Appendix Figures

A new hERG allosteric modulator rescues genetic and drug-induced Long-QT Syndrome phenotypes in cardiomyocytes from isogenic pairs of patient induced pluripotent stem cells

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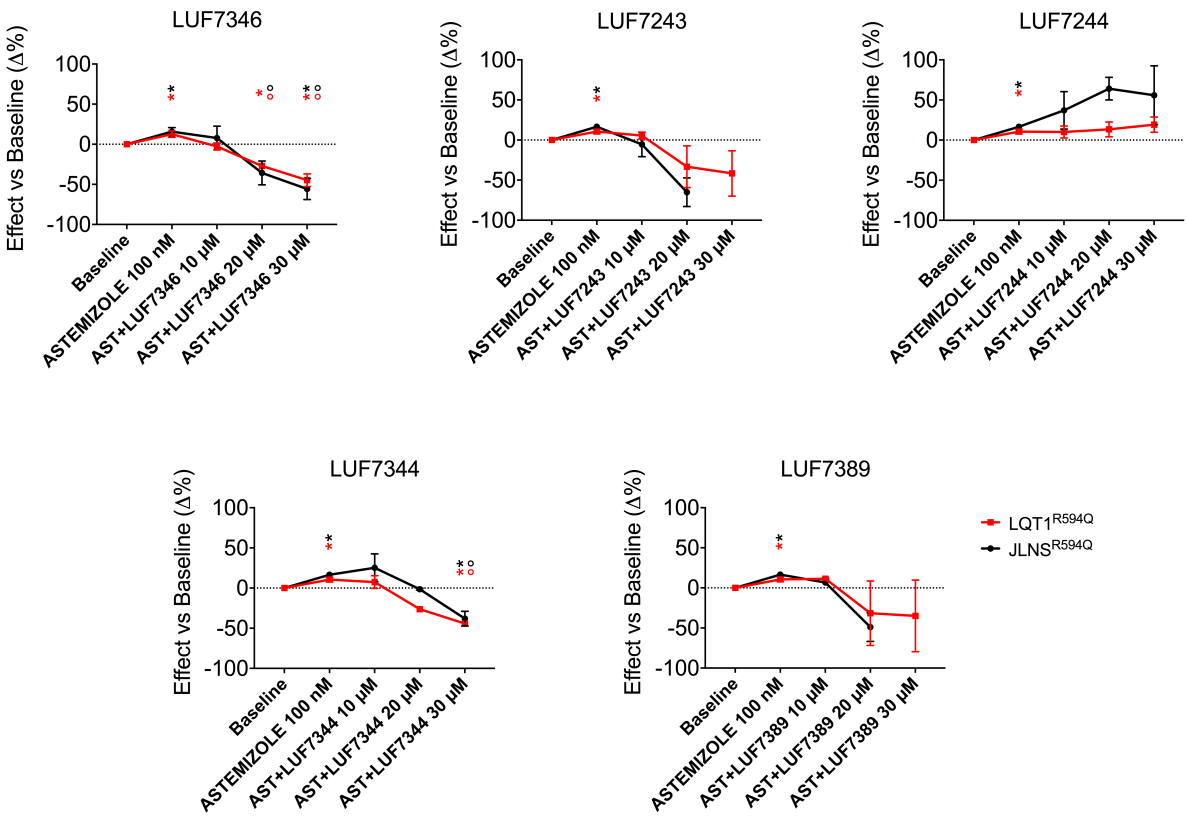
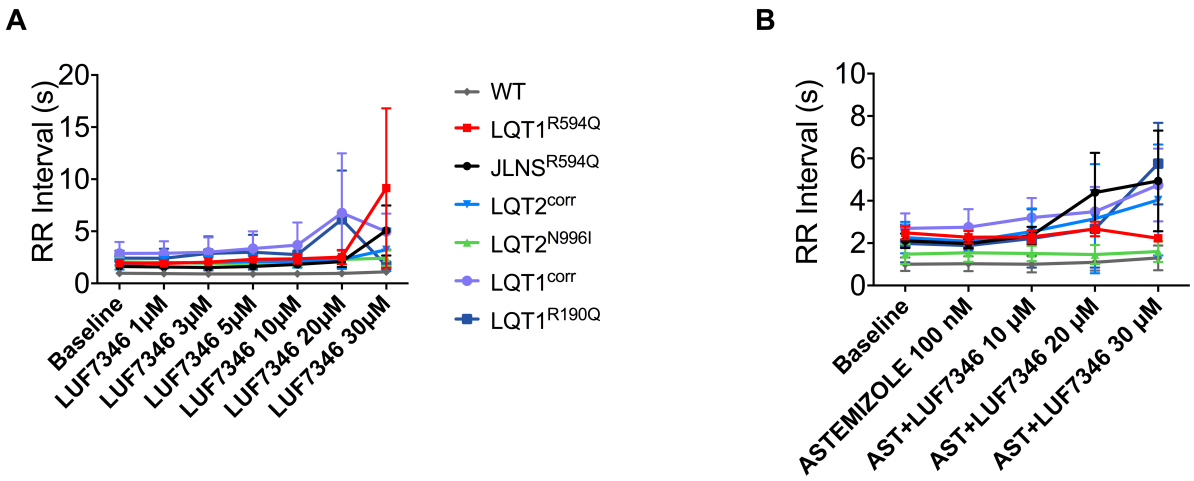
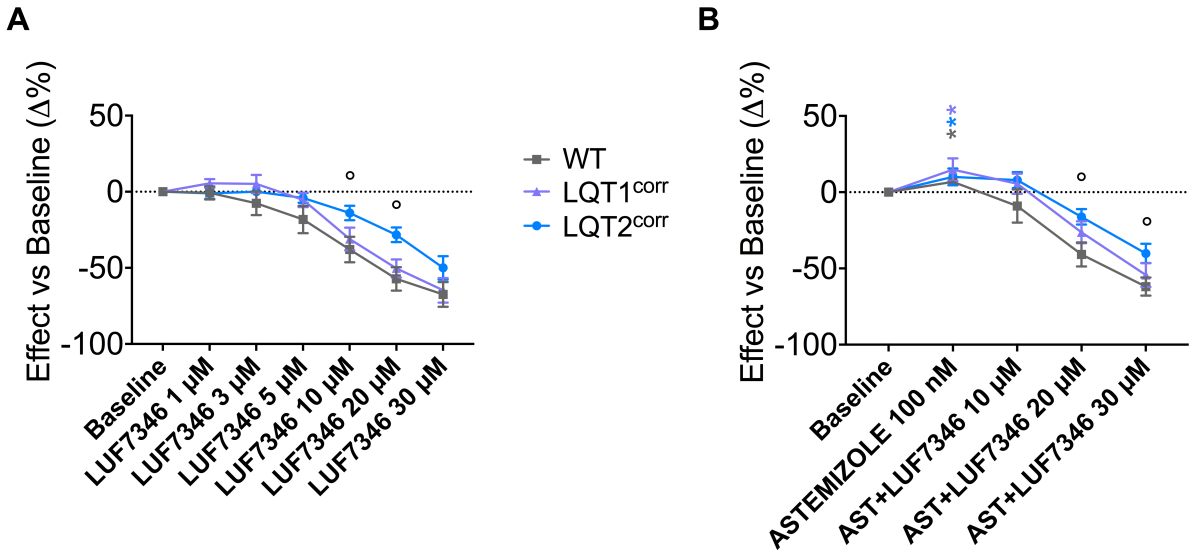


Appendix Figure S1: Effect of allosteric modulators on QT interval measured in hiPSC-CMs.

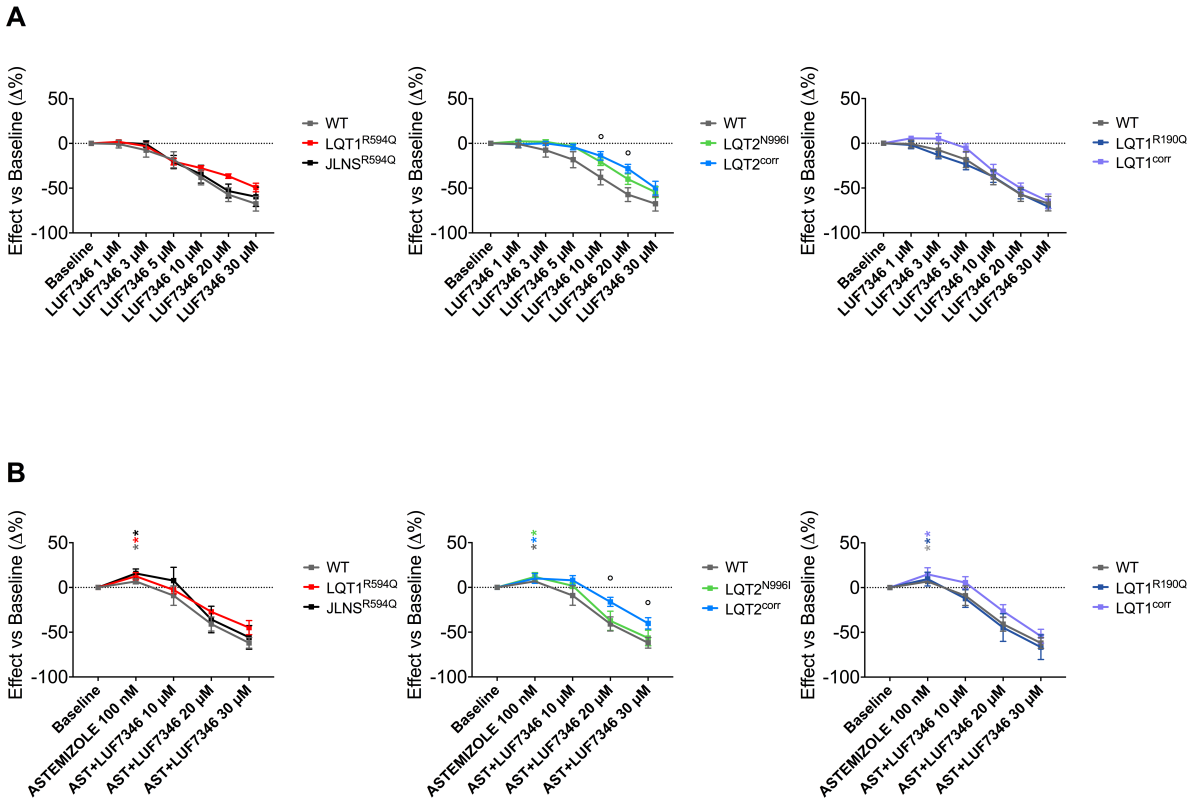
Pilot experiments on MEA displaying the effect of different LUF compounds in drug-induced LQTS. * = $p < 0.05$ vs respective baseline. ° = $p < 0.05$ vs AST. The colour of the symbols indicates the relative statistical significance. N: 3-10.



Appendix Figure S2: LUF7346 does not alter beating frequency on spontaneously beating hiPSC-CMs monolayers. A) Average effects of increasing concentrations of LUF7346 on the RR interval measured with MEA. N: 14-37. B) Average effects of AST and increasing concentrations of LUF7346 in the presence of AST, on the RR interval measured with MEA. N: 7-14.



Appendix Figure S3: Comparison of LUF7346 effect on QT interval of control hiPSC-CMs. A) Average effects of increasing concentrations of LUF7346 on the QT interval measured with MEA. N: 8-17. ° = $p < 0.05$ vs WT and LQT1^{corr}. B) Average effects of AST and increasing concentrations of LUF7346 in the presence of AST on the QT interval measured with MEA. * = $p < 0.05$ vs respective baseline. The colour of the asterisks indicates comparisons and relative statistical significance. ° = $p < 0.05$ vs WT and LQT1^{corr}. N: 6-9.



Appendix Figure S4: Comparison of LUF7346 effect among isogenic hiPSC lines.

A) Average of the effect of increasing concentrations of LUF7346 on QT interval duration compared to baseline. ° = $p < 0.05$ vs WT. The colour of the symbols indicates comparisons and relative statistical significance. N: 7-14. B) Average data of the effect of AST and increasing concentrations of LUF7346 in the presence of AST on QT interval durations, compared to baseline. * = $p < 0.05$. The colour of the symbols indicates the relative statistical significance. N: 7-12.

Appendix Table S1 - The percentage specific binding of [^{3}H]dofetilide to the hERG channel after 6 min of dissociation in the absence ($B_{control}$) or presence of 10 or 50 μM of the indicated compounds (B). Values are means (±SEM) of at least three independent experiments performed in duplicate.

Compounds	%B/$B_{control}$	
	10 μM	**50 μM**
Control	100	100
+LUF7243	71±2	23±3
+LUF7244	43±2	38±5
+LUF7344	47±2	28±1
+LUF7346	44±1	16±0.01
+LUF7389	38±3	26±3
n	>3	>3

Appendix Table S2- Parameters from Major-axis regression analysis in all hiPSC-CMs analysed.

WT			
	Uncorrected	**Bazett's formula**	**Fridericia's formula**
R^2	0.2679	0.5189	0.4508
1/slope	-0.01197	-0.006264	-0.007484
Deviation from 0	NS	*	*
p-value	0.1535	0.0284	0.0477
$LQT1^{R594Q}$			
	Uncorrected	**Bazett's formula**	**Fridericia's formula**
R^2	0.05125	0.279	0.0939
1/slope	0.07485	-0.04008	-0.06946
Deviation from 0	NS	*	*
p-value	0.0904	<0.0001	0.0204
$JLNS^{R594Q}$			
	Uncorrected	**Bazett's formula**	**Fridericia's formula**
R^2	0.3157	0.2306	0.1037
1/slope	0.107	-0.0261	-0.03653
Deviation from 0	NS	*	NS
p-value	0.578	0.0035	0.0592
$LQT2^{corr}$			
	Uncorrected	**Bazett's formula**	**Fridericia's formula**
R^2	0.1035	0.3587	0.2824
1/slope	-0.0265	-0.01516	-0.01685
Deviation from 0	NS	*	*
p-value	0.2422	0.0183	0.0415
$LQT2^{N996I}$			
	Uncorrected	**Bazett's formula**	**Fridericia's formula**
R^2	0.001487	0.1312	0.06852
1/slope	-0.1356	-0.01798	-0.02317
Deviation from 0	NS	NS	NS
p-value	0.8613	0.082	0.2166
$LQT1^{corr}$			

	Uncorrected	Bazett's formula	Fridericia's formula
R^2	0.04683	0.004937	0.01185
1/slope	-0.01909	-0.102	0.1919
Deviation from 0	NS	NS	NS
p-value	0.4574	0.8113	0.9151
$LQT1^{R190Q}$			
	Uncorrected	**Bazett's formula**	**Fridericia's formula**
R^2	0.2733	0.01581	0.1194
1/slope	0.004213	0.05819	0.009301
Deviation from 0	NS	NS	NS
p-value	0.099	0.4749	0.2979