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ORIGINAL RESEARCH

Effect of Mavacamten on Echocardiographic Features in Chinese Patients with Obstructive Hypertrophic Cardiomyopathy: Results from the EXPLORER-CN Study

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ABSTRACT

Introduction: Mavacamten, a cardiac myosin inhibitor, has demonstrated positive outcomes in left ventricular outflow tract (LVOT) gradient reduction and improvements of symptoms and function in Chinese patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM) in EXPLORER-CN. This exploratory analysis aimed to evaluate the effect of mavacamten on echocardiographic measures of cardiac structure and function and its relationship with other clinical biomarkers.

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Methods: Key echocardiographic parameters acquired over 30 weeks from 81 patients ($n=54$ on mavacamten and $n=27$ on placebo) were assessed in a central laboratory.
Results: At 30 weeks, greater improvements in measures of diastolic function were observed with mavacamten versus placebo, including lateral E/e' (least-squares mean [LSM] change from baseline [CFB] – 5.1 vs. 0.6; between-group LSM difference – 5.7; 95% confidence interval [CI] – 7.6 to – 3.7), septal E/e' (LSM CFB – 6.0 vs. – 0.3; between-group LSM difference – 5.7; 95% CI – 7.8 to – 3.7), and left atrial volume index (LAVI) (LSM CFB – 11.7 vs. – 3.5 ml/m^2; between-group LSM difference – 8.2; 95% CI – 12.0 to – 4.4) (nominal $p<0.001$ for all). Twelve patients (23.1%) treated with mavacamten had complete resolution of mitral valve systolic anterior motion (SAM) versus two patients (7.4%) receiving placebo. Among mavacamten-treated patients, reductions in resting and Valsalva LVOT gradients, left ventricular (LV) mass index, LAVI, and lateral and septal E/e' were associated with reduced N-terminal pro-B-type natriuretic peptide levels (nominal $p<0.0001$ for all). In the mavacamten group, reductions in LVOT gradients and LV end-diastolic interventricular septal thickness were associated with improved patient-reported Kansas City Cardiomyopathy Questionnaire Overall Summary Score (nominal $p<0.05$ for all).
Conclusions: Clinically meaningful improvements were evident in Chinese patients treated with mavacamten compared with placebo in several hallmarks of obstructive HCM, including measures of LV diastolic function, SAM, and LVOT gradient. These results add further evidence to support the positive effects of mavacamten in cardiac remodeling.
Registration: ClinicalTrials.gov identifier: NCT05174416.

Keywords: Echocardiography; Mavacamten; Hypertrophic cardiomyopathy

Key Summary Points

Why carry out this study?

Mavacamten has been shown to improve clinical symptoms and health status in Chinese patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM).

However, data are lacking on whether these improvements were accompanied by changes in important disease-related markers of cardiac structure and function in these patients.

What was learned from the study?

Our findings expand the evidence of a favorable treatment effect of mavacamten on echocardiographic changes in Chinese patients with obstructive HCM, a population who were underrepresented in global trials.

Greater improvements in left ventricular outflow tract (LVOT) gradients and measures of diastolic function, including lateral or septal e' and E/e', and left atrial volume index, were seen in the mavacamten group versus the placebo group.

Also, more patients in the mavacamten group had complete resolution of mitral valve systolic anterior motion than the placebo group.

The favorable cardiac remodeling observed with mavacamten in Chinese patients with obstructive HCM was in line with the global population in the EXPLORER-HCM trial.

INTRODUCTION

Left ventricular outflow tract (LVOT) obstruction and left ventricular (LV) hypertrophy are major hallmarks of obstructive hypertrophic cardiomyopathy (HCM) [1]. One key pathophysiology underlying the LVOT obstruction is hypercontractility due to excessive

myosin-actin cross-bridging [2, 3], which in turn leads to the dynamic pressure gradient between the left ventricle and the aorta [4–6]. In patients with HCM, LVOT obstruction is an important prognostic factor for heart failure (HF), atrial fibrillation (AF), stroke, disease progression, and mortality [7, 8]. In addition, diastolic dysfunction, which is a key functional trait of HCM, holds prognostic significance for all-cause mortality in patients with HCM [9].

Echocardiography is the cornerstone for diagnosis and monitoring of HCM [6, 10]. Echocardiography can measure key parameters that reflect structural and functional cardiac abnormalities in HCM, including LVOT gradient, LV hypertrophy, and systolic and diastolic function, which also serve as measures of patient response to treatment. While newer imaging modalities have emerged over the years, transthoracic echocardiography remains the recommended tool for the assessment of HCM due to its availability and accessibility [10].

Mavacamten is a first-in-class cardiac myosin inhibitor that directly targets the underlying pathophysiology of HCM by reducing excess actin–myosin cross-bridges, thereby lowering myocardial contractility and ventricular stiffness in HCM [11–13]. Mavacamten resulted in significant reductions in LVOT gradients and improvements in exercise capacity (indicated by peak oxygen consumption, pVO_2) and patient symptom and function, as measured by New York Heart Association (NYHA) class, following 30 weeks of treatment in patients with obstructive HCM in the global phase 3 EXPLORER-HCM trial [14]. Further, favorable changes in cardiac structure and function with mavacamten treatment were also demonstrated in the cardiac magnetic resonance (CMR) substudy [15] and secondary analysis on key echocardiographic features [16] of EXPLORER-HCM. The clinical benefits of mavacamten were shown to extend to the Chinese population as well in the phase 3 EXPLORER-CN trial conducted exclusively in Chinese patients [17].

The objective of this exploratory analysis of EXPLORER-CN was to examine the effect of mavacamten on cardiac structure and function assessed by echocardiography and how these changes relate to changes in the cardiac biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP), health-related quality of life (as assessed by the Kansas City Cardiomyopathy Questionnaire [KCCQ]-23 Overall Summary Score [KCCQ-23 OSS]), and NYHA functional classification of Chinese patients with obstructive HCM. Findings on relationships between changes in cardiac structure and function, cardiac biomarkers, and patient-reported health status may provide insights on the possible mechanisms underlying the clinical benefits of mavacamten in patients with obstructive HCM.

METHODS

Study Design and Participants

EXPLORER-CN (NCT05174416) was a phase 3, double-blind, placebo-controlled trial in which patients with symptomatic obstructive HCM were randomized 2:1 to mavacamten or placebo at 12 sites in China. This trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice. The protocol was approved by institutional review boards/ethics committees at each site. All patients provided written informed consent prior to entering the study.

The study design and the primary efficacy and safety results have been reported elsewhere [17]. Briefly, adults aged ≥ 18 years and diagnosed with obstructive HCM, with body weight > 45 kg, unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac conditions (such as hypertension or aortic stenosis) or systemic disease and maximal LV wall thickness of ≥ 15 mm (or ≥ 13 mm with positive family history of hypertrophic cardiomyopathy), peak LVOT gradient ≥ 50 mmHg at rest or with Valsalva, LV ejection fraction (LVEF) ≥ 55%, and NYHA class II–III were eligible for inclusion. Key exclusion criteria included history of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening, paroxysmal AF at screening, and current or

planned treatment with disopyramide, ranolazine, cibenzoline, or a combination of beta-blockers and diltiazem or verapamil.

Procedure and Assessment

Echocardiograms (at rest and with Valsalva) were acquired at screening, day 1 (baseline), and weeks 4, 6, 12, 18, 24, 26, and 30 (end of treatment) during the double-blind phase. All echocardiograms were acquired according to a prespecified imaging protocol by certified sonographers and analyzed by an independent central imaging laboratory (Calyx China Co., Ltd) blinded to treatment assignment and according to American Society of Echocardiography recommendations [18, 19]. To assess intra- and inter-rater variabilities, a secondary review process was implemented whereby a subset of cases were reevaluated by the same reviewer (intra-rater) and different reviewers (inter-rater) to ensure reproducibility. For any reviewer who had discrepancies at more than 20% of the timepoints, the independent central imaging laboratory personnel would further review the data to determine if preventative actions were necessary.

Key measures for cardiac structure dimensions included LV mass index (LVMI), maximal LV wall thickness, interventricular septal wall thickness, and LV end-diastolic (LVED) posterior and maximal wall thickness. Measures for LV diastolic function included left atrial volume index (LAVI), lateral or septal e' (i.e., lateral or septal early diastolic mitral annular velocity, respectively) and lateral or septal E/e' (i.e., ratio of early mitral peak velocity of early filling [E] to lateral or septal early diastolic mitral annular velocity, respectively).

Blood samples were collected for NT-proBNP at screening and throughout all prespecified study visits. KCCQ-23 [20], a heart failure-specific patient-reported health status measure validated in HCM [21], was administered on day 1 and weeks 6, 12, 18, and 30 of the study. Combined scores from physical limitations, symptoms, quality of life, and social limitations domains were reflected as KCCQ-23 OSS.

LVOT gradients were assessed as provoked peak LVOT gradient following Valsalva maneuver and instantaneous peak LVOT gradient at rest. Mitral valve systolic anterior motion (SAM) was assessed as either present, absent, or not measurable; patients who had SAM at baseline and the absence of SAM at week 30 were considered to have complete resolution of SAM. Mitral regurgitation (MR) was visually assessed and graded as absent (no insufficiency), trace, mild, moderate, or not visualized.

Statistical Analyses

Changes in echocardiographic parameters from baseline to week 30 were analyzed in the intention-to-treat population, which included all randomized patients. Echocardiographic parameters at baseline were summarized with descriptive statistics, based on the last non-missing data before the first dose of study drug. For continuous echocardiographic variables (e.g., LAVI, e', and E/e'), comparison between treatment arms for changes from baseline were analyzed using a mixed model for repeated measurements, with baseline value, treatment group, time points, interaction between treatment and time point, and a stratification factor based on beta-blocker usage (yes or no) as fixed effects and patient as random effect. Categorical variables, including absence of SAM, were summarized using counts and percentages.

The relationship between the changes from baseline to week 30 in echocardiographic measures and NT-proBNP or KCCQ-23 OSS were assessed by linear regression modeling. For the relationship with NT-proBNP, simple linear regression was fitted by the treatment group on the change in log2 transformed NT-proBNP with the change in each echocardiographic parameter of interest as the explanatory variable. The fitted lines were overlaid with scatter plots. For relationship with KCCQ-23 OSS, multivariable linear regression models included baseline value for each echocardiographic parameter and baseline KCCQ-23 OSS, adjusted for baseline patient age, sex, systolic blood pressure, and body mass

index (except LAVI). The response variable was the change from baseline of KCCQ-23 OSS.

Missing data were not imputed. *P* values and 95% confidence intervals (CIs) were not adjusted for multiplicity due to the exploratory nature of the analyses. *P* values < 0.05 were considered as statistically significant. SAS version 9.4 or higher (SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

Among the 81 patients with symptomatic obstructive HCM included in EXPLORER-CN, 54 were randomized to mavacamten and 27 to placebo. Baseline characteristics have been reported previously [17]. Briefly, mean age was 51.9 years, 71.6% were male, and 76.5% had NYHA class II status (Supplemental Table S1). Most characteristics were comparable between treatment groups, except for a greater proportion of men (75.9% vs. 63.0%), a greater number of patients with NYHA class II status (81.5% vs. 66.7%) and poor CYP2C19 metabolizers (13.0% vs. 3.7%), and lower baseline NT-proBNP levels (geometric mean, 810.5 vs. 1250.3 ng/l) in the mavacamten group versus the placebo group (Supplemental Table S1).

Baseline echocardiographic features are shown in Table 1, with elevated *e′* (6.6 ± 2.0 vs. 5.5 ± 2.6 cm/s for lateral *e′*, 4.5 ± 1.3 vs. 4.1 ± 1.6 cm/s for septal *e′*), *E*/*e′* (14.0 ± 7.5 and 16.8 ± 6.7 cm/s for lateral *E*/*e′*, 19.8 ± 7.6 and 20.8 ± 4.9 cm/s for septal *E*/*e′*), LVMI (152.3 ± 47.8 and 174.3 ± 73.2 g/m^2), maximal LV wall thickness (22.9 ± 4.9 and 24.3 ± 6.4 mm), and LAVI (43.3 ± 12.1 and 47.5 ± 14.7 ml/m^2) values for both the mavacamten and the placebo groups. Elevated LVOT gradients at rest (74.6 ± 35.0 and 73.4 ± 32.2 mmHg) and with Valsalva (106.8 ± 43.2 and 99.8 ± 41.1 mmHg) were also observed, in line with the study eligibility criteria.

The majority of patients (97.5%) completed the 30-week, double-blind treatment period (Supplemental Figure S1). Two patients in the placebo group discontinued treatment prematurely, one due to withdrawal for personal reasons and the other due to COVID-19-related issues.

Structural Changes

At week 30, LVMI was reduced with mavacamten compared with placebo (least-squares mean [LSM] change from baseline [CFB] – 28.3 vs. 16.4 g/m^2), with an LSM difference of – 44.7 g/m^2 between treatment groups (95% CI – 61.5 to – 27.8; nominal $p < 0.001$) (Table 2, Fig. 1). Similarly, decreases in LVED interventricular septal thickness (LSM CFB – 2.7 vs. 0.9 mm; between-group LSM difference – 3.6 mm; 95% CI – 5.2 to – 1.9), LVED posterior wall thickness (LSM CFB – 0.7 vs. 1.1 mm; between-group LSM difference – 1.7 mm; 95% CI – 2.8 to – 0.7), and LVED maximal wall thickness (LSM CFB – 2.5 vs. 1.2 mm; between-group LSM difference – 3.6 mm; 95% CI – 5.3 to – 2.0) also favored the mavacamten group compared with marginal increases in the placebo group (nominal $p < 0.001$ for all).

Functional and Physiological Changes

At week 30, improvements in indicators of LV diastolic function were observed with mavacamten versus placebo. Improvements in lateral e′ (LSM CFB 1.7 vs. – 0.6 cm/s; between-group LSM difference 2.3 cm/s; 95% CI, 1.5 to 3.2), septal e′ (LSM CFB 1.4 vs. 0 cm/s; between-group LSM difference 1.4 cm/s; 95% CI 0.8 to 2.0), lateral *E*/*e′* (LSM CFB – 5.1 vs. 0.6; between-group LSM difference – 5.7; 95% CI, – 7.6 to – 3.7), and septal *E*/*e′* (LSM CFB – 6.0 vs. – 0.3; between-group LSM difference – 5.7; 95% CI – 7.8 to – 3.7) were in favor of mavacamten treatment over placebo at week 30 (nominal $p < 0.001$ for all) (Table 2, Fig. 1). Furthermore, greater reduction in LAVI was also seen in the mavacamten group compared with the placebo group (LSM CFB – 11.7 vs. – 3.5 ml/m^2; between-group LSM difference – 8.2; 95% CI – 12.0 to – 4.4; nominal $p < 0.001$).

With regard to LV volume parameters, both LVED volume index (LSM CFB – 4.4 vs. – 3.5 ml/m^2; between-group LSM difference – 0.9 ml/m^2; 95% CI – 5.1 to 3.3) and LV end-systolic

Table 1 Baseline echocardiographic parameters

Variable	Mavacamten ($n = 54$)	Placebo ($n = 27$)
LVOT gradient, mmHg		
Resting	74.6 ± 35.0	73.4 ± 32.2
Valsalva	106.8 ± 43.2	99.8 ± 41.1
LVEF, %	77.8 ± 6.9	77.0 ± 6.7
LAVI, ml/m^2	43.3 ± 12.1	47.5 ± 14.7
LVMI, g/m^2	152.3 ± 47.8	174.3 ± 73.2
LVED interventricular septal thickness, mm	21.0 ± 4.6	22.8 ± 6.0
LVED posterior wall thickness, mm	10.9 ± 2.3	11.7 ± 4.8
LVED maximal wall thickness, mm	22.9 ± 4.9	24.3 ± 6.4
Lateral *e′*, cm/s	6.6 ± 2.0	5.5 ± 2.6
Septal *e′*, cm/s	4.5 ± 1.3	4.1 ± 1.6
Lateral *E*/*e′* ratio	14.0 ± 7.5	16.8 ± 6.7
Septal *E*/*e′* ratio	19.8 ± 7.6	20.8 ± 4.9
LVED volume index, ml/m^2	58.6 ± 14.8	61.1 ± 13.3
Left ventricular end-systolic volume index, ml/m^2	13.2 ± 6.0	14.3 ± 6.0
Left ventricular stroke volume, ml	82.1 ± 22.0	84.3 ± 19.3
Cardiac output, l/min	5.0 ± 1.3	5.4 ± 1.7
Systolic anterior motion	52 (96.3%)	27 (100%)
Mitral regurgitation		
No insufficiency	0	0
Trace	13 (24.1%)	4 (14.8%)
Mild	29 (53.7%)	13 (48.1%)
Moderate	12 (22.2%)	7 (25.9%)

Data are presented as mean ± standard deviation or number (percentage)

e′ early diastolic mitral annular velocity, *E*/*e′* ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *LAVI* left atrial volume index, *LVED* left ventricular end-diastolic, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *LVOT* left ventricular outflow tract

volume index (LSM CFB − 3.1 vs. − 2.8; between-group LSM difference − 0.3; 95% CI − 2.4 to 1.7) decreased from baseline across treatment groups at week 30, with no differences between groups (Table 2). In parallel, LV stroke volume (LVSV) decreased from baseline in both treatment groups (LSM CFB − 3.4 vs. − 3.9 ml; between-group LSM difference 0.4 ml; 95% CI − 5.2 to 6.1), while no change was noted for cardiac output (CO) (LSM CFB 0.2 vs. − 0.1 l/min; between-group LSM difference 0.3 l/min; 95% CI − 0.2 to 0.7). There were no differences between the treatment groups for all measures above.

In a subgroup analysis according to baseline NYHA class, improvements in the echocardiographic measures mentioned above, including

Table 2 Changes from baseline[a] to week 30 in echocardiographic parameters

Variable	Mavacamten[a] ($n = 54$)	Placebo[a] ($n = 27$)	LSM difference (95% CI)	Nominal p value
LVOT gradient, mmHg				
Resting	− 51.1	19.2	− 70.3 (− 89.6 to − 50.9)	< 0.001
Valsalva	− 49.0	6.0	− 55.0 (− 69.1 to − 40.9)	< 0.001
LVEF, %	3.7	3.0	0.6 (− 1.7 to 3.0)	0.588
LAVI, ml/m^2	− 11.7	− 3.5	− 8.2 (− 12.0 to − 4.4)	< 0.001
LVMI, g/m^2	− 28.3	16.4	− 44.7 (− 61.5 to − 27.8)	< 0.001
LVED interventricular septal thickness, mm	− 2.7	0.9	− 3.6 (− 5.2 to − 1.9)	< 0.001
LVED posterior wall thickness, mm	− 0.7	1.1	− 1.7 (− 2.8 to − 0.7)	< 0.001
LVED maximal wall thickness, mm	− 2.5	1.2	− 3.6 (− 5.3 to − 2.0)	< 0.001
Lateral e', cm/s	1.7	− 0.6	2.3 (1.5 to 3.2)	< 0.001
Septal e', cm/s	1.4	0	1.4 (0.8 to 2.0)	< 0.001
Lateral E/e' ratio	− 5.1	0.6	− 5.7 (− 7.6 to − 3.7)	< 0.001
Septal E/e' ratio	− 6.0	− 0.3	− 5.7 (− 7.8 to − 3.7)	< 0.001
LVED volume index, ml/m^2	− 4.4	− 3.5	− 0.9 (− 5.1 to 3.3)	0.677
Left ventricular end-systolic volume index, ml/m^2	− 3.1	− 2.8	− 0.3 (− 2.4 to 1.7)	0.747
Left ventricular stroke volume, ml	− 3.4	− 3.9	0.4 (− 5.2 to 6.1)	0.884
Cardiac output, l/min	0.2	− 0.1	0.3 (− 0.2 to 0.7)	0.230

e' early diastolic mitral annular velocity, E/e' ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *LAVI* left atrial volume index, *LSM* least-squares mean, *LVED* left ventricular end-diastolic, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *LVOT* left ventricular outflow tract

[a]Changes were LSM

LVOT gradient at rest or with Valsalva, LAVI, and lateral or septal E/e' ratios, with mavacamten treatment versus placebo were seen in both NYHA class II or III subgroups (Supplemental Table S2).

In terms of physiological parameters, 52 patients in the mavacamten group and all 27 patients in the placebo group presented with mitral valve SAM at baseline (Table 1). After 30 weeks of treatment, complete resolution of SAM occurred in 12 of 52 patients (23.1%) in the mavacamten group and two out of 27 patients (7.4%) in the placebo group. All 54 (100%) patients in the mavacamten group presented with MR at baseline, with 12 (22.2%), 29 (53.7%), and 13 (24.1%) patients with moderate, mild, and trace MR, respectively (Table 1); by week 30, overall improvement was seen with no patients having moderate MR and 18 (33.3%) and 36 (66.7%) patients with mild and trace MR, respectively. In the placebo group, 27 patients presented with MR at baseline, of which 7 (25.9%), 15 (55.6%), and 5 (18.5%) patients presented with moderate, mild, and trace MR at baseline; the corresponding values were 4 (14.8%), 12 (44.4%), and 8 (29.6%) patients, respectively, at week 30.

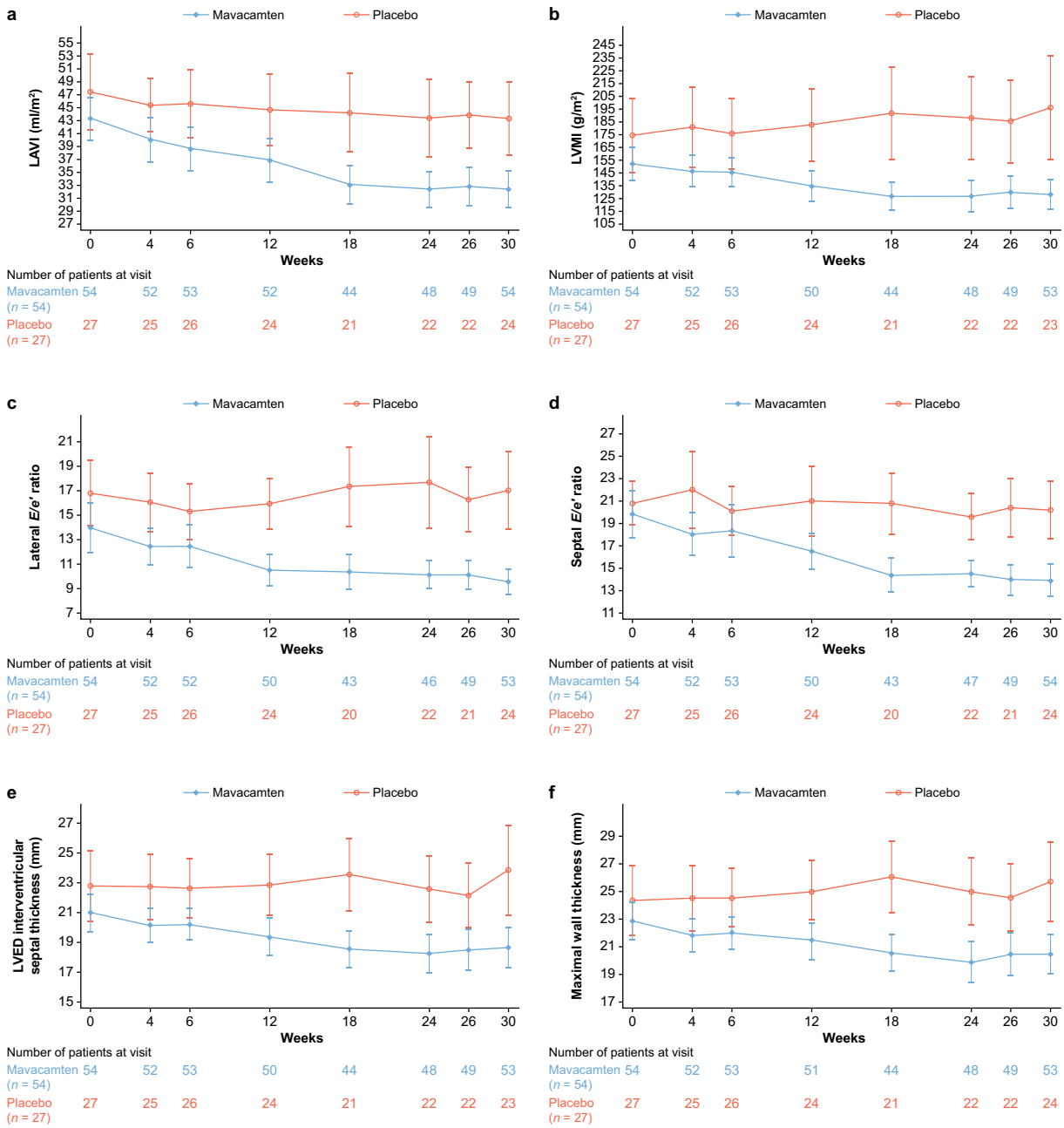

Fig. 1 Echocardiographic parameters over time. *Line graphs* show mean (95% CI) echocardiographic parameters from baseline to week 30, including **a** LAVI, **b** LVMI, **c** lateral *E*/*e*′ ratio, **d** septal *E*/*e*′ ratio, **e** LVED interventricular septal thickness, and **f** maximal wall thickness. *CI* confidence interval, *E*/*e*′ ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *LAVI* left atrial volume index, *LVED* left ventricular end-diastolic, *LVMI* left ventricular mass index

Relationship Between Biomarker Changes and Treatment Effects on Echocardiographic Parameters

Based on linear regression of log2 changes in NT-proBNP and echocardiographic changes, there appears to be significant linear relationships between reduction in serum NT-proBNP levels and improvements in echocardiographic measures of cardiac structure and function, including LVOT gradients at rest or with Valsalva, LAVI, LVMI, and lateral or septal E/e' values in the mavacamten group (nominal $p<0.0001$) (Fig. 2). Positive linear relationships were also observed in the placebo group between reductions in serum NT-proBNP levels and reductions in LVOT gradients at rest or with Valsalva and LVMI (nominal $p<0.05$ for all).

Relationship Between Changes in Health-Related Quality of Life and Treatment Effects on Echocardiographic Parameters

Post hoc exploratory analyses of the longitudinal association between health-related quality of life measure (as measured by KCCQ-23 OSS) and echocardiographic parameters demonstrated that reductions in LVOT gradient at rest (nominal $p=0.028$) or with Valsalva (nominal $p=0.012$) following mavacamten treatment appeared to be statistically significantly associated with improved KCCQ-23 OSS (Table 3). In addition, reduction in LVED interventricular septal thickness was also significantly associated with improvement in KCCQ-23 OSS (nominal $p=0.026$). Other echocardiographic measures did not appear to have association with changes in KCCQ-23 OSS.

DISCUSSION

While current standard pharmacologic therapies for obstructive HCM offer symptomatic relief, they do not address the underlying pathophysiological mechanisms of HCM. Mavacamten has been shown to improve clinical symptoms and health status in Chinese patients with symptomatic obstructive HCM, but data are lacking on whether these improvements were accompanied by changes in important disease-related markers of cardiac structure and diastolic function in these patients. This analysis of echocardiographic assessments of Chinese patients with obstructive HCM in EXPLORER-CN demonstrated that mavacamten treatment for 30 weeks led to clinically meaningful improvements in cardiac structure and function assessed by transthoracic echocardiography imaging, including LAVI, LVMI, LVED interventricular septal thickness, LVED posterior or maximal wall thickness, and E/e' ratio. Of note, these improved parameters represent key pathophysiological features of obstructive HCM, thus adding further support for the mechanism of action of mavacamten in addressing the underlying pathophysiology of the disease. Improvements in echocardiographic measures of cardiac diastolic function have also been noted in the VALOR-HCM trial, which showed that mavacamten reduced the need for septal reduction therapy at week 56 [22]. Importantly, our findings expand the evidence of a favorable treatment effect of mavacamten on echocardiographic changes in a diverse population, including Chinese patients, in whom poor CYP2C19 metabolizers are more prevalent and body mass index tends to be lower compared with global patients.

Abnormalities in mitral valve SAM are a key feature of obstructive HCM, and the degree and severity of SAM are associated with LVOT obstruction, clinical symptoms, and outcomes in HCM [23]. Considering that mitral valve SAM is a key mediator of the dynamic LVOT gradient seen in obstructive HCM, the benefit of mavacamten in resolving SAM is particularly relevant for patients with obstructive HCM. After 30 weeks of treatment with mavacamten, the proportion of patients achieving complete resolution of mitral valve SAM was three times larger than in the placebo group (23.1% vs. 7.4%). In line with SAM resolution, mavacamten-treated patients had better resolution of MR than those receiving placebo, with all 12 patients who presented with moderate MR at baseline experiencing improvement to mild or trace MR by week 30, while four patients in the placebo group

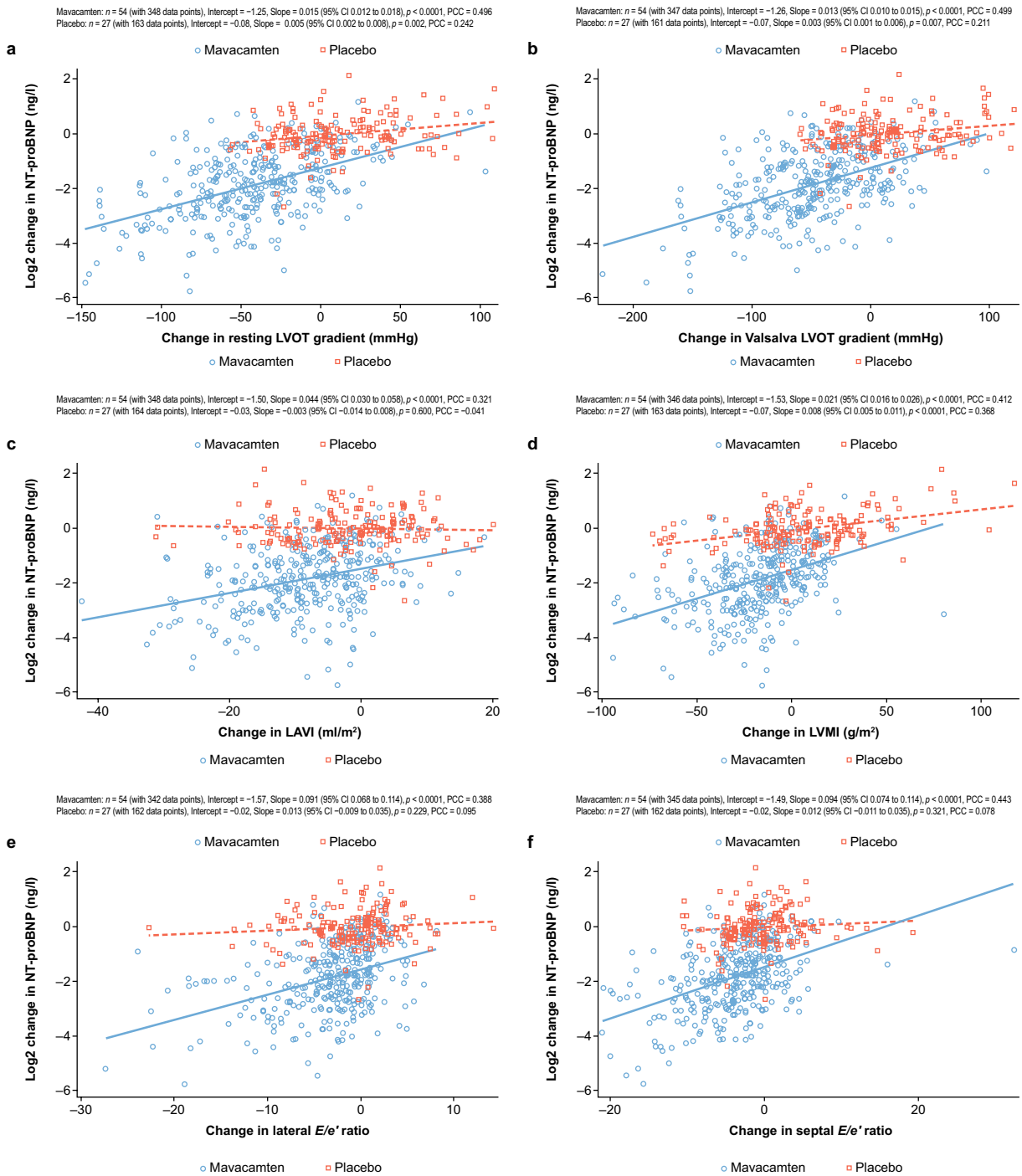

Fig. 2 Relationship of log2 NT-proBNP change and echocardiographic changes. Scatterplots of linear regression of the log2 change in NT-proBNP on changes in echocardiographic parameters, including **a** resting LVOT gradient, **b** Valsalva LVOT gradient, **c** LAVI, **d** LVMI, **e** lateral *E*/*e*′ ratio, and **f** septal *E*/*e*′ ratio. All *p* values denote nominal *p*. *CI* confidence interval, *E*/*e*′ ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *LAVI* left atrial volume index, *LVED* left ventricular end-diastolic, *LVMI* left ventricular mass index, *LVOT* left ventricular outflow tract, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *PCC* Pearson correlation coefficient

Table 3 Longitudinal associations of changes in echocardiographic parameters with changes in KCCQ-23 OSS from baseline to 30 weeks

	Estimate for KCCQ-23 OSS (95% CI)	*p* value
Resting LVOT gradient per 10 mmHg reduction	0.91 (0.10 to 1.72)	0.028
Valsalva LVOT gradient per 10 mmHg reduction	0.77 (0.17 to 1.36)	0.012
Systolic anterior motion of mitral valve	– 3.95 (– 11.76 to 3.85)	0.316
LVEF per 5% reduction	0.54 (– 2.78 to 3.86)	0.747
LAVI per 10 ml/m^2 reduction	0.82 (– 2.84 to 4.49)	0.656
Lateral *E*/*e*′ per 5-unit reduction	0.91 (– 2.54 to 4.37)	0.599
Septal *E*/*e*′ per 5-unit reduction	1.21 (– 2.11 to 4.54)	0.469
Left ventricular stroke volume per 5 ml increase	– 1.77 (– 3.22 to – 0.32)	0.018
LVMI per 10 g/m^2 reduction	0.35 (– 0.43 to 1.13)	0.371
Posterior wall thickness per 1 mm reduction	0.63 (– 0.83 to 2.08)	0.394
LVED interventricular septal thickness	– 0.94 (– 1.77 to – 0.12)	0.026
LVED maximal wall thickness	– 0.72 (– 1.55 to 0.10)	0.086

CI confidence interval, *e*′ early diastolic mitral annular velocity, *E/e*′ ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *KCCQ-23 OSS* Kansas City Cardiomyopathy Questionnaire-23 Overall Summary Score, *LAVI* left atrial volume index, *LVED* left ventricular end-diastolic, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *LVOT* left ventricular outflow tract

remained with moderate MR status at week 30 (seven patients had moderate MR at baseline). In keeping with the beneficial effects of mavacamten in SAM resolution, significant reductions in LVOT gradient at rest and during Valsalva have been observed with mavacamten versus placebo [10]. Despite the remarkable reductions in LVOT gradients, cardiac output remained unchanged following mavacamten treatment. The incidence of treatment-emergent adverse events was also similar between the mavacamten and placebo groups, and no patients had LVEF < 50% or developed HF at week 30, as reported previously [17], suggesting that there are no excessive reductions in LVOT gradients leading to low-output symptoms.

Following the resolution of SAM and relief of LVOT obstruction, improvements in LV filling pressure can be expected with improved hemodynamics. *E*/*e*′ ratios, which are indicators of diastolic function associated with instantaneous LV filling pressure [24], were improved with mavacamten in our study: both ratios of lateral *E*/*e*′ (9.6) and septal *E*/*e*′ (13.9) in the mavacamten group were reduced to within normal range while the corresponding values in the placebo group (20.2 and 17.0, respectively) remained elevated at week 30 (average *E*/*e*′ ratio > 14 is considered abnormal) [25]. These changes are consistent with the reductions seen with mavacamten treatment in the global population in the EXPLORER-HCM (– 3.8 and – 3.5 for lateral and septal *E*/*e*′, respectively) and the VALOR-HCM (– 3.3 for average *E*/*e*′) trials [16, 22]. Another indicator of LV filling pressure, LAVI, which was elevated at baseline (mean, 43.3 and 47.5 ml/m^2 for the mavacamten and placebo groups, respectively), was reduced to a mean of 32.4 ml/m^2, a level considered to be within the normal range [25], in response to mavacamten treatment, while LAVI remained elevated in the placebo group (mean, 43.4 ml/m^2). In the global populations, mean change in LAVI was – 7.5 ml/m^2 at week 30 in the EXPLORER-HCM trial and – 5.2 ml/m^2 at week 16 in the VALOR-HCM trial [16, 22]. Furthermore, the LSM reduction

in LAVI of 11.7 ml/m^2 with mavacamten is consistent with a mean reduction of 17.4 ml/m^2 assessed by CMR imaging following mavacamten treatment in EXPLORER-CN [17]. Of note, a favorable effect of cardiac myosin inhibition in cardiac remodeling has also been shown in the SEQUOIA-HCM CMR substudy [26]. Taken together, the echocardiographic changes seen are consistent with the global populations in the EXPLORER-HCM and VALOR-HCM trials [16, 22], indicating that the beneficial treatment effects of mavacamten in improving the pathophysiology of obstructive HCM also extends to the Chinese population.

Improvements in the echocardiographic parameters mentioned above following mavacamten treatment were likely mechanical consequences of mavacamten's inhibitory effect on actin–myosin cross-bridges. Suppression of cross-bridge formation can potentially reduce LV stiffness and improve LV compliance, thereby leading to lower filling pressures. Mavacamten was also shown to promote detachment of actin-myosin cross-bridges in preclinical biophysical studies, resulting in improved diastolic relaxation [27]. In addition, inhibition of myosin adenosine triphosphatase activity by mavacamten was shown to decrease sarcomere power and force generation in preclinical animal models, thus alleviating the hypercontractile state [12, 28, 29], which is desirable for improving hemodynamics in patients with obstructive HCM. The ensuing reduction in hypercontractility may contribute to the resolution of SAM and LVOT obstruction, thereby improving LV filling pressure, consistent with the clinical finding of reduced E/e' ratio seen with mavacamten.

As elevated E/e' ratios and LAVI were predictive of adverse long-term outcomes, including HF, AF, stroke, and sudden cardiac death [9, 30–35], improvements in these measures and other parameters related to LV mass and wall thickness could potentially have long-term clinical benefits such as a reduction in cardiovascular events, though this would require validation with longer follow-up. On the other hand, the potential to reverse these markers of diastolic function to within normal range with just 30 weeks of mavacamten treatment holds important implications for HCM management. Of note, the curves for these indices of LV filling pressure separated between the treatment groups as soon as week 4; this separation was sustained to week 30, which corresponds to the separation of curves seen with LVOT peak gradient at rest or during Valsalva. In addition, improvements in these indicators were observed regardless of the NYHA functional status of patients at baseline, although the small sample size in each subgroup warrants caution in interpretation of results.

In the present study, reductions in selected echocardiographic measures such as LVOT gradients at rest or with Valsalva and LAVI appeared to be correlated with reductions in NT-proBNP, consistent with findings in the global EXPLORER-HCM echocardiographic substudy [16]. NT-proBNP is a known indicator of cardiac wall stress, which has been shown to be predictive of adverse outcomes and deaths in patients with HCM. While other HCM therapies such as metoprolol and disopyramide reduced LVOT gradients and improved NYHA functional class in patients with obstructive HCM, the treatment effects on NT-proBNP were minimal [36, 37]. In addition, the correlations between improvements in LAVI and E/e' with a reduction in NT-proBNP levels suggest that mavacamten has a beneficial effect through reducing LV filling pressure that accompanies relief of LVOT obstruction.

Beyond what has been reported previously, we also analyzed the association between key echocardiographic parameters and the patient-reported health status indicator of KCCQ-23 OSS as well as changes in echocardiographic measures stratified by NYHA class in this study. Previously, mavacamten was associated with a greater improvement in KCCQ-23 OSS across all KCCQ subscales versus placebo, with more patients achieving ≥ 10 points increase in KCCQ-23 OSS with mavacamten [38]. In addition, decreases in LVOT gradient at rest or with Valsalva and LVED interventricular septal wall thickness have all been shown to be associated with improved KCCQ-23 OSS in patients with obstructive HCM [39]. Our findings of moderate associations between KCCQ-23 OSS improvement with reductions in LVED interventricular septal

thickness and LVOT gradient at rest or with Valsalva in the Chinese population are in line with those observed in the global EXPLORER-HCM trial. Taken together, these findings suggest that the reduction of LVOT obstruction, with greater reduction following mavacamten treatment versus placebo, is associated with better quality of life for patients with HCM.

Limitations include relatively small sample size and short duration of study. As only patients with NYHA class II–III were included due to study eligibility criteria, our findings are not generalizable to other populations of HCM. The study only included the use of beta-blockers as a stratification factor, so there may be other potential confounders such as prior septal reduction therapy or the presence of AF that might have influenced results. Also, accurate assessment of MR is limited due to its highly erratic nature in obstructive HCM. In addition, there may be potential variabilities inherent in echocardiographic measurements, although echocardiography was conducted according to standardized protocols and analyzed at a central laboratory.

CONCLUSIONS

At week 30, mavacamten showed clinically meaningful improvements in pathophysiologic markers of obstructive HCM assessed by transthoracic echocardiography, including measures related to cardiac structure and LV diastolic function, in parallel with SAM resolution and relief of LVOT obstructions, versus the placebo group. These results indicate favorable cardiac remodeling with mavacamten in Chinese patients with obstructive HCM, despite a short treatment period. Improvements in LVOT gradients, LAVI, and E/e' ratios were associated with reductions in NT-proBNP, while reductions in LVOT gradients and LVED interventricular septal thickness were correlated with better KCCQ-23 OSS.

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Declarations

Conflict of Interest. All authors reported medical writing support for the manuscript from Bristol Myers Squibb. Yu-Mao Chen, Yue Zhong, Yu Chen Barrett, and Jing Zheng are employees of Bristol Myers Squibb and own stocks of Bristol Myers Squibb. Zhuang Tian, Xiaoyan Li, Liwen Li, Qing Zhang, Jian'an Wang, Yunqi Shi, Daoquan Peng, Ping Yang, Wei Ma, Fang Wang, Wei Jin, Xiang Cheng, and Shuyang Zhang confirm that they have no conflicts of interest to declare.

Ethical Approval. This trial was conducted in accordance with the principles of the Declaration of Helsinki and Guideline for Good Clinical Practice. The protocol has been approved by institutional review boards/ethics committees at each site. All patients have provided written informed consent prior to entering study.

SUPPLEMENTARY INFORMATION

Below is the link to the electronic supplementary material.Supplementary material file1 (DOCX 111 KB)

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