Table 1 Echocardiographic Data for Untreated and SCH00013-Treated *Lmna*$^{+/+}$ and *Lmna*$^{H222P/H222P}$ Mice

	IVSd (mm)	PWd (mm)	LVM (mg)	LVEDD (mm)	LVESD (mm)	LVFS (%)	LVEF (%)	Heart Rate (beats/min)
Data for male mice age 2, 4, 6, and 8 months								
2 months of age								
Untreated *Lmna*$^{+/-}$ (n = 15)	0.49 ± 0.01	0.50 ± 0.01	45.2 ± 1.18	3.28 ± 0.04	1.85 ± 0.03	43.7 ± 0.59	81.5 ± 0.59	500 ± 7
SCH *Lmna*$^{+/+}$ (n = 22)	0.50 ± 0.01	0.54 ± 0.01	46.7 ± 1.36	3.21 ± 0.03	1.80 ± 0.03	43.9 ± 0.75	81.7 ± 0.76	523 ± 9
Untreated *Lmna*$^{H222P/H222P}$ (n = 21)	0.50 ± 0.01	0.49 ± 0.01	46.0 ± 1.17	3.30 ± 0.03	1.98 ± 0.03*	39.6 ± 0.93*	76.5 ± 1.19*	524 ± 7
SCH *Lmna*$^{H222P/H222P}$ (n = 17)	0.49 ± 0.02	0.51 ± 0.02	46.0 ± 1.76	3.28 ± 0.03	1.92 ± 0.02†	41.1 ± 0.60†	78.4 ± 0.77†	536 ± 10
4 months of age								
Untreated *Lmna*$^{+/-}$ (n = 12)	0.48 ± 0.02	0.53 ± 0.02	48.3 ± 1.90	3.38 ± 0.06	1.94 ± 0.05	42.8 ± 0.82	80.5 ± 0.82	542 ± 12
SCH *Lmna*$^{+/+}$ (n = 22)	0.52 ± 0.01	0.54 ± 0.01	51.7 ± 1.36	3.38 ± 0.03	1.95 ± 0.03	42.5 ± 0.68	80.0 ± 0.72	526 ± 7
Untreated *Lmna*$^{H222P/H222P}$ (n = 21)	0.47 ± 0.01	0.47 ± 0.01*	55.4 ± 2.05	3.80 ± 0.07‡	2.64 ± 0.08‡	30.9 ± 1.07‡	66.7 ± 1.44‡	560 ± 10
SCH *Lmna*$^{H222P/H222P}$ (n = 17)	0.49 ± 0.01	0.50 ± 0.01	55.8 ± 2.09	3.69 ± 0.06§	2.33 ± 0.06§‖	37.0 ± 0.92§¶	72.9 ± 1.97†#	543 ± 7
6 months of age								
Untreated *Lmna*$^{+/-}$ (n = 12)	0.49 ± 0.01	0.53 ± 0.02	56.1 ± 2.10	3.64 ± 0.04	2.10 ± 0.03	42.3 ± 0.46	79.9 ± 0.63	532 ± 9
SCH *Lmna*$^{+/+}$ (n = 21)	0.50 ± 0.01	0.50 ± 0.01	56.1 ± 1.47	3.68 ± 0.05	2.19 ± 0.05	40.6 ± 0.65	78.2 ± 0.64	537 ± 7
Untreated *Lmna*$^{H222P/H222P}$ (n = 17)	0.43 ± 0.01**	0.42 ± 0.02‡	57.5 ± 2.28	4.34 ± 0.12‡	3.36 ± 0.15‡	23.0 ± 1.29‡	53.9 ± 2.59‡	516 ± 18
SCH *Lmna*$^{H222P/H222P}$ (n = 17)	0.46 ± 0.01††	0.43 ± 0.01§	58.8 ± 2.30	4.10 ± 0.10§	3.01 ± 0.12§#	27.0 ± 1.29§#	60.6 ± 2.08§#	533 ± 7
8 months of age								
Untreated *Lmna*$^{+/-}$ (n = 12)	0.50 ± 0.01	0.49 ± 0.02	54.1 ± 2.57	3.62 ± 0.07	2.07 ± 0.06	43.0 ± 0.64	80.8 ± 0.62	535 ± 11
SCH *Lmna*$^{+/+}$ (n = 21)	0.49 ± 0.01	0.49 ± 0.01	58.1 ± 2.20	3.80 ± 0.08	2.19 ± 0.08	39.9 ± 0.81	77.7 ± 0.92	544 ± 8
Untreated *Lmna*$^{H222P/H222P}$ (n = 7)	0.37 ± 0.01‡	0.36 ± 0.02‡	52.0 ± 5.27	4.37 ± 0.12‡	3.63 ± 0.10‡	15.9 ± 0.88‡	41.0 ± 1.65‡	566 ± 20
SCH *Lmna*$^{H222P/H222P}$ (n = 7)	0.38 ± 0.01§	0.37 ± 0.01§	54.4 ± 3.65	4.38 ± 0.15§	3.50 ± 0.16§	19.5 ± 0.79§	48.3 ± 3.08§	552 ± 11
Data for female mice age 2, 4, 6, 8, and 10 months								
2 months of age								
Untreated *Lmna*$^{+/-}$ (n = 7)	0.47 ± 0.02	0.52 ± 0.01	42.9 ± 1.93	3.14 ± 0.03	1.80 ± 0.05	41.9 ± 1.52	82.5 ± 0.95	535 ± 13
SCH *Lmna*$^{+/+}$ (n = 14)	0.49 ± 0.01	0.51 ± 0.01	40.9 ± 1.38	3.10 ± 0.02	1.77 ± 0.03	42.7 ± 0.80	80.5 ± 0.84	521 ± 10
Untreated *Lmna*$^{H222P/H222P}$ (n = 18)	0.51 ± 0.01	0.49 ± 0.01	43.7 ± 0.91	3.18 ± 0.02	1.84 ± 0.03	42.7 ± 0.67	79.1 ± 0.74	544 ± 7
SCH *Lmna*$^{H222P/H222P}$ (n = 14)	0.50 ± 0.02	0.50 ± 0.01	41.2 ± 0.80	3.12 ± 0.03	1.85 ± 0.04	40.9 ± 0.77	78.2 ± 0.77	551 ± 10
4 months of age								
Untreated *Lmna*$^{+/-}$ (n = 7)	0.50 ± 0.02	0.56 ± 0.02	43.1 ± 2.23	3.24 ± 0.03	1.72 ± 0.02	43.2 ± 0.43	81.0 ± 0.42	521 ± 15
SCH *Lmna*$^{+/+}$ (n = 14)	0.50 ± 0.01	0.52 ± 0.02	47.1 ± 1.35	3.28 ± 0.04	1.88 ± 0.03	42.3 ± 0.73	80.3 ± 0.71	530 ± 16
Untreated *Lmna*$^{H222P/H222P}$ (n = 18)	0.47 ± 0.01	0.46 ± 0.01‡	45.9 ± 1.27	3.48 ± 0.05‡	2.24 ± 0.07‡	36.0 ± 0.84‡	72.8 ± 1.06‡	553 ± 8
SCH *Lmna*$^{H222P/H222P}$ (n = 14)	0.49 ± 0.01	0.50 ± 0.02	46.5 ± 2.04	3.32 ± 0.04#	2.05 ± 0.030††#	38.2 ± 0.49§#	75.2 ± 0.61††	557 ± 11
6 months of age								
Untreated *Lmna*$^{+/-}$ (n = 7)	0.49 ± 0.01	0.50 ± 0.02	43.0 ± 2.09	3.28 ± 0.05	1.82 ± 0.04	42.7 ± 0.44	80.5 ± 0.44	519 ± 12
SCH *Lmna*$^{+/+}$ (n = 14)	0.49 ± 0.01	0.49 ± 0.01	45.8 ± 1.91	3.33 ± 0.04	1.87 ± 0.03	43.8 ± 0.39	81.2 ± 0.35	521 ± 8
Untreated *Lmna*$^{H222P/H222P}$ (n = 16)	0.46 ± 0.01	0.44 ± 0.01*	46.5 ± 1.38	3.66 ± 0.07‡	2.57 ± 0.10‡	30.0 ± 1.43‡	64.9 ± 2.06‡	555 ± 9
SCH *Lmna*$^{H222P/H222P}$ (n = 14)	0.46 ± 0.02	0.45 ± 0.01†	45.2 ± 2.54	3.44 ± 0.06#	2.23 ± 0.07§‖	35.4 ± 1.05§‖	71.6 ± 1.22§‖	558 ± 7
8 months of age								
Untreated *Lmna*$^{+/-}$ (n = 7)	0.47 ± 0.03	0.49 ± 0.02	42.4 ± 1.67	3.24 ± 0.05	1.80 ± 0.03	44.4 ± 0.76	82.3 ± 0.84	510 ± 16
SCH *Lmna*$^{+/+}$ (n = 14)	0.47 ± 0.01	0.47 ± 0.01	44.3 ± 1.33	3.36 ± 0.04	1.91 ± 0.03	43.0 ± 0.52	80.8 ± 0.45	539 ± 8
Untreated *Lmna*$^{H222P/H222P}$ (n = 16)	0.40 ± 0.01**	0.38 ± 0.01‡	47.4 ± 1.41	3.99 ± 0.07‡	3.16 ± 0.09‡	21.2 ± 1.15‡	51.1 ± 1.84‡	572 ± 9
SCH *Lmna*$^{H222P/H222P}$ (n = 14)	0.42 ± 0.01†	0.43 ± 0.01†‖	48.8 ± 2.60	3.80 ± 0.13††	2.72 ± 0.17§#	29.3 ± 2.03§‖	63.2 ± 3.20§‖	542 ± 9
10 months of age								
Untreated *Lmna*$^{+/-}$ (n = 7)	0.49 ± 0.01	0.47 ± 0.01	44.3 ± 1.45	3.32 ± 0.04	1.88 ± 0.03	43.6 ± 0.58	81.4 ± 0.38	529 ± 13
SCH *Lmna*$^{+/+}$ (n = 13)	0.49 ± 0.01	0.50 ± 0.01	46.6 ± 1.05	3.36 ± 0.03	1.93 ± 0.03	42.5 ± 0.41	80.4 ± 0.38	540 ± 11
Untreated *Lmna*$^{H222P/H222P}$ (n = 7)	0.35 ± 0.02‡	0.37 ± 0.03**	52.1 ± 4.09	4.40 ± 0.11‡	3.74 ± 0.14‡	15.1 ± 1.72‡	38.9 ± 3.83‡	506 ± 28
SCH *Lmna*$^{H222P/H222P}$ (n = 7)	0.42 ± 0.02††	0.43 ± 0.02††	54.4 ± 4.51	4.05 ± 0.16§	3.11 ± 0.21§#	23.6 ± 2.36§#	54.4 ± 4.21§#	547 ± 21

Cardiac function was evaluated by transthoracic echocardiographic analyses of the left ventricle (LV). The left ventricular mass (LVM) and the percentage of left ventricular fractional shortening (LVFS) were calculated as follows: [(IVSd + PWd + EDD)3 − EDD3] × 1.055 and (LVEDD − LVESD)/LVEDD × 100, respectively. *p < 0.05, **p < 0.01, and ‡p < 0.001, versus age-matched untreated *Lmna*$^{-/+}$ mice. †p < 0.05, ††p < 0.01, and §p < 0.001, versus age-matched SCH00013-treated *Lmna*$^{+/-}$ mice. #p < 0.05, ‖p < 0.01, and ¶p < 0.001. versus age-matched untreated *Lmna*$^{H222P/H222P}$ mice.

IVSd = interventricular septal wall thickness in diastole; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVM = left ventricular mass; PWd = posterior wall thickness in diastole.

We next investigated the gene expression in the hearts from untreated and treated *Lmna*$^{+/+}$ and *Lmna*$^{H222P/H222P}$ female mice, because the beneficial effect of SCH00013 was prominent in female mice. In the hearts from untreated *Lmna*$^{H222P/H222P}$ mice, *Nppa*, *Nppb*, *Myh7*, and *Myl7* messenger ribonucleic acids were significantly increased, and the upregulation of *Nppa* and *Myl7* was significantly reduced in the treated mice (Online Fig. S6). We also found increased messenger ribonucleic acid expression of proto-oncogene *Fos* and extracellular matrix remodeling-related genes *Tgfb1*, *Tgfb2*, and *Col1a2* in the untreated *Lmna*$^{H222P/H222P}$ mice, whereas these changes were suppressed by the treatment (Online Fig. S6). Left ventricles from the untreated *Lmna*$^{H222P/H222P}$ mice showed 2.2-fold and 1.7-fold increases of Nppa and Mlc2 proteins, respectively, as compared with the untreated *Lmna*$^{+/+}$ mice, and the increased expression was suppressed by the treatment (Online Fig. S7). In addition, we investigated whether the apoptotic signal was induced by the *Lmna* mutation, because there is an association among apoptosis, cardiac myocyte drop-out, ventricular remodeling, and deterioration of systolic performance in various experimental models of heart failure. However, the number of transferase-mediated dUTP nick-end labeling–positive cells was not increased in the hearts of *Lmna*$^{H222P/H222P}$ mice, and western blot analyses showed no or little expression of Fas-L or Fas proteins, respectively, in the *Lmna*$^{H222P/H222P}$ mice (Online Fig. S8). These results demonstrated that the apoptosis was not associated with the cardiac phenotypes in *Lmna*$^{H222P/H222P}$ mice and suggested that loss of cardiomyocytes was caused by cell death mechanisms other than the apoptosis.

The molecular mechanisms for the beneficial effect of SCH00013 remained unclear, but it might be related to the phosphodiesterase III activity. This possibility is unlikely, however, because SCH00013 inhibited the phosphodiesterase III activity at much higher concentration (IC_{50} = 64.9 μmol/l) than the concentration at which it produced the positive inotropic effect (IC_{50} = 9.2 μmol/l) in guinea pig hearts (3); and we showed that the plasma concentration of SCH00013 in the *Lmna*$^{H222P/H222P}$ mice ranged from 1 to 2 μmol/l, although we did not measure the concentration in the hearts. By contrast, because the Ca^{2+} sensitivity of cardiac muscle contraction was not decreased in the *Lmna*$^{H222P/H222P}$ mice at 3 months of age (Online Fig. S9), the Ca^{2+} sensitizing effect might not play a major role at the early stage, but the Ca^{2+} sensitizing effect of SCH00013 was enhanced in the stretched muscles (5), raising a possibility that the Ca^{2+} sensitivity in the failed heart might be different. Although the molecular mechanisms should be clarified, our findings implied that the Ca^{2+} sensitizer could be a plausible option for preventing disease progression of DCM.

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APPENDIX

For supplementary information and supplementary figure legends, please see the online version of this article.

Letters to the Editor

A Meta-Analysis of Remote Monitoring of Heart Failure Patients

Structured disease management improves the prognosis of patients with chronic heart failure and has already been included in the current treatment guidelines. Along with better medication and increased use of defibrillators, planned periodic visits have also become routine in clinical practice. Remote patient monitoring (RPM) is a different type of structured disease management. Although the RPM systems (telephone support, network care, device-assisted monitoring) and health care environments are heterogeneous, the crucial difference from usual care is that RPM enables daily contact with healthcare experts and thus facilitates regular short-term evaluation of the disease status and early intervention. The elaborate meta-analysis by Klersy et al. (1) pointed out considerable benefits to be gained from RPM in terms

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