Supporting information

Table S1 Summary of selected data for patients who experienced LVEF <50% in the EXPLORER cohort of MAVA-LTE

Patient, age (years)/sex		Study visit	LVEF, %	NT-proBNP, ng/L	NYHA class[a]	Mavacamten dose, mg	Mavacamten PK, ng/mL	Background HCM therapy	CYP2C19 phenotype	Gene variant pathogenicity	Relevant AEs recorded at time of LVEF <50% event	Permanent discontinuation of treatment owing to LVEF <50% event
1, 64/M	At time of LVEF <50% event	Week 36	45	74	II	10	595	Atenolol 50 mg QD	NM	*VCL* variant of uncertain significance	Ejection fraction decreased; dry cough	No
	At latest assessment	Week 228	68	128	I	5	329					
2, 68/M	At time of LVEF <50% event	Week 138[b]	35	301[c]	II	5	972	Metoprolol succinate 100 mg QD	NM	None	Ejection fraction decreased; atrial fibrillation	No
	At latest assessment	Week 204	61	85	I	2.5	436					

3, 73/M	At time of LVEF <50% event	Week 60	35	3461	I	10	826	Metoprolol succinate 100 mg QD	ND[d]	None	Ejection fraction decreased; atrial flutter	Yes (serious TEAE of ejection fraction decreased)
	At latest assessment	Unscheduled visit (5 weeks after event)	51	ND	I	0	79.1					
4, 69/M	At time of LVEF <50% event	Week 36	45	349	I	2.5	95.8	Carvedilol 25 mg BID	RM	*GAA* and *MYOM1* variants of uncertain significance	Hypertension	Yes (stopping criteria met)
	At latest assessment	EOT (16 weeks after event)	60	501	II	0	0.2					
5, 61/M	At time of LVEF <50% event	Week 24	48	828	I	10	988	Metoprolol tartrate 75 mg BID	IM	ND[e]	None	Yes (stopping criteria met)
	At latest assessment	EOT (9 weeks after event)	60	149	I	0	115					

6, 66/F	At time of LVEF <50% event	Week 108	30	3029	III	15	90.4[f]	Metoprolol succinate 25 mg QD	NM	ND[e]	Ejection fraction decreased; atrial fibrillation; dizziness; pre-syncope; fatigue	Not applicable[g]
	At latest assessment	Week 108[g]	30	3029	III	15	90.4					
7, 77/F	At time of LVEF <50% event	Week 4[b]	45	1620[c]	II	5	414[f]	Metoprolol succinate 100 mg QD; diltiazem 120 mg QD	NM	ND[e]	Ejection fraction decreased; atrial fibrillation	Yes (serious TEAE of ejection fraction decreased)
	At latest assessment	EOT (4 weeks after event)	50	4744	II	0	199					
8, 79/F	At time of LVEF <50% event	Week 108	38	1102	II	10	1410	Diltiazem 180 mg BID	RM	Pathogenic *GAA* variant; likely pathogenic	Ejection fraction decreased; cardiac failure; sinus	No

	At latest assessment	Week 156	65	87	II	5	562			*CSRP3* variant; *CBL* variant of uncertain significance	tachycardia; intracardiac thrombus; mitral valve incompetence; tricuspid valve incompetence; pulmonary hypertension	
9, 70/F	At time of LVEF <50% event	Week 54[e]	39	140[c]	III	10	1010	Bisoprolol 5 mg BID	NM	*A2ML1, BAG3,* and *CPT2* variants of uncertain significance	Asthenia	No
	At latest assessment	Week 156	58	51	II	5	770					
10, 54/M	At time of LVEF <50% event	Week 16	44	2589[c]	II	15	884	Bisoprolol 10 mg QD	IM	None	Atrial fibrillation	No
	At latest assessment	Week 180	57	532	II	5	503					

11, 67/F	At time of LVEF <50% event	Week 48[b]	41	411[c]	II	10	291[f]	Verapamil 80 mg BID	NM	Pathogenic *MYH7* variant; *MYH7* variant of uncertain significance	None	No
	At latest assessment	Week 156	64	592	I	5	369					
12, 54/M	At time of LVEF <50% event	Week 48	43	421	II	10	878	Metoprolol succinate 100 mg QD	RM	None	Ejection fraction decreased; atrial fibrillation	Yes (TEAE of ejection fraction decreased)[h]
	At latest assessment	Week 96[h]	59	111	I	5	605					
13, 54/M	At time of LVEF <50% event	Week 36	48	1167	II	10	651	Metoprolol succinate 100 mg QD	Not PM[i]	None	Ejection fraction decreased; atrial fibrillation	No
	At latest assessment	Week 60[j]	64	126	II	5	290					
14, 74/M	At time of LVEF <50% event	Week 144	40	390[c]	III	15	1380	Metoprolol succinate 75 mg QD	RM	*DES* variant of uncertain significance	None	No
	At latest assessment	Week 156	63	749	II	10	542					

15, 48/M	At time of LVEF <50% event	Week 120	46	19	I	10	554	Bisoprolol 2.5 mg QD	RM	*MYBPC3* variant of uncertain significance	Ejection fraction decreased	No
	At latest assessment	Week 144	68	<37	I	5	356					
16, 62/M	At time of LVEF <50% event	Week 16	45	157[c]	I	10	1150	Nadolol 80 mg QD	IM	None	Ejection fraction decreased	No
	At latest assessment	Week 180	61	135	I	5	471					
17, 64/M	At time of LVEF <50% event	Week 144	45	378	III	5	373	Bisoprolol 5 mg QD	IM	*CSRP3* variant of uncertain significance	Atrial fibrillation	No
	At latest assessment	Week 156	65	222	II	2.5	183					
18, 72/F	At time of LVEF <50% event	Week 120	48	156[c]	II	5	948	Verapamil 240 mg QD	NM	None	Dizziness; LV dysfunction; wall motion score index abnormal; fatigue	No
	At latest assessment	Week 156	65	172	III	2.5	349					

19, 58/M	At time of LVEF <50% event	Week 4[k]	36	678	II	5	324	Verapamil 80 mg – 80 mg – 120 mg	IM	ND[e]	Ejection fraction decreased; prolonged QTcF; dyspnoea	No[l]
	At latest assessment	EOT[l] (2 weeks after second event[l])	54	275	II	0	75.5					
20, 61/M	At time of LVEF <50% event	Week 16	48	106[c]	I	10	671	Bisoprolol 15 mg QD	NM	Benign *GAA* variant; *PRKAG2* variant of uncertain significance	Ejection fraction decreased	No
	At latest assessment	Week 180	65	82	I	2.5	141					

A2ML1, alpha-2-macroglobulin-like 1 gene; AE, adverse event; *BAG3*, BAG family molecular chaperone regulator 3 gene; BID, twice daily; *CBL*, Casitas B-lineage lymphoma gene; *CSRP3*, cysteine and glycine-rich protein 3 gene; *CPT2*, carnitine palmitoyltransferase 2 gene; CYP2C19, cytochrome P450 2C19; *DES*, desmin gene; EOS, end of study; EOT, end of treatment; *GAA*, alpha-glucosidase gene; HCM, hypertrophic cardiomyopathy; IM, intermediate metabolizer; LTE, Long-Term Extension; LV, left ventricular; LVEF, left ventricular ejection fraction; *MYBPC3*, myosin-binding protein C gene; *MYH7*, myosin heavy chain 7 gene; *MYOM1*, myomesin-1 gene; ND, not determined; NM, normal metabolizer; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetics; *PRKAG2*, protein kinase AMP-activated non-catalytic subunit gamma 2 gene; QD, once daily; QTcF, QT interval corrected using Fridericia's formula; RM, rapid metabolizer; TEAE, treatment-emergent adverse event; *VCL*, vinculin gene.

Patients 2, 6, 8, 14, 15, 17, 18, and 19 experienced the LVEF <50% event described since the previous data cut-off.

[a]NYHA class was assessed on day 1 and at weeks 6, 12, 48, 108, 120, 132, 144, 156, 180, 204, and 228. The assessments from the closest study visit before the LVEF <50% event (scheduled or unscheduled visits) are presented.

[b]LVEF <50% event recorded during unscheduled visit.

[c]NT-proBNP concentration was not recorded during the visit; the value was taken from the last assessment before the LVEF <50% event.

[d]CYP2C19 metabolizer phenotype was not recorded for this patient.

[e]Genetic testing was not performed for this patient.

[f]Mavacamten PK was not recorded during the visit; the value was taken from the most recent assessment before the LVEF <50% event.

[g]LVEF <50% event occurred on the last visit before the 31 August 2023 data cut-off date. The site-read LVEF of this patient was confirmed to be ≥50% in a follow-up visit that occurred after the 31 August 2023 data cut-off date.

[h]Patient permanently discontinued treatment following LVEF <50% and elective hospitalization to perform electrical cardioversion of atrial fibrillation. The patient later re-enrolled into study and had reached week 96 of their second enrolment period by the data cut-off date.

[i]CYP2C19 metabolizer phenotype was recorded as ‘not poor metabolizer’.

[j]Patient permanently discontinued treatment and later re-enrolled into the study. At the data cut-off date, the patient had reached week 60 of their second enrolment period.

[k]Of the second enrolment period.

[l]Patient permanently discontinued treatment at week 72 of the second enrolment period owing to an additional (non-consecutive) LVEF <50% event that occurred while the patient was receiving mavacamten 2.5 mg.

Table S2 Reasons for permanent treatment and study discontinuation

	Number of patients
Reason for treatment discontinuation	
TEAEs[a]	14[b]
Death	5[c]
Ejection fraction decreased	4[b,d,e]
Acute myocardial infarction	2[f]
Atrial fibrillation	1[d]
Cardiac failure	1[g]
Fatigue	1
Muscular weakness	1
Prolonged QTcF	1[e]
Systemic lupus erythematosus	1
Stopping criteria[h]	7[i]
Withdrawal	3
Lost to follow-up	1
Reason for study discontinuation	
TEAEs	10
Death	5[c]
Ejection fraction decrease	1[d,e]
Cardiac failure	1[g]
Fatigue	1
Muscular weakness	1
Systemic lupus erythematosus	1

Stopping criteria[h]	3
Withdrawal	4
Lost to follow-up	1
Other	1

TEAEs were recorded and defined based on the discretion of the principal investigator. It was possible for patients who experienced a TEAE that resulted in permanent treatment/study discontinuation to re-enrol and resume treatment.

LVEF, left ventricular ejection fraction; QTcF, QT interval corrected using Fridericia's formula; TEAE, treatment-emergent adverse event.

[a]Some patients had more than one TEAE as their reason for treatment discontinuation.

[b]One patient was included based on the TEAE recorded as 'Drug Interrupted' which led to full treatment discontinuation.

[c]Cardiac arrest (*n* = 1; cardiac arrest was a sudden unwitnessed event), acute myocardial infarction (*n* = 1), bacterial endocarditis (*n* = 1), intracerebral haemorrhage due to arteriovenous malformation (*n* = 1), and progression of liver metastases with cholangitis and new onset biliary dilatation (*n* = 1).

[d]One patient permanently discontinued treatment and study following TEAEs of ejection fraction decreased and atrial fibrillation (elective hospitalization to perform electrical cardioversion of atrial fibrillation). The patient later re-enrolled in study and resumed treatment. Thus, the TEAE of ejection fraction decreased no longer contributes towards the total number of study discontinuations.

[e]One patient permanently discontinued treatment and study owing to prolonged QTcF. The patient re-enrolled in the study, resumed treatment, and discontinued treatment and study for a second time following a non-serious TEAE of ejection fraction decreased that was not related to treatment. Thus, the TEAE of prolonged QTcF no longer contributes towards the total number of study discontinuations.

[f]One event of acute myocardial infarction resulted in death (captured in 'Death' row).

[g]TEAE of cardiac failure was attributed to erroneous dosing, and in-hospital echocardiogram showed LVEF of 40%; patient experienced cardiac failure event while admitted in the hospital owing to a serious TEAE of pneumonia.

[h]Study-defined stopping criteria included an LVEF ≤30%, new or worsening heart failure associated with systolic dysfunction, drug-induced liver toxicity, LVEF <50%, excessive QTcF prolongation, and/or

mavacamten plasma concentrations ≥1000 ng/mL at two consecutive visits or while receiving mavacamten 2.5 mg, the participant requests to discontinue study drug, and the sponsor requests that the participant permanently discontinues study drug.

[i]Four patients resumed treatment in the re-enrolment period.

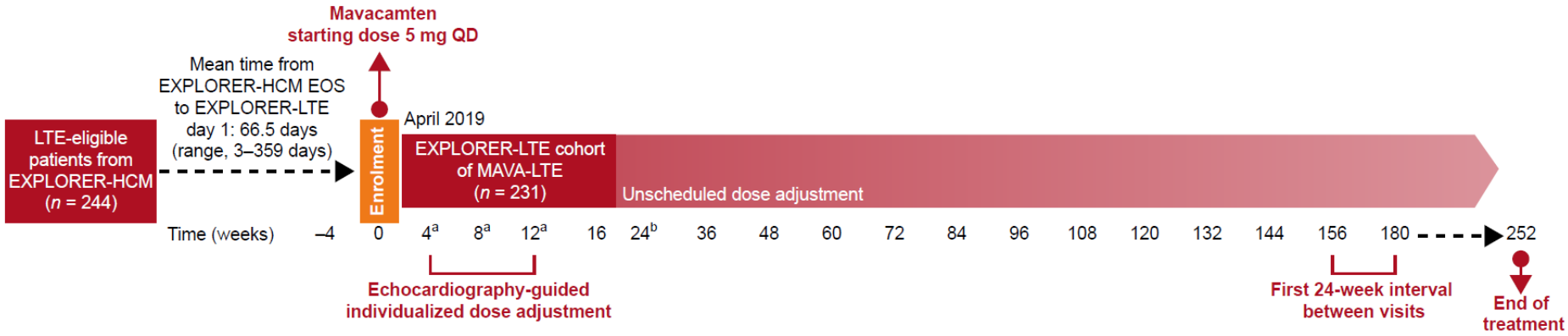

Figure S1 Study design.

Patients completed an 8-week washout period after treatment in EXPLORER-HCM before enrolment in MAVA-LTE.

[a]Dose adjustments were based on site-read echocardiography measures of Valsalva LVOT gradient and LVEF only.

[b]Dose adjustment was also possible at week 24 after site-read echocardiography assessment of postexercise LVOT gradient. Subsequent to week 24, dose adjustment was possible if site-read Valsalva LVOT gradient was >30 mm Hg and LVEF was ≥50%.

EOS, end of study; HCM, hypertrophic cardiomyopathy; LTE, Long-Term Extension; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; QD, once-daily.

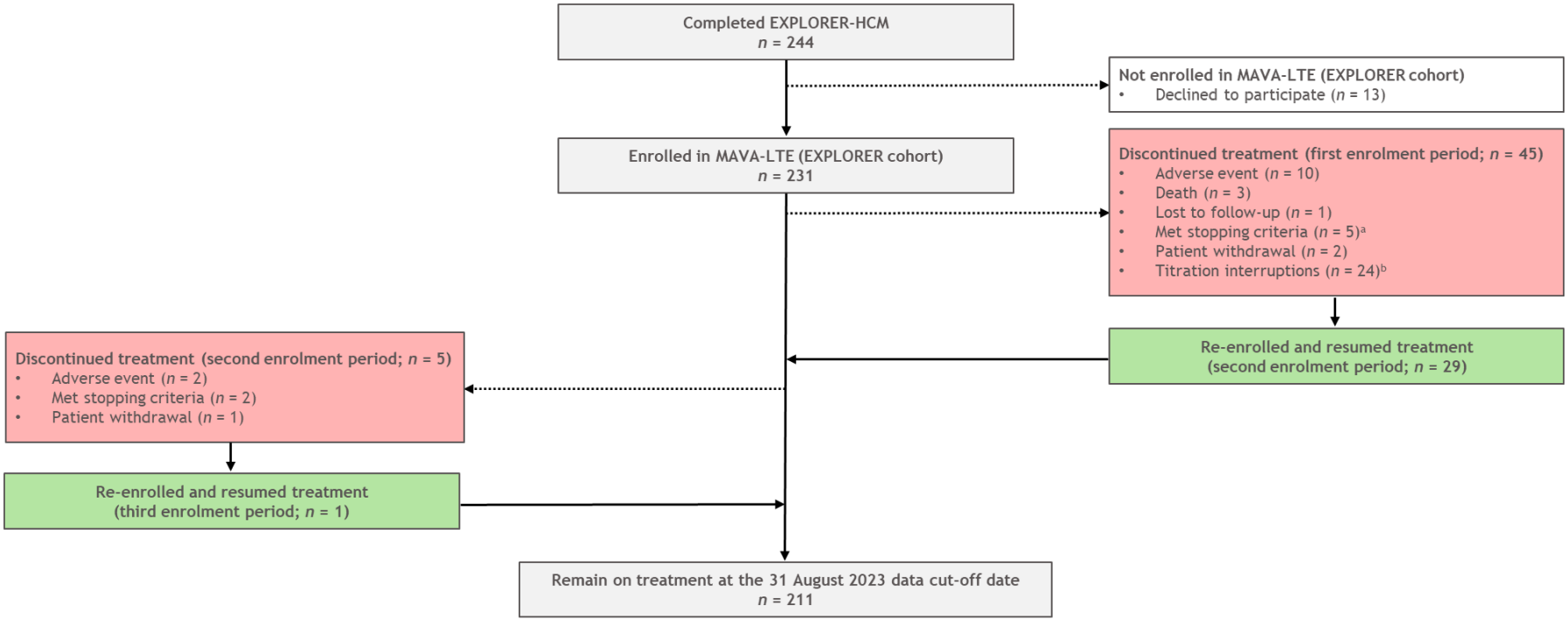

Figure S2 Patient disposition.

[a]LVEF-related results (n = 2), QTcF prolongation (n = 2), and site withdrawal of patient (n = 1).

[b]Missed assessments due to COVID-19 accounted for 21 of 24 titration interruption-related treatment discontinuations.

HCM, hypertrophic cardiomyopathy; LTE, Long-Term Extension; LVEF, left ventricular ejection fraction; QTcF, QT interval corrected using Fridericia's formula.

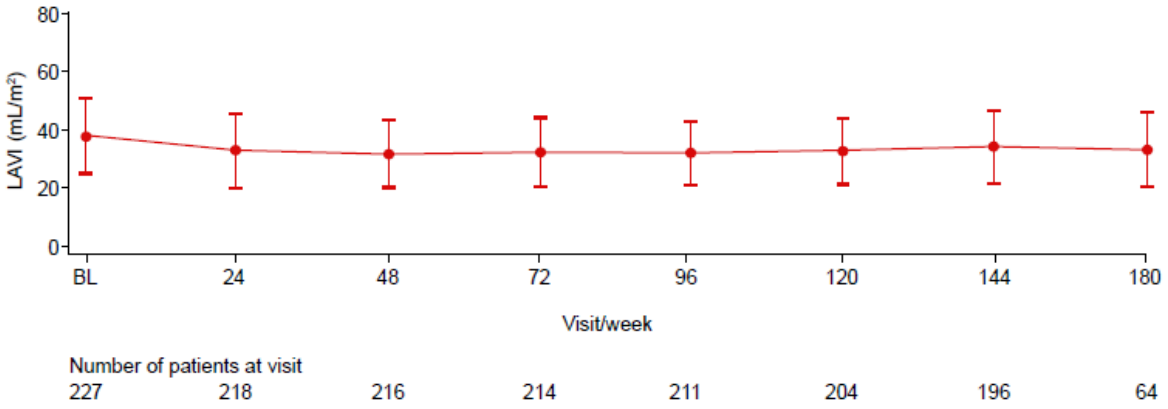

Figure S3 Mean (SD) LAVI over time.

The number of patients at each time point refers to the number of patients who had a visit scheduled at each week and for whom data are available. BL, baseline; LAVI, left atrial volume index; SD, standard deviation.

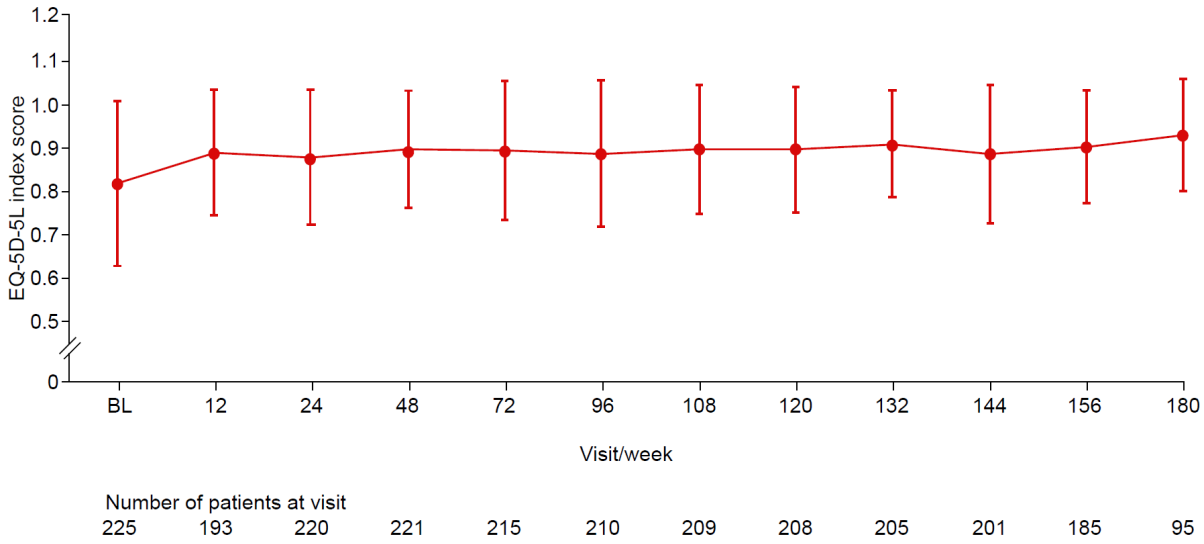

Figure S4 Mean (SD) EQ-5D-5L total index score over time.

The number of patients at each time point refers to the number of patients who had a visit scheduled at each week and for whom data are available.

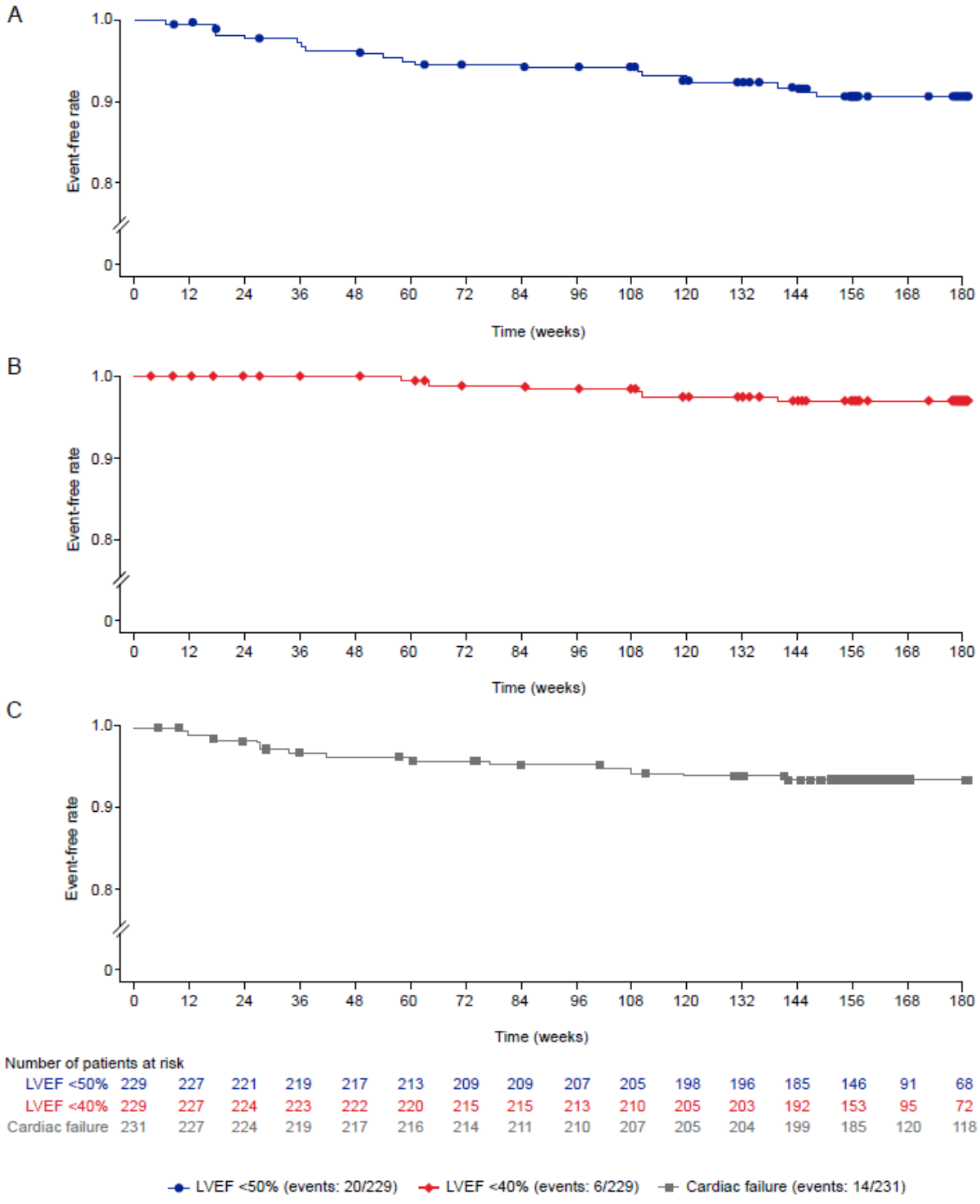

Figure S5 Event-free rate of occurrences of LVEF <50% (A), LVEF <40% (B), and TEAEs of cardiac failure (C) over time.

For patients with <56 days between enrolment periods, events contribute based on initial dosing (LVEF <50% and LVEF <40% analyses). LVEF, left ventricular ejection fraction; TEAE, treatment-emergent adverse event.

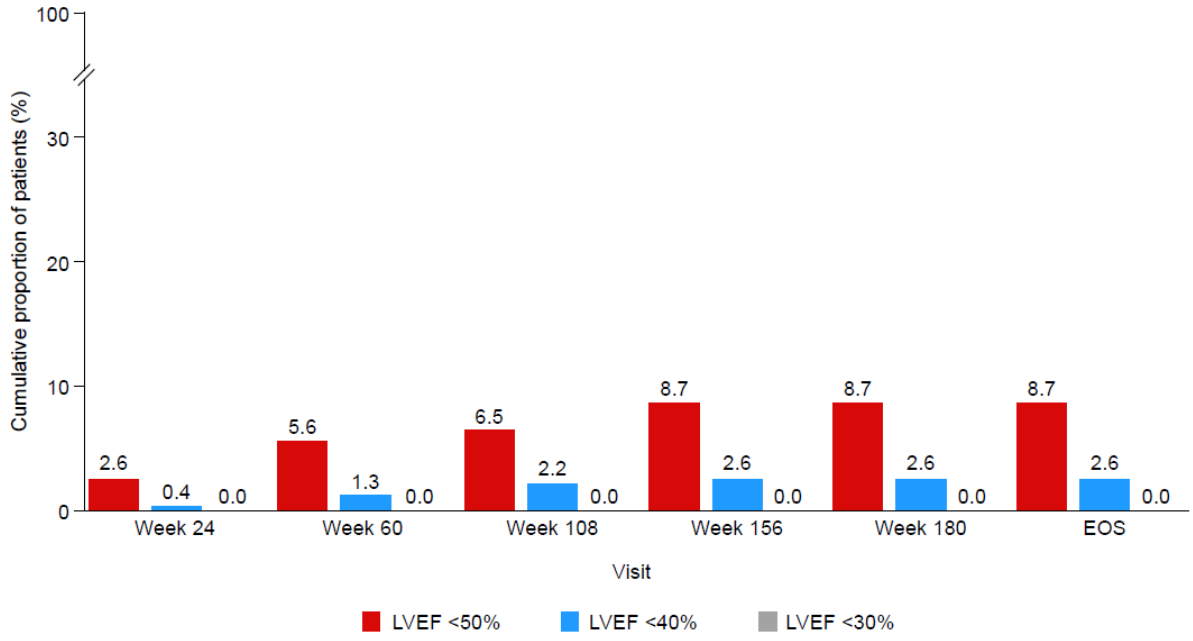

Figure S6 Cumulative incidence of occurrences of LVEF <50%, <40%, and <30% by study visit.

No patient experienced LVEF <30% during treatment in the study. EOS, end of study; LVEF, left ventricular ejection fraction.

Appendix 1: Questions asked to derive Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath domain score

1. Were you short of breath during the past 24 hours?
2. Were you short of breath during light physical activity such as walking slowly or cooking during the past 24 hours?
3. Were you short of breath during moderate physical activity such as cleaning the house or lifting heavy objects?
4. How often did you have shortness of breath during the past 24 hours?

Appendix 2: Details of patients who experienced new drug-related serious treatment-emergent adverse events since the previous interim analysis

Overall, five additional serious treatment-emergent adverse events (TEAEs) reported in five patients (2.2%) were considered to be related to the study drug (ejection fraction decreased, *n* = 3; atrial fibrillation, *n* = 1; atrial flutter, *n* = 1). One of these five patients required elective hospitalization for treatment of atrial fibrillation 5 weeks after discontinuing treatment due to an event of left ventricular ejection fraction (LVEF) of <50% while receiving mavacamten 10 mg. The patient re-enrolled in the study 3 weeks after the drug-related serious TEAE and resumed mavacamten treatment at 5 mg. At the time of the current data cut-off, the patient had been receiving mavacamten 5 mg for 96 weeks. The patient who experienced a drug-related serious TEAE of atrial flutter with rapid ventricular response had their 10 mg dose interrupted for the duration of their 3-day hospitalization. Once discharged, the patient resumed treatment at the same dose. Treatment was interrupted for two of the three patients with drug-related serious TEAEs of ejection fraction decreased and their dose was reduced by one level upon resumption of treatment per protocol. The remaining patient experienced a TEAE of ejection fraction decreased concurrently with acute myocardial infarction while receiving mavacamten 15 mg; this patient resumed treatment at the same dose following a 4-week interruption. All five patients who experienced drug-related serious TEAEs after the previous analysis remain on treatment at the data cut-off date of 31 August 2023.

Appendix 3: Additional details of patients who experienced LVEF <50%

At the time of the 22 events, 2, 5, 12, and 3 patients were receiving mavacamten doses of 2.5, 5, 10, and 15 mg, respectively. All 20 patients were receiving background therapy with either a beta-blocker (*n* = 16) or a calcium channel blocker (*n* = 4) at the time of the LVEF <50% event. Eight (40%) of the 20 patients who experienced LVEF <50% had intercurrent atrial fibrillation or flutter at the time of the event (of which none were considered to be serious). None of the three patients with a cytochrome P450 2C19 poor metabolizer phenotype experienced an LVEF of <50%.

Appendix 4: Clinical narratives for the two patients who underwent septal reduction therapy during the MAVA-LTE (EXPLORER cohort) study

Patient 1

The patient (a 64-year-old man) received a diagnosis of hypertrophic cardiomyopathy (HCM) on 3 April 2018. His relevant medical history upon enrolment in the EXPLORER-HCM trial included atrial fibrillation, non-sustained ventricular tachycardia, shortness of breath, liver failure, and Crohn's disease receiving immunosuppression and pulmonary veins ablation for atrial fibrillation.

The patient received placebo in the EXPLORER-HCM study. On 5 June 2020, the patient received his first dose of open-label mavacamten 5 mg in MAVA-LTE (EXPLORER cohort) and continued receiving 5 mg until week 8.

Other conditions occurring at the time of the adverse event (bacterial endocarditis) included atrial fibrillation paroxysmal, congestive heart failure, Crohn's disease, gastrointestinal bleeding, hypertension, stage 3 chronic kidney disease, and morbid obesity. Concomitant medications at the time of event included adalimumab, potassium chloride, metoprolol succinate, rivaroxaban, torsemide, loratadine, metronidazole, and spironolactone.

On study day 70, the patient was admitted to an outside hospital intensive care unit (ICU) after receiving a diagnosis of sepsis requiring intravenous antibiotics. Initial blood cultures showed persistent methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia. A transthoracic echocardiogram (TTE) was performed, which showed mitral valve endocarditis.

It was noted that, in addition to the aforementioned infection issues, the patient had problems with atrial fibrillation with rapid ventricular response. He was treated with an amiodarone drip before transitioning to oral amiodarone, and his atrial fibrillation was considered to be under control. The study drug was withheld owing to the event.

On study day 71, a TTE showed normal left ventricular systolic function with a LVEF of 55% (± 3%). There was no significant change compared with the previous TTE results.

On study day 72, repeat blood culture results still showed the presence of MSSA.

On study day 75, the patient was transferred back to the site for management of the bacteraemia. Compared with the previous TTE performed on study day 71, the TTE revealed a large frond-like vegetation measuring 4 cm × 1.5 cm attached to the atrial side of the mitral valve with trivial mitral regurgitation (MR). Left ventricular systolic function was normal, with an LVEF of 60% (± 3%).

On study day 76, blood culture results showed Gram-positive cocci in clusters, and MSSA was identified by mass spectrometry.

On study day 78, a transoesophageal echocardiogram showed a large mitral valve vegetation. Preoperative diagnoses included mitral valve bacterial endocarditis, obstructive HCM, and atrial fibrillation. Owing to a potential risk of embolization, the patient underwent mitral valve replacement. At the same time, he underwent a septal myectomy and a maze procedure, and the surgery was technically successful. Postoperatively, the patient had respiratory failure in which obesity was considered a comorbidity. He was intubated and was under inotropic support with epinephrine. Three attempts at extubation were performed and each lasted a few days before re-intubation. The patient also developed postoperative renal failure requiring dialysis. Supportive management (inotropic support, dialysis, and intubation) was continued.

On study day 115, at 16:38, the patient died of cardiac arrest secondary to multisystem organ failure induced by haemorrhagic shock due to acute gastrointestinal bleeding. The investigator assessed the event of bacterial endocarditis and considered it to be not related to study treatment. The investigator indicated that the adverse event was not reasonably temporally associated with study treatment administration and was expected in this targeted

disease and/or population. It was also confirmed that the septal myectomy performed during mitral valve replacement was not undertaken because of failure of mavacamten. The adverse event did not abate after discontinuation of study treatment. The study drug was never reintroduced.

Concurrent Crohn's disease, immunosuppression (likely due to treatment with adalimumab for serious infections), chronic kidney disease, and morbid obesity were potential confounders for this event. There were no other adverse events experienced by the patient during the study.

Patient 2

The patient (a 53-year-old woman) received a diagnosis of HCM in 2003 and has a family history of HCM with no family history of sudden cardiac death. The patient's HCM history upon enrolment in the EXPLORER-HCM trial included paroxysmal atrial fibrillation, chest pain, and palpitations. There was no other relevant medical history. Other conditions occurring at the time of the event (worsening of systemic lupus erythematosus [SLE]) included acute pericarditis, hypercholesterolaemia, smoker, headache, and anxiety. Concomitant medications at the time of event included atorvastatin, bisoprolol, metamizole, amiloride, hydrochlorothiazide, diazepam, colchicine, enoxaparin, rivaroxaban, ibuprofen, amiodarone, furosemide, magnesium, potassium chloride, pantoprazole, prednisone, alprazolam, and lorazepam.

The patient received mavacamten in EXPLORER-HCM and completed the study on 19 February 2020. In MAVA-LTE (EXPLORER cohort), the patient received her first and last doses of open-label mavacamten 5 mg on 21 February 2020 and 27 March 2020 (study day 36), respectively. The patient discontinued from the study on 10 June 2020 owing to the

adverse event of SLE. SLE was first reported while the patient was still in EXPLORER-HCM, and she received her first dose of study drug in MAVA-LTE while hospitalized for acute pericarditis due to SLE. On study day 12, the patient was discharged from hospital.

On study day 27, the patient reported ongoing dyspnoea with minimal exertion; she denied fever or cough. The patient also reported feeling worse, experienced a worsening of pericarditis, and noticed itchy skin lesions on her abdominal area on approximately study day 17. The patient was admitted to hospital on the same day with suspected drug-induced lupus versus SLE that would provide an explanation of the symptoms (pericarditis, anaemia, and skin lesions). During the hospital admission, an echocardiogram showed a dynamic gradient of up to 100 mm Hg with systolic anterior motion and moderate MR. Biopsy of the abdominal skin lesion revealed findings compatible with subacute lupus erythematosus. Progressing anaemia (haemoglobin decreased to 7.4 g/dL) without externalization of bleeding and skin lesions were also suggestive of subacute lupus. Medications initiated during the previous hospitalizations were ibuprofen, colchicine, lorazepam, and alprazolam (patient was receiving diazepam previously), pantoprazole, amiodarone, and mavacamten. After further assessment, it was determined that mavacamten had no reported immunological adverse effects, and pantoprazole was found to have induced cutaneous lupus symptoms. Chest X-ray showed pulmonary oedema.

On study day 29, an echocardiogram showed no significant change from the previous echocardiogram.

On study day 36, the patient received the last dose of study drug. It was decided to suspend mavacamten pending a pericardial window procedure and re-evaluate once the patient was clinically stable. Before stopping the study drug, the patient experienced a reduction in her

resting left ventricular outflow tract (LVOT) gradient. The patient's condition had worsened, and she had developed a loud murmur grade 5/6 and had become hypotensive. An echocardiogram showed a mild pericardial effusion with severe MR, a hyperdynamic LVEF of 76%, and a Valsalva LVOT gradient of 125 mm Hg while the patient was receiving beta-blockers, amiodarone, and diuretics. The patient had not experienced atrial fibrillation while being monitored in hospital, although there was concern about possible development of atrial fibrillation in view of the severity of the MR. Previously, the patient's LVEF was normal with residual mild pericardial effusion, but after stopping mavacamten, she experienced very severe LVOT obstruction and severe MR. The site felt that the patient required additional treatment and considered reintroducing mavacamten.

On study day 39, a therapeutic diagnostic pericardiocentesis (400–500 mL) was performed without complications (a pericardial window was not needed) under local anaesthesia. After the procedure, the patient's condition evolved unfavourably, reporting dyspnoea with minimal effort, asthenia, and a tendency to hypotension.

On study day 40, the investigator mentioned that the patient was doing well and was without fever or cough. The patient was clinically stable the following day.

On study day 43, the patient had more skin lesions and more erythema. After pericardiocentesis, the patient's condition evolved unfavourably, reporting dyspnoea with minimal effort, asthenia, and a tendency to hypotension and low cardiac output, thus needing to be admitted to an ICU, in which she required support with esmolol and sodium. As per the conclusions from the site, it was unlikely that the skin lesions could be related to mavacamten treatment, because the study drug had been discontinued 7 days earlier. On the same day, the patient decompensated owing to severe LVOT obstruction and MR. She was then readmitted

to the ICU and her condition became stable with treatment with an esmolol drip and noradrenaline for haemodynamic support.

The investigator commented that the presence of antibodies (antinuclear antibodies, anti-Ro antibodies, low complement) that have been described in cases of lupus pericarditis, as well as elevated adenosine deaminase (but not pathognomonic), were present in the pericardial fluid. Repeat autoimmune markers were more indicative of SLE, with low probability of a drug-induced lupus. Drug-induced lupus could not be the cause of the initial hospitalization for pericarditis, because no drug was initiated before the first hospitalization. The rheumatology service (which had ruled out SLE previously), believed that all signs and symptoms could be explained by SLE and, therefore, that the reactions were not drug-related.

Alcohol septal ablation was considered for the patient for the following reasons: evolution of severe left ventricular hypertrophy and obstruction, New York Heart Association class III symptoms, two ICU admissions demanding haemodynamic support, dismissal for septal myectomy, a developing tolerance to disopyramide, and discontinuing treatment with mavacamten for possible pharmacological lupus.

On study day 54, the alcohol septal ablation procedure was performed. An echocardiogram showed high diastolic flow at the level of the antero-superior septum that could have corresponded to a septal coronary fistula. Immediately after the procedure, LVOT gradient and MR showed significant reduction. The patient was clinically stable after the procedure.

On study day 64, the serious adverse event worsening of SLE was considered to have been resolved and the patient was discharged from hospital.

The patient's cardiac condition was much improved after receiving bisoprolol and disopyramide. The patient was clinically stable after discharge and was able to climb two floors/flights of stairs. The patient was also able to walk without experiencing dizziness or

chest pain, and she had no gross macroscopic bleeding. The skin lesions remained. An electrocardiogram showed normal results. An echocardiogram showed no pericardial effusion, an LVEF within normal limits, a resting LVOT gradient of 60 mm Hg, and a Valsalva LVOT gradient of 82 mm Hg. The investigator assessed the event of worsening of SLE as being not related to study drug. The investigator indicated that the event of worsening of acute pericarditis was attributed to the event of SLE. The adverse event of SLE did not abate after discontinuation of study treatment. The study drug was never reintroduced. A rheumatology evaluation performed by an external independent expert rheumatologist on 24 April 2020 concluded that it concurred with the diagnosis of SLE. Other adverse events experienced by the patient during the observation period for this interim analysis included anaemia, retroperitoneal haematoma, and cardiac failure (all considered to be unrelated to mavacamten treatment).