutrisiran (25mg) or placebo. Patients underwent standardized prespecified echocardiograms at baseline (BL), months 12, 18, 24, and 30. Changes in echocardiographic parameters from BL to month 30 were evaluated using mixed models for repeated measures with the BL value, treatment group, visit, treatment-by-visit interaction, BL tafamidis use, treatment-by-BL tafamidis use interaction, type of ATTR amyloidosis, and age group included as fixed effect terms.
Results: Among the 654 participants with available echocardiographic data at BL (median age 77 years, 93% male, 88% wild-type TTR), mean LVEF was 56 ± 13%, absolute global longitudinal strain (GLS) 14 ± 3%, and mean LV wall thickness 1.8 ± 0.3 cm. Over 30 months, vutrisiran significantly attenuated decline in LVEF (least squares mean difference: 2.03%; 95% CI: 0.34, 3.73), absolute GLS (1.23%; 95% CI: 0.73, 1.73), and LV stroke volume (4.05 mL; 95% CI: 1.72, 6.38) compared with placebo. Vutrisiran also significantly decreased the ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity (E/e') (-1.82; 95% CI: -2.67, -0.97) and attenuated increases in mean LV wall thickness (-0.43 mm; 95% CI: -0.82, -0.03) and LV mass index (-10.6 g/m2; 95% CI: -18.0, -3.3). There were no statistically significant differences in left atrial size or presence of mitral regurgitation at 30 months. The magnitude of the treatment differences was generally even greater in the vutrisiran monotherapy subgroup (n=395).
Conclusions: Consistent with its beneficial effects on cardiovascular events and death, vutrisiran attenuated disease progression in patients with ATTR-CM across multiple domains of cardiac structure and function. These favorable effects on both systolic and diastolic function further support its use as a disease-modifying therapy for patients with ATTR-CM.