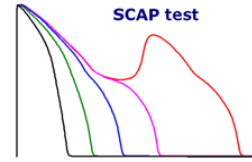


Safe Cardiac Action Potential Test



Ionic current	I_{NaL} (Late Na^+ current)		
Testing	50 and 100 % inhibition		
Results	<i>In silico</i> cardiac action potential study (ORd model) ⁽¹⁾		
	<p>Simulation conditions:</p> <ul style="list-style-type: none"> Cell geometry, channel conductance, state variables and scaling factors for endo-, mid- and epicardial myocytes as described in ORd model External ionic concentrations (mM): $[Na^+]_o$: 140 - $[Ca^{2+}]_o$: 1.8 - $[K^+]_o$: 5.4 Cycle length : 1000 msec Beat number: 100 	<p>Effect of ion channel on AP^{CL}:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = $APD_{50}^{mid} - APD_{50}^{epi}$ (at CL of 1000 msec) RUD = $APD_{50}^{P_{400}} - APD_{50}^{P_{1000}}$ <p>where $APD_{50}^{P_x}$ = APD_{50} with - APD_{50} without compounds at CL x</p>
	<p style="text-align: center;">Human epicardial myocytes</p>	<p style="text-align: center;">Transmural dispersion of repolarisation</p>	
	<p style="text-align: center;">Human midmyocardial myocytes</p>	<p style="text-align: center;">Reverse use dependence on midmyocardial myocytes</p>	
<p style="text-align: center;">Human endocardial myocytes</p>			
Summary			
	<p style="text-align: right;">Abbreviations</p> <ul style="list-style-type: none"> AP : action potential APA : AP amplitude APD_{40, 50 or 90} : AP duration at 40, 60 or 90 % of APA APDP : APD prolongation CL : cycle length EFTPC_{max} : maximal effective free therapeutic plasma concentration IC₅₀ : 50% inhibition concentration msec : millisecond mV : millivolt RMP : resting membrane potential TDR : reverse use dependence T_{40, 60} : APD₅₀-APD₄₀ or APD₅₀-APD₆₀ ("triangulation") TdP : torsade de pointes TDR : transmural dispersion of repolarization V_m : membrane voltage V_{max} : maximal rate of AP rise 		
References	<p>1. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061</p> <p>2. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61</p>		

Comments or discussion to be sent to: bchristophe@scaptest.com

see also our papers: *Pharm.Rep.* (2013) **65**:1281-1293 or *Br.J.Pharmac.Res.* (2015) **7**:88-101