

Safe cardiac action potential test (www.scaptest.com) : a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization

Part II : description of 50 additional drugs

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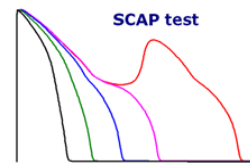
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Aim of the database

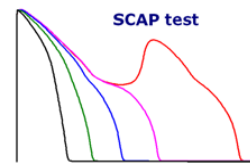
The aim of the present database is to describe the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization. This is based on the study of the effects of drugs on the non-failing human ventricular myocyte (endo-, mid- and epicardial subtypes) action potential reconstructed by computational simulation (O'Hara-Rudy dynamic algorithm) in order to identify cardiac action potential abnormalities such as high variations and/or occurrence of:

- resting membrane potential (RMP)
- action potential amplitude (APA)
- maximal rate of action potential rise (V_{\max})
- action potential duration (APD)
- triangulation (T)
- early afterdepolarization (EAD)
- transmural dispersion of repolarization (TDR)
- reverse use dependence (RUD)
- integrated sum of $I_{CaL} + I_{Kr} + I_{Ks} + I_{NaL} + I_{to} + I_{K1}$ (qNet)
- minimal rate of action potential decrease at EAD take-off voltage (V_{\min})

These various parameters are useful in order to assume a more accurate predictability of pro-arrhythmic liabilities of new drug candidate in the cardiac safety pharmacology screening process, which is the aim of the comprehensive *in vitro* pro-arrhythmia assay (CiPA) initiative.

The *in silico* cardiac safety profile of each drug (150 drugs described in this first version) is illustrated by a separate page describing the effects induced by each compound on these various parameters.

The results are summarized regarding the expected pro-arrhythmia profile of the various compounds as described by the CredibleMeds classification evaluating their propensity to induce torsade de pointes.



Algorithm used

- ORd model: O'Hara T, Virág L, Varró A, Rudy Y (2011) Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. PLoS Comput Biol, 7(5):e1002061.

Simulation conditions

- Cell geometry : as described in ORd model
- Channel conductance: as described in ORd model
- State variables: as described in ORd model
- Scaling factors among endo-, mid- and epi myocardial cells: as described in ORd model
- External ionic concentrations : $[Na^+]_o$, $[Ca^{++}]_o$ and $[K^+]_o$ of 140, 1.8 and 5.4 mM
- Cycle length (CL): 1000 msec
- Beat number: 100

Action potential reconstruction

- Calculation of action potential parameters from endo-, mid- and epicardial myocytes in the absence and the presence of drug.
- Drug tested at 1-, 3-, 10-, 30- and 100-fold $EFTPC_{max}/IC_{50s}$ ratios (maximal effective free therapeutic concentration divided by 50% inhibition concentration induced by a compound on each cardiac ionic current). More precise x-fold determined in case of EAD occurrence.

Effect of drugs on ion channel

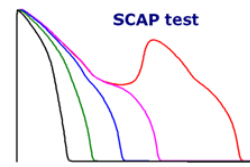
- Conductance of the channel (g_j) modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) determined from the tested $EFTPC_{max}/IC_{50s}$ ratio.

$$I_j = g_j O (V - E_{ion})$$

g_j = maximal conductance of channel 'j'
 O = open probability of channel 'j'
 V = voltage membrane
 E_{ion} = reversal potential for species of ions which flows through channel 'j'

$$g_j = g_{control,j} \left[1 + \left(\frac{D}{[IC50]_j} \right)^n \right]^{-1}$$

g_j = maximal conductance of channel 'j'
 $g_{control,j}$ = drug-free maximal conductance of channel 'j'
 $IC50$ = 50% of inhibition of a drug for channel 'j'
 D = drug concentration (EFTPC for example)
 n = hill slope



TDR estimation methodology

- Calculation of action potential duration (APD_{95}) from epi- and midmyocardial myocytes at CL of 1000 msec
- $TDR = APD_{95mid} - APD_{95epi}$

RUD estimation methodology

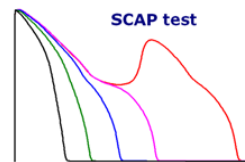
- Calculation of action potential duration prolongation (APD_{90P}) induced by a compound (vs. absence of compound) on the midmyocardial myocytes at CL of 1000 and 4000 msec
- $RUD = APD_{90P_{4000}} - APD_{90P_{1000}}$ where

$$APD_{90P_x} = APD_{90} \text{ with } - APD_{90} \text{ without compound at CL } x$$

Calculation of the Ion Channel inhibition index

- IC index = $(AF_{K_r} / ((AF_{NaL} + AF_{CaL}) / 2)) * 100$ where

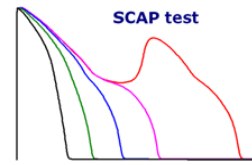
AF_{K_r} , AF_{NaL} and AF_{CaL} = active fraction (%) of I_{K_r} , I_{NaL} and I_{CaL} currents in the presence of compound calculated from each EFTPC_{max}/IC_{50s} ratio tested.



Classification of compounds regarding their torsade de pointes (TdP) risk

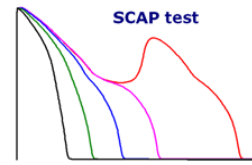
- **Redfern** TdP risk classification : (Cardiovasc Res 2003, 58 : 32-45)
 - Class 1 (class IA or III anti-arrhythmics with large but acceptable TdP risk)
 - Class 2 (compounds withdrawn from the market due to unacceptable TdP risk)
 - Class 3 (compounds with numerous TdP reports)
 - Class 4 (compounds with isolated TdP reports)
 - Class 5 (compounds without any published TdP reports).
- **CredibleMeds** TdP risk classification : (www.crediblemeds.org)
 - Class 1 (compounds with risk of TdP)
 - Class 2 (compounds with possible risk of TdP)
 - Class 3 (compounds with conditional risk of TdP)
 - Class 4 (compounds reviewed but not classified in class 1, 2 or 3)
- **Kramer** TdP risk classification: (Sci Rep 2013, 3 : 2100)
 - Class 1 (torsadogenic compounds)
 - Class 2 (non-torsadogenic compounds)
- **CiPA** TdP risk classification: (www.ilsixtra.org/hesi/science/cardiac/cipa/Project)
 - Class 1 (compounds with high risk)
 - Class 2 (compounds with intermediate risk)
 - Class 3 (compounds with low risk)
- **Wiśniowska and Polak** TdP risk classification: (Drug discovery today 2017, 22 : 10-16)
 - xx /xx (number of studies with TdP+ or TdP- reports)

Safe Cardiac Action Potential Test



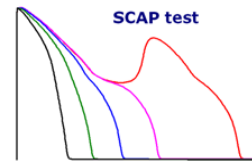
Drug	<h2 style="color: red;">Alosetron</h2> <p>Serotonin 5-HT₃ receptor antagonist used to treat diarrhea-predominant irritable bowel syndrome no longer marketed in USA (Onakpoya et al (2016) BMC Med. 14: 10)</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{To}: ---- μM (---) I_{Kr}: 3.2 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.00467 μM</p> <p>Kock KM et al (2004) Aliment Pharmacol Ther 20: 223-230</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: not classified with TdP risk (class 4) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: not reported</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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]_o: 140 - [Ca²⁺]_o: 1.8 - [K⁺]_o: 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{max}: g_{max} * (EFTPC_{max} / (EFTPC_{max} + IC₅₀))ⁿ / g_{max}: g_{max} * (IC₅₀ / (IC₅₀ + EFTPC_{max}))ⁿ / n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀ mid - APD₆₀ epi (at CL of 1000 msec) RUD = APD₉₀ epi - APD₉₀ epi <p>where APD₉₀ epi = APD₉₀ with - APD₉₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL/2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Alosetron x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<ol style="list-style-type: none"> 1. Ekins et al. (2002) J Pharmacol. Toxicol. Methods 30(1): 427-434 2. Redfern WS et al. (2003) Cardiovasc. Res. 59: 32-45 3. Kramer J et al. (2013) Sci. rep. 3: 2100 4. Woolley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.elsevier.org/elsevierdata/cardiac/cipa/Project 6. Wiñówska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061.8 8. Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 96: 15-26 		
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₆₀₋₉₀: AP duration at 60 or 90% of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{Na}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD60}: APD₆₀-APD₉₀ or APD₆₀ (~triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>		

Safe Cardiac Action Potential Test



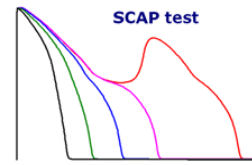
Drug	<h2 style="color: red;">Aprindine</h2> <p>Potassium voltage-gated cardiac channel (K_v11.1) and Na⁺/Ca²⁺ exchange blocker used as Class Ib antiarrhythmic to treat arrhythmias</p>			
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 0.23 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.239 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: numerous TdP reports (class 3) Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: not reported CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 2/0 (TdP+/TdP-)</p>	
<p>In silico cardiac action potential study (ORD model) ⁽⁷⁾</p>				
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flow through channel</small></p> $g_j = g_{jmax} \left(1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right)^{-1}$ <p><small>g_{jmax}: drug free maximal conductance of channel IC_{50j}: 50% of inhibition of a drug for channel n: drug concentration (EFTPC) for example n Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀1000 - APD₅₀1000 where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL+AFCaL)/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Cr}, I_{NaL} and I_{CaL}</p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>			
	<p>Summary</p>			
References	<ol style="list-style-type: none"> Pearlstein RA et al. (2016) <i>Curr. Top. Med. Chem.</i> 16: 1792-1838 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woolley RL (2015) www.CredibleMeds.org CPA (2016) www.ilisextra.org/hesi/science/cardiac/cipa/Project Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{40, 50, 90} : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{CaT}+I_{Kr}+I_{Ks}+I_{K1}+I_{CaL}, RMP : resting membrane potential, RUD : reverse use dependence, T_{40, 50, 90} : APD₅₀-APD₉₀ or APD₅₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{50%} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

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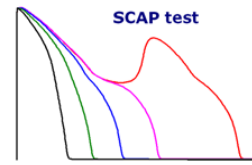
Drug	<h2 style="color: red;">Asenapine</h2> <p>5-HT_{2a} and D₂ receptor antagonist used as antipsychotic to treat bipolar I disorder and schizophrenia</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 0.3 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.000699 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: possible risk of TdP (Class 2) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 0/1 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORD model) ⁽⁷⁾			
<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 drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{max,j}: maximal conductance of channel / IC₅₀: 50% of inhibition of a drug for channel / C: drug concentration (EFTPC for example) / n: Hill slope</small></p> $g_j = g_{max,j} \left[1 + \left(\frac{C}{IC_{50}} \right)^n \right]^{-1}$ <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ 1000 - APD₅₀ 1000 where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFK_r / ((AFN_L + AFCA_L) / 2)) * 100 where AFK_r, AFN_L and AFCA_L = active fraction (%) of the I_{Ca}, I_{NaL} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Asenapine x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<ol style="list-style-type: none"> 1. www.tox-portal.com and www.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilseextra.org/hesi/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
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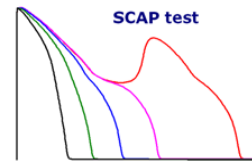
Drug	Atomoxetine Noradrenaline reuptake inhibitor used to treat attention deficit and hyperactivity disorder			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 6.26 μM (0.6) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.0178 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : Possible risk of TdP (Class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/1 (TdP+/TdP-)	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
	Simulation conditions: • 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	Effect of drugs on AP⁽⁸⁾: • channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC _{max} and IC _{50s} $f_j = g_j O(V - E_{ion})$ $g_j = \beta_{channel,j} \left[1 + \left(\frac{EFTPC_{max,j}}{IC_{50,j}} \right)^n \right]^{-1}$ <small> g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel β_{channel,j}: scaling factor for channel IC_{50,j}: 50% of inhibition of drug for channel n: drug cooperativity (EFTPC for example) nHill slope </small>	TDR and RUD estimation: • TDR = APD ₅₀ mid - APD ₅₀ epi (at CL of 1000 msec) • RUD = APD ₅₀ endo - APD ₅₀ epi where APD ₅₀ P _i = APD ₅₀ with - APD ₅₀ without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFK _r ((AFN _L L - AFC _L L)/2)) * 100 where AFK _r , AFN _L L and AFC _L L = active fraction (%) of the I _{CaL} , I _{NaL} and I _{CaT}	
Results	Human epicardial myocytes 	Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes 	Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 		
	Human endocardial myocytes 			
	Summary			
References	<ol style="list-style-type: none"> 1. www.tps-portal.com and www.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Wonsley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilisixtra.org/hesi/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	AP : action potential, APA : AP amplitude, APD _{50, 90, 99, 99.99} : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mv : millivolt, qNet : integration sum of I _{CaL} , I _{CaT} , I _{NaL} , I _{Na} , I _{Kr} , I _{Ks} , I _{K1} , I _h , I _{to} , I _{to2} , RMP : resting membrane potential, RUD : reverse use dependence, T _{AP, 50} : APD ₅₀ -APD ₉₀ or APD ₅₀ -APD ₉₉ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second			

Safe Cardiac Action Potential Test



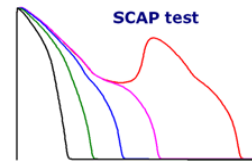
Drug	<h2 style="color: red;">Bedaquiline</h2> <p>Mycobacterial ATP synthase inhibitor used to treat pulmonary multiresistant tuberculosis</p>			
Raw data	<p>IC₅₀s (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{Kr}: 0.368 μM (0.7) I_{Na}: ---- μM (---) I_{Ks}: ---- μM (---)</p> <p>I_{to}: ---- μM (---) I_{Nal}: ---- μM (---) I_{K1}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.00990 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: possible risk of TdP (Class 2) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 0/1 (TdP+/TdP-)</p>	
In silico cardiac action potential study (ORd model) ⁽⁷⁾				
	<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 - [Ca²⁺]_o: 1.8 - [K⁺]_o: 5.4 Cycle length : 1000 msec Beat number: 100 	<p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{max}: drug free maximal conductance of channel / IC₅₀: 50% of inhibition of a drug for channel / O: drug concentration (EFTPC for example) in nM / E_{ion}</small></p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ EFTPC_{max} APD₅₀ 1000 where APD₅₀ EFTPC_{max} = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFK_r/(AFN_L+AFCa_L)/2)*100 where AFK_r, AFN_L and AFCa_L = active fraction (%) of the I_{Kr}, I_{CaL} and I_{CaT}</p>	
Results	<p>Human epicardial myocytes</p>	<p>Transmural dispersion of repolarisation</p>		
	<p>Human midmyocardial myocytes</p>	<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 		
	<p>Human endocardial myocytes</p>			
	<p>Summary</p>			
References	<ol style="list-style-type: none"> www.toxportal.com and www.drugbank.com Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 Kramer J et al. (2013) Sci. rep. 3: 2100 Woolley RL (2015) www.CredibleMeds.org CPA (2016) www.scaptest.com/has/hascardiac/cipa/Project Wisniewska B et al. (2017) Drug discovery today 22: 10-15 O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061,8 Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 Christophe B et al. (2019) J Pharmacol Toxicol Methods 96: 15-26 			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀₋₉₀ : AP duration at 50, 60 or 90 % of APA, APD₅₀ : APD prolongation, au. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaV1L}+I_{CaV1T}+I_{CaV2L}+I_{CaV2T}, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD50} : APD₅₀ of APD₅₀ (*triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

Safe Cardiac Action Potential Test



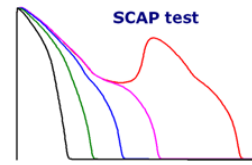
Drug	Bosutinib Tyrosine kinase inhibitor used to treat chronic myelogenous leukemia		
Raw data	IC_{50s} (slope) ⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 0.3 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max} ⁽¹⁾ 0.0226 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible risk of TdP (Class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/1 (TdP+/TdP-)
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<div style="display: flex; justify-content: space-between;"> <div data-bbox="320 584 683 750"> <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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 </div> <div data-bbox="683 584 1029 750"> <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = \frac{g_{max,j}}{1 + \left(\frac{EFTPC_{max}}{IC_{50,j}}\right)^n}$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel g_{max,j}: maximal conductance of channel IC_{50,j}: 50% of inhibition of drug for channel n: drug concentration (EFTPC for example) nHill slope</small></p> </div> <div data-bbox="1029 584 1423 750"> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ epi - APD₅₀ endo <p>where APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ca}, I_{Na} and I_{CaL}</p> </div> </div>			
Human epicardial myocytes 		Transmural dispersion of repolarisation 	
Human midmyocardial myocytes 		<p style="text-align: center;">Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
Human endocardial myocytes 			
Summary			
References	<ol style="list-style-type: none"> 1. www.toxportal.com and www.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilisextra.org/hesi/science/cardiaccipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	AP : action potential, APA : AP amplitude, APD ₅₀ to APD ₉₅ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{Ca} +I _{Na} +I _{NaL} +I _{K1} +I _{K2} , RMP : resting membrane potential, RUD : reverse use dependence, T _{APD,50} : APD ₅₀ -APD ₉₀ or APD ₅₀ -APD ₉₅ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second		

Safe Cardiac Action Potential Test



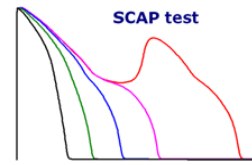
Drug	Bupivacaine Voltage-gated Na ⁺ (Na _v 1.5) channel blocker used as local anesthetic in a wide variety of superficial and invasive procedures		
Raw data	IC_{50s} (slope)⁽¹⁾ <i>I</i> _{CaL} : 35.481 μM (1.0) <i>I</i> _{T0} : ---- μM (---) <i>I</i> _{Kr} : 10.715 μM (1.0) <i>I</i> _{NaL} : 4.467 μM (1.0) <i>I</i> _{Na} : 3.090 μM (1.0) <i>I</i> _{K1} : ---- μM (---) <i>I</i> _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.260 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : not reported
In silico cardiac action potential study (ORd model)⁽⁷⁾			
	Simulation conditions: • 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	Effect of drugs on AP⁽⁸⁾: • channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC _{max} and IC _{50s} $I_j = g_j O(V - E_{ion})$ $g_j = g_{j,control} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50s}} \right)^n \right]^{-1}$ <small> ^{g_j}: maximal conductance of channel⁽⁹⁾ ^O: open probability of channel⁽⁹⁾ ^{E_{ion}}: voltage membrane ^{E_{rev}}: reversal potential for species of ions which flows through channel⁽⁹⁾ ^{g_{j,control}}: maximal conductance of channel⁽⁹⁾ ^{IC_{50s}}: 50% inhibitory concentration of channel⁽⁹⁾ ⁿ: drug concentration (EFTPC for example) ^{nH}: Hill slope </small>	TDR and RUD estimation: • TDR = APD ₆₀ mid - APD ₆₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ 1000/APD ₆₀ 1000 where APD ₆₀ P _i = APD ₆₀ with - APD ₆₀ without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr((AFNaL+AFCaL)/2)) ¹⁰⁰ where AFKr, AFNaL and AFCaL = active fraction (%) of the I _{CaL} , I _{NaL} and I _{CaL}
Results	Human epicardial myocytes 	Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 	Reverse use dependence on midmyocardial myocytes 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
	Human endocardial myocytes 		
	Summary		
References	1. Watt ED et al. (2022) <i>J Pharmacol. Tox. Methods</i> 118 : 107213 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58 : 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 4. Woolley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.bioextra.org/bes/science/cardiac/cipa/Project 6. Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7 : e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol. Toxicol. Methods</i> 96 : 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, APD ₆₀ 90 : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{Kr} +I _{Ks} +I _{NaL} +I _{CaT} , RMP : resting membrane potential, RUD : reverse use dependence, T ₆₀ 90 : APD ₉₀ -APD ₆₀ or APD ₉₀ (*triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second		

Safe Cardiac Action Potential Test



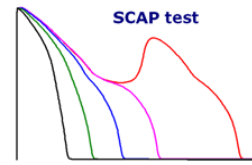
Drug	<h2 style="color: red;">Carbamazepine</h2> <p>Mechanism of action not fully elucidated, used as anticonvulsant to treat various types of seizures and pain resulting from trigeminal neuralgia</p>		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 371.5 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: ---- μM (---) I_{NaL}: 93.2 μM (1.0) I_{Na}: 398.1 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>9.481 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: not classified with TdP risk (class 4) CiPA⁽⁵⁾: not reported WP⁽⁶⁾: not reported</p>
In silico cardiac action potential study (ORD model)⁽⁷⁾			
<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]_o, 1.8 - [K]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j \cdot 0 \cdot (V - E_{ion})$ $g_j = \beta_{channel,j} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50,j}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ β_{channel,j}: Cooper probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{max,j}: maximal conductance of channel⁽⁹⁾ IC_{50,j}: drug free maximal conductance of channel⁽⁹⁾ n: slope (50% of inhibition of a drug for channel) C: drug concentration (EFTPC for example) n Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀APD₆₀ / APD₆₀ (at CL of 1000 msec) <p>where APD₆₀P_i = APD₆₀ with - APD₆₀ without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr((AFNLaL-AFCaL)/2))¹⁰⁰</p> <p>where AFKr, AFNLaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>			
Results	Human epicardial myocytes		Transmural dispersion of repolarisation
	Human midmyocardial myocytes		Reverse use dependence on midmyocardial myocytes
Summary			
	<p>References</p> <ol style="list-style-type: none"> Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118: 107213 Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58: 32-45 Kramer J et al. (2013) <i>Sci rep</i> 3: 2100 Woolley RL (2015) www.CredibleMeds.org CPA (2016) www.bioextra.org/bes/science/cardiac/cipa/Project Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput Biol</i> 7: e1002061 Mirams GR et al. (2011) <i>Cardiovasc Res</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
<p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, APD₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, au. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{CaT}, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD60} : APD₆₀-APD₉₀ or APD₆₀ (triangulation), T_{APD90} : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

Safe Cardiac Action Potential Test



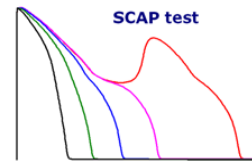
Drug	<h2 style="color: red;">Carvedilol</h2> <p>Non-selective β-adrenergic antagonist used to treat mild to severe heart failure, hypertension or left ventricular dysfunction following myocardial infarction in clinically stable patients</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 0.51 μM (0.8) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.005117 μM</p> <p>Gehr TW et al. (1999) <i>Eur. J. Clin. Pharmacol.</i> 55: 269-277</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: not classified with TdP risk (class 4) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: not reported</p>
<p>In silico cardiac action potential study (ORd model) ⁽⁷⁾</p>			
<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 - [Ca²⁺]_o 1.8 - [K⁺]_o 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{max}: 50% of maximal conductance of channel / O₅₀: 50% of inhibition of a drug for channel / Drug concentration (EFTPC for example) / n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ EFTPC_{max} - APD₅₀ P₁₀₀₀ where APD₅₀ P₁₀₀₀ = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL+AFCaL)/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}</p>			
<p>Results</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1- CL 1000 msec without compound 2- CL 4000 msec without compound 3- CL 1000 msec with compound 4- CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Carvedilol x-fold EFTPC_{max} vs. IC_{50s}</p> <p>APD₅₀ (msec) vs IC index (a.u.)</p>		
References	<ol style="list-style-type: none"> 1. Kawakami K et al. (2006) <i>Br. J. Pharmacol.</i> 147: 642-665 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.alscpa.org/has/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e10020618 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀₋₉₅ : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mv : millivolt, qNet : integration sum of I_{CaL}+I_{Kr}+I_{NaL}+I_{Na}+I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD50} : APD₅₀ of APD₅₀ or APD₉₀ ("triangulation"), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



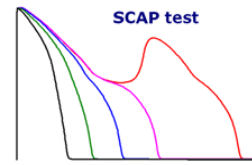
Drug	<h2 style="color: red;">Ceritinib</h2> <p>Anaplastic lymphoma kinase (ALK) inhibitor used to treat ALK positive metastatic non-small cell lung cancer (NSCLC)</p>			
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 0.4 μM (1.0) I_{hNaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.058 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: Possible risk of TdP (class 2) CiPA ⁽⁵⁾: not reported Wp ⁽⁶⁾: 0/1 (TdP+ / TdP-)</p>	
In silico cardiac action potential study (ORd model) ⁽⁷⁾				
<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 - [Ca²⁺]_o: 1.8 - [K⁺]_o: 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = \frac{g_{max,j}}{1 + \left(\frac{EFTPC_{max}}{IC_{50,j}}\right)^n}$ <p><small>g_j: maximal conductance of channel / g_{open}: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{max,j}: maximal conductance of channel / IC_{50,j}: 50% of inhibition of a drug for channel / n: drug concentration (EFTPC for example) / nHill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>				
Results	Human epicardial myocytes		Transmural dispersion of repolarization	
	Human midmyocardial myocytes			
	Human endocardial myocytes			
Summary				
References	<p>1. www.tandfonline.com and Wu Y-L (2020) Lung Cancer 150: 240-246 2. Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 3. Kramer J et al. (2013) Sci. rep. 3: 2100 4. Wooley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.isixtra.org/has/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061.8 8. Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 95: 15-26</p>			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₄₀₋₉₀: AP duration at 40, 60 or 90 % of APA, APD₂: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{Kr}+I_{hNaL}+I_{NaL}+I_{K1}, RMP: resting membrane potential, RUD: reverse use dependence, T_{90,60}: APD₉₀-APD₆₀ or APD₆₀-APD₉₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{max}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

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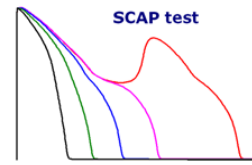
Drug	<h2 style="color: red;">Clomipramine</h2> <p>5-HT reuptake inhibitor used as antidepressant to treat obsessive-compulsive disorders</p>		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 15.3 μM (1.0) I_{to}: ---- μM (---)</p> <p>I_{Kr}: 0.13 μM (0.43) I_{NAL}: ---- μM (---)</p> <p>I_{Na}: 2.6 μM (1.0) I_{K1}: ---- μM (---)</p> <p>I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.00584 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported</p> <p>Kramer⁽³⁾: not reported</p> <p>CredibleMeds⁽⁴⁾: conditional risk of TdP (class 3)</p> <p>CIPA⁽⁵⁾: not reported</p> <p>WP⁽⁶⁾: 2/1 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORD model)⁽⁷⁾			
<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 - [Ca²⁺]_o 1.8 - [K⁺]_o 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j \cdot O(V - E_{ion})$ $g_j = \frac{g_{max,j}}{1 + \left(\frac{EFTPC_{max}}{IC_{50,j}}\right)^n}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{max,j}: maximal conductance of channel⁽⁹⁾ IC_{50,j}: 50% of inhibition of drug for channel⁽⁹⁾ n: drug concentration (EFTPC for example) n Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀mid - APD₉₀epi <p>where APD₆₀P_i = APD₆₀ with - APD₆₀ without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFK_r((AFN_L - AFCA_L)/2)) * 100</p> <p>where AFK_r, AFN_L and AFCA_L = active fraction (%) of the I_{CaL}, I_{Kr} and I_{CaT}</p>			
Results	<p>Human epicardial myocytes</p>	<p>Transmural dispersion of repolarisation</p>	
	<p>Human midmyocardial myocytes</p>	<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>		
	Summary	<p>Clomipramine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>EAD at CL of 4000 msec</p>	
References	<ol style="list-style-type: none"> 1. www.txc.scintal.com and www.gsdnighbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Wosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.heart.org/heartdisease/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 92: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, au. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{CaT}+I_{Kr}+I_{Ks}+I_{K1}+I_{K2}, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD90} : APD₉₀ or APD₉₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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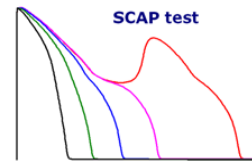
Drug	<h2 style="color: red;">Crizotinib</h2> <p>Tyrosine kinase inhibitor used to treat metastatic non-small cell lung cancer</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 8.9 μM (1.0) I_{hNaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.01991 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: possible risk of TdP (Class 2) where CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 0/1 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion})$ $g_j = g_{jmax} \left(1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right)^{-1}$ <p><small>g_{jmax}: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel g_{jmax}: maximal conductance of channel IC_{50j}: 50% of inhibition of drug for channel n: drug concentration (EFTPC for example) nHill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFK_r / (AFN_{aL} + AFCaL / 2)) * 100 where AFK_r, AFN_{aL} and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>			
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound
	<p>Human endocardial myocytes</p>		
Summary			
References	<ol style="list-style-type: none"> www.tov-portal.com and www.go.drugbank.com Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 Kramer J et al. (2013) Sci. rep. 3: 2100 Woosley RL (2015) www.CredibleMeds.org CiPA (2016) www.ilseixtra.org/hesi/science/cardiac/cipa/Project Wisniewska B et al. (2017) Drug discovery today 22: 10-16 O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061,8 Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 Christophe B et al. (2019) J Pharmacol Toxicol Methods 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{40,50,90} : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{CaT}, I_{hNaL}, I_{hNaL}, I_{hCaL}, I_{hCaL}, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD,90} : APD₉₀-APD₅₀ or APD₉₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_{max} : maximal rate of AP rise, V_{max} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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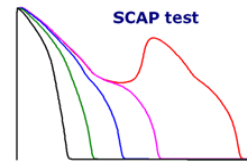
Drug	Dasabuvir Direct-acting antiviral agent used to treat specific hepatitis C virus infections in combination with other antiviral agents		
Raw data	IC_{50s} (slope) ⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 3.2 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max} ⁽¹⁾ 0.001 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : not reported
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel / g_{open}: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / O: 1 - (EFTPC_{max} / (EFTPC_{max} + IC_{50s}))^{nHill} / nHill: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p>IC index calculation ⁽⁹⁾:</p> $IC\ index = (AFK_r / ((AFN_{aL} + AFCaL) / 2)) * 100$ <p><small>where AFK_r, AFN_{aL} and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</small></p>			
Human epicardial myocytes 		Transmural dispersion of repolarization 	
Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
Human endocardial myocytes 			
Summary			
References	<ol style="list-style-type: none"> Kovacic ZM et al. (2023) <i>Pharmaceuticals</i> 16: 488 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woolley RL (2015) www.CredibleMeds.org CPA (2016) www.lilixtra.org/hesi/science/cardiac/cipa/Project Wiñówska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	AP: action potential, APA: AP amplitude, APD ₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APD ₉₀ : APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I _{CaL} +I _{Kr} +I _{Ks} +I _{NaL} +I _{Na} +I _{K1} , RMP: resting membrane potential, RUD: reverse use dependence, T ₄₀₋₆₀ : APD ₆₀ -APD ₄₀ or APD ₆₀ (~triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{min} : minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second		

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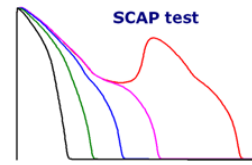
Drug	<h2 style="color: red;">Digoxin</h2> <p>Na-K ATPase inhibitor used to treat mild to moderate heart failure or to control ventricular response rate in chronic atrial fibrillation</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 0.054 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.00127 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: not classified with TdP risk (class 4) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 1/0 (TdP+/TdP-)</p>
<p>In silico cardiac action potential study (ORd model) ⁽⁷⁾</p>			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = \frac{g_{max,j}}{1 + \left(\frac{EFTPC_{max}}{IC_{50,j}}\right)^n}$ <p><small>g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{max,j}: maximal conductance of channel / IC_{50,j}: 50% of inhibition of drug for channel / n: drug concentration (EFTPC) for example / nHill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀endo - APD₅₀epi <p>where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL+AFCaL)/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <p>1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound</p>	
<p>Human endocardial myocytes</p>			
Summary	<p>Digoxin x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<p>1. www.tov-portal.com and www.go.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilsestra.org/hes/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{40, 50, 90} : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC₅₀ : ion channel inhibition index, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{Na}+I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{40, 50} : APD₅₀-APD₄₀ or APD₅₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



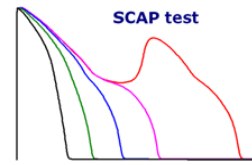
Drug	<h2 style="color: red;">Doxepin</h2> <p>Noradrenaline and serotonin reuptake inhibitor used to treat depression, anxiety, manic-depressive disorder and insomnia</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 2.14 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.013996 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: isolated TdP reports (class 4) Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: conditional risk of TdP (class 3) CIPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 4/1 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} \left(1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right)^{-1}$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel g_{j,max}: maximal conductance of channel IC_{50j}: 50% of inhibition of a drug for channel n: drug concentration (EFTPC for example) nHill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p>where APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{Kr} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Doxepin x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Reverse use dependence on midmyocardial myocytes</p>		
References	<ol style="list-style-type: none"> 1. www.tdxportal.com and Geister U et al (2001) <i>Arzneimittelforschung</i> 51: 189-196 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.lisextra.org/hes/science/cardiac/cipa/projet 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{40,50,90} : AP duration at 40, 50 or 90 % of APA, APD : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC₅₀ : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{Kr}, I_{Ks}, I_{NaL}, I_{Na}, I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{40,50} : APD₄₀-APD₅₀ or APD₅₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



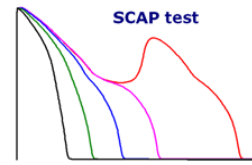
Drug	<h2 style="color: red;">Felodipine</h2> <p>Voltage-gated L-type Ca⁺⁺ channel (Ca_v1.2) blocker used to treat hypertension</p>		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 0.012 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 8.128 μM (1.0) I_{NaL}: 0.437 μM (1.0) I_{Na}: 8.511 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0003 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: not classified with TdP risk (class 4) CiPA⁽⁵⁾: not reported WP⁽⁶⁾: not reported</p>
In silico cardiac action potential study (ORd model)⁽⁷⁾			
<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_i]_o, 140 - [Ca⁺⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 		<p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{j,max}: maximal conductance of channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug for channel⁽⁹⁾ n: drug concentration (EFTPC for example) nH: Hill slope</small></p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀mid - APD₉₀epi <p>where APD₆₀ = APD₆₀with - APD₆₀without compound at CL x</p> <p>IC index calculation⁽⁹⁾: IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary			
References	<ol style="list-style-type: none"> Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118: 107213 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woosley RL (2015) www.CredibleMeds.org CPA (2016) www.lisextra.org/hes/science/cardiac/cipa/Project Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD_{40,60,90}: AP duration at 40, 60 or 90% of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{Na}+I_{K1}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD60}: APD₆₀-APD₉₀ or APD₆₀ (~triangulation), T_{APD90}: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>		

Safe Cardiac Action Potential Test



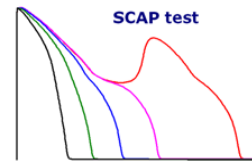
Drug	<h2 style="color: red;">Fenspiride</h2> <p>Histamine H₁ antagonist and phosphodiesterase (PDE_{3, 4 and 5}) inhibitor used to treat respiratory diseases no longer marketed in Europe (1)</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{Kr}: 15.14 μM (1.0) I_{Na}: ---- μM (---) I_{Ks}: ---- μM (---)</p> <p>I_{To}: ---- μM (---) I_{Nal}: ---- μM (---) I_{K1}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.7121 μM</p> <p>Montes B et al. (1993) Eur J Clin Pharmacol. 45: 169-172</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: not reported CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: not reported</p>
<h3>In silico cardiac action potential study (ORd model) ⁽⁷⁾</h3>			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel / (1 + (EFTPC_{max} / IC₅₀)ⁿ) O: open probability of channel / (1 + (EFTPC_{max} / IC₅₀)ⁿ) E_{ion}: reversal potential for species of ions which flows through channel / (1 + (EFTPC_{max} / IC₅₀)ⁿ) n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀APD₅₀ (at CL of 1000 msec) <p>where APD₆₀P_i = APD₆₀ with - APD₆₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>			
<h3>Results</h3>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Fenspiride x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<ol style="list-style-type: none"> Anonymous (2019) EMA/317731/2019 Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 Kramer J et al. (2013) Sci. Rep. 3: 2100 Woosley RL (2015) www.CredibleMeds.org CPA (2016) www.hiesteria.org/html/section/clinical/ciipa/Project Wisniewska B et al. (2017) Drug discovery today 22: 10-16 O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061.8 Mirami GR et al. (2011) Cardiovasc. Res. 91: 53-61 Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL} + I_{CaT} + I_{NaL} + I_{NaP}, RMP : resting membrane potential, RUD : reverse use dependence, T_{90,50} : APD₉₀/APD₅₀ or APD₉₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



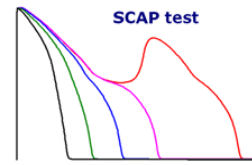
Drug	<h2 style="color: red;">Fluconazole</h2> <p>Lanosterol 14-α-demethylase enzyme inhibitor used to treat various fungal infections including candidiasis</p>			
Raw data	<p>IC₅₀s (slope)⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 48.2 μM (0.32) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>87.9222 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: known risk of TdP (Class 1) CIPA⁽⁵⁾: not reported WP⁽⁶⁾: 3/1 (TdP+/TdP-)</p>	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O(V - E_{ion})$ $g_j = g_{j,control} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel / g_{control}: drug free maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_j: maximal conductance of channel / g_{control}: drug free maximal conductance of channel / IC₅₀: 50% of inhibition of a drug for channel / EFTPC: concentration (EFTPC for example) / n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ epi - APD₅₀ 1000 <p><small>where: APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x</small></p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100 <small>where: AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaT}</small></p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>			
	<p>Summary</p>			
References	<ol style="list-style-type: none"> 1. www.tox-portal.com and www.go.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.ilisextra.org/hes/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061,8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD_{40/50/90}: AP duration at 40, 50 or 90% of APA, APD: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{CaT}+I_{NaL}+I_{Na}+I_{K1}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD50}: APD₅₀-APD₁₀₀ or APD₅₀ (~triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V₅₀: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

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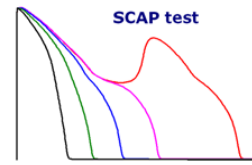
Drug	<h2 style="color: red;">Furosemide</h2> <p>Sodium-potassium-chloride (NKCC1 and NKCC2) cotransporter inhibitor used to treat hypertension and edema in congestive heart failure, liver cirrhosis, renal disease and hypertension</p>			
Raw data	<p>IC₅₀s (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 25.5 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.23927 μM</p> <p>Bragatto MS (2011) <i>J. Bioequiv. Availab.</i> 3: 191-197</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: isolated report of TdP (class 4) Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: conditional risk of TdP (class 3) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 1/2 (TdP+/TdP-)</p>	
In silico cardiac action potential study (ORd model) ⁽⁷⁾				
<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 drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾</small></p> $O_j = \frac{g_{max,j}}{g_{max,j} + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n}$ <p><small>n: Hill slope g_{max,j}: drug free maximal conductance of channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug on channel⁽⁹⁾ O: drug concentration (EFTPC for example) in Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ APD₅₀ / 1000 where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100</p> <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}</p>				
Results	Human epicardial myocytes		Transmural dispersion of repolarization	
	Human midmyocardial myocytes			
	Human endocardial myocytes		Reverse use dependence on midmyocardial myocytes	
		<p>1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound</p>		
Summary				
References	<p>1. Kauthale RR et al. (2015) <i>J. Appl. Toxicol.</i> 35: 799-805 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.lisextra.org/hasi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD_{40,60 or 90}: AP duration at 40, 60 or 90% of APA, APD_p: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mv: millivolt, qNet: integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{Na}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD}: APD₅₀-APD₉₀ or APD₅₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

Safe Cardiac Action Potential Test



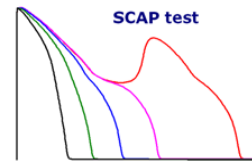
Drug	<h2 style="color: red;">Galantamine</h2> <p>Acetylcholinesterase inhibitor used to treat mild to moderate dementia of Alzheimer's type</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 760.0 μM (1.0) I_{Nal}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.0291 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: conditional risk of TdP (class 3) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 1/0 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel</small></p> $g_j = g_{jmax} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right]^{-1}$ <p><small>g_{jmax}: drug free maximal conductance of channel IC_{50j}: 50% of inhibition of drug for channel n: drug concentration (EFTPC) in example n Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p><small>where APD₉₀P_i = APD₉₀ with - APD₉₀ without compound at CL x</small></p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFK_r / ((AFN_L + AFCa_L) / 2)) * 100</p> <p><small>where AFK_r, AFN_L and AFCa_L = active fraction (%) of the I_{Ca}, I_{Na} and I_{CaL}</small></p>			
Results	Human epicardial myocytes		Transmural dispersion of repolarisation
	Human midmyocardial myocytes		Reverse use dependence on midmyocardial myocytes
Human endocardial myocytes			
Summary			
References	<p>1. Malone K et al. (2020) <i>Ther. Adv. Drug Saf.</i> 11: 2042098620942416 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.lisixtra.org/hes/science/cardiac/cipa/Project 6. Wisnioswska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061_8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J. Pharmacol. Toxicol. Methods</i> 96: 15-26</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{40,60,90} : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{CaT}, I_{Na}, I_{K1}, I_{K2}, I_{Kr}, I_{Ks}, I_{to}, I_h, I_h, I_h, I_h, I_h, I_h, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD,90} : APD₉₀-APD₁₀₀ or APD₉₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



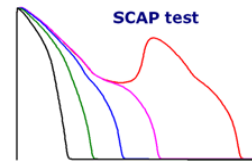
Drug	Granisetron 5-HT ₃ -receptor antagonist used to treat nausea and vomiting in cancer therapy and postoperatively			
Raw data	IC_{50s} (slope) ⁽¹⁾ <i>I</i> _{CaL} : 2.6 μM (1.0) <i>I</i> _{T0} : ---- μM (---) <i>I</i> _{Kr} : 3.73 μM (1.0) <i>I</i> _{NaL} : ---- μM (---) <i>I</i> _{Na} : ---- μM (---) <i>I</i> _{K1} : ---- μM (---) <i>I</i> _{Ks} : ---- μM (---)	EFTPC_{max} ⁽¹⁾ 0.00831 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible risk of TdP (Class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 1/1 (TdP+/TdP-)	
In silico cardiac action potential study (ORD model) ⁽⁷⁾				
Simulation conditions: <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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 Effect of drugs on AP ⁽⁸⁾: <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = \beta_{overex} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel / Open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{max}: maximal conductance of channel / IC_{50j}: 50% of inhibition of a drug for channel / O: drug concentration (EFTPC for example) / n: Hill slope</small></p> TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ APD₅₀ / APD₅₀ epi <p>where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x</p> IC index calculation ⁽⁹⁾: $IC \text{ index} = (AFKr((AFNaL - AFCaL)/2)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ca}, I_{Na} and I_{CaL}</p>				
Results	Human epicardial myocytes 		Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
	Human endocardial myocytes 			
Summary				
References	<ol style="list-style-type: none"> 1. www.tov-portal.com and www.go.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilisextra.org/hesi/science/ctd/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{40, 50, 90} : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{Ca}+I_{Na}+I_{NaL}+I_{K1}+I_{K2}, RMP : resting membrane potential, RUD : reverse use dependence, T_{40, 50} : APD₄₀-APD₅₀ or APD₅₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

Safe Cardiac Action Potential Test



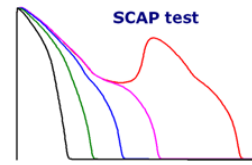
Drug	<h2 style="color: red;">Grepafloxacin</h2> <p>Fluoroquinolone antibiotic used to treat various gram positive and gram negative bacterial infections no longer marketed worldwide (Onakpoya et al (2016) BMC Med. 14: 10)</p>		
Raw data	<p>IC₅₀s (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 50.00 μM (1.13) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p style="text-align: center;">2.754 μM</p> <p>(Lusbasch et al (2000) Antimicrob Agents Chemother 44: 2600-2603)</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: unacceptable TdP risk (class 2) Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: known risk of TdP (class 1) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 6/0 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 		<p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O(V - E_{ion}) \left[1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ I_{CaL}: L-type transmembrane conductance of channel⁽⁹⁾ I_{CaT}: T-type transmembrane conductance of channel⁽⁹⁾ n: Hill slope</small></p>	
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
<p>Summary</p>			
References	<ol style="list-style-type: none"> 1. Kang J et al. (2001) Mol Pharmacol, 59: 122-126 2. Redfern WS et al. (2003) Cardiovasc. Res. 59: 32-45 3. Kramer J et al. (2013) Sci.rep. 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.hiastest.org/html/scientific/indicia/Project 6. Winiłowska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7: e10020618 8. Mirams GR et al. (2011) Cardiovasc. Res. 92L: 53-61 9. Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{CaT}+I_{Na}+I_{NaL}, RMP : resting membrane potential, RUD : reverse use dependence, T_{50,90} : APD₅₀/APD₉₀ or APD₅₀/*triangulation, TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



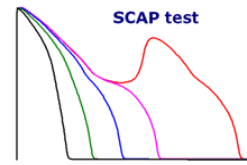
Drug	<h2 style="color: red;">Imatinib</h2> <p>Tyrosine kinase inhibitor used to treat various leukemias, myelodysplastic/myeloproliferative disease, systemic mastocytosis, hypereosinophilic syndrome, dermatofibrosarcoma protuberans and gastrointestinal stromal tumors</p>			
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 19.51 μM (0.9) I_{Nal}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.18458 μM</p> <p>De Alwis D et al. (2024) www.hesiglobal.org/crdtdatabase</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: Possible risk of TdP (class 2) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 0/2 (TdP+/TdP-)</p>	
<p>In silico cardiac action potential study (ORd model) ⁽⁷⁾</p>				
<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]_o: 140 - [Ca²⁺]_o: 1.8 - [K⁺]_o: 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾</small></p> $\theta_j = \theta_{control,j} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right]^{-1}$ <p><small>θ_j: normalized conductance of channel⁽⁹⁾ EFTPC_{max}: 50% of maximal conductance of channel⁽⁹⁾ IC_{50j}: 50% of inhibition of a drug for channel⁽⁹⁾ n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀endo - APD₅₀epi <p>where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100</p> <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}</p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <p>1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound</p>	
	<p>Human endocardial myocytes</p>			
	Summary	<p>x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<p>1. Dong Q et al. (2013) <i>Biol. Pharm. Bull.</i> 36: 268-275 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.lisixtra.org/hesi/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{50, 60 or 90} : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u.: arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mv : millivolt, qNet : integration sum of I_{CaL}, I_{CaT}, I_{Na}, I_{NaP}, I_{NaT}, I_{NaL}, RMP : resting membrane potential, RUD : reverse use dependence, T₅₀ : APD₅₀/APD₉₀ or APD₅₀/APD₉₀ ("triangulation"), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

Safe Cardiac Action Potential Test



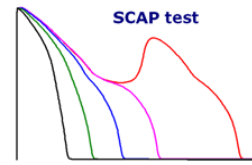
Drug	Irbesartan Angiotensin AT ₁ receptor antagonist used to treat hypertension, delay progression of diabetic nephropathy and congestive heart failure			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : 7.2 μM (1.0) I _{Kr} : 193.0 μM (0.7) I _{NAL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : 314.6 μM (1.1)	EFTPC_{max}⁽¹⁾ 0.7 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : not reported Wp ⁽⁶⁾ : not reported	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
Simulation conditions: <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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 Effect of drugs on AP⁽⁸⁾: <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = \beta_{channel,j} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50,j}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ β_{channel,j}: maximal conductance of channel⁽⁹⁾ IC_{50,j}: 50% of inhibition of a drug for channel⁽⁹⁾ n: drug concentration (EFTPC for example) nHill slope</small></p> TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀endo - APD₅₀epi <p>where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x</p> IC index calculation⁽⁹⁾: IC index = (AFKr _i (AFNAL _i - AFCL _i)/2)*100 where AFKr, AFNAL and AFCL = active fraction (%) of the I _{CaL} , I _{CaT} and I _{Ca}				
Results	Human epicardial myocytes 		Translational dispersion of repolarization 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
	Human endocardial myocytes 			
	Summary 			
References	<ol style="list-style-type: none"> Moreno J et al. (2003) <i>J Pharmacol. exp. Ther.</i> 304: 862-873 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woodley RL (2015) www.CredibleMeds.org CPA (2016) www.lisixtra.org/hes/science/cardiac/cipa/Project Wiñówska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 95: 15-26 			
Abbreviations	AP: action potential, APA: AP amplitude, APD ₅₀₋₉₅ : AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I _{CaL} +I _{CaT} +I _{Ca} +I _{Na} +I _{K1} , RMP: resting membrane potential, RUD: reverse use dependence, T ₅₀₋₉₀ : APD ₅₀ -APD ₉₀ or APD ₉₀ (triangulation), TdP: torsade de pointes, TDR: translational dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{max} : minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second			

Safe Cardiac Action Potential Test



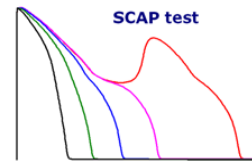
Drug	<h2 style="color: red;">Isradipine</h2> <p>Voltage-gated L-type Ca⁺⁺ channel (Ca_v1.2) blocker used to treat hypertension</p>			
Raw data	<p>IC₅₀s (slope)⁽¹⁾</p> <p>I_{CaL}: 0.002 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 20.417 μM (1.0) I_{NaL}: 7.762 μM (1.0) I_{Na}: 21.38 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0003 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: possible risk of TdP (Class 2) CiPA⁽⁵⁾: not reported WP⁽⁶⁾: 2/1 (TdP+/TdP-)</p>	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
<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⁺⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾</small></p> $g_j = g_{jmax} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_{jmax}: maximal conductance of channel⁽⁹⁾ EFTPC_{max}: 50% of maximal conductance of channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug for channel⁽⁹⁾ n: drug concentration (EFTPC for example) nH: slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀APD₆₀APD₃₀APD₁₀ where APD₉₀P_i = APD₉₀with - APD₉₀without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>			
	summary			
References	<p>1. Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118: 107213 2. Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci rep</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.lisextra.org/hes/science/cardiacc/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput Biol</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc Res</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD_{40,60,90}: AP duration at 40, 60 or 90% of APA, APD_P: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}, I_{CaT}, I_{CaP}, I_{CaB}, I_{CaS}, I_{CaX}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD}: APD₉₀-APD₆₀ or APD₆₀-APD₃₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

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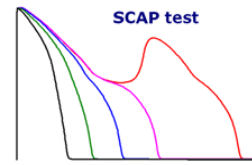
Drug	<h2 style="color: red;">Loperamide</h2> <p>mu-opioid receptor agonist used to treat non specific or chronic diarrhea caused by inflammatory bowel disease or gastroenteritis no longer marketed worldwide as syrup or drops (Onakpoya et al (2016) BMC Med 14: 10)</p>			
Raw data	<p>IC₅₀s (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{CaT}: ---- μM (---) I_{Kr}: 0.0541 μM (1.0) I_{NaL}: ---- μM (---) I_{NaI}: 0.239 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.0000650 μM</p> <p><small>Eur. J. Clin. Pharmacol 2006,62:463-472</small></p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: conditional risk of TdP (class 3) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 1/1 (TdP+/TdP-)</p>	
<p>In silico cardiac action potential study (ORd model) ⁽⁷⁾</p>				
<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 ion concentrations (mM): [Na]_o, 140 - [Ca]_o, 1.8 - [K]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $b_j = g_{\text{normal},j} \left[1 + \left(\frac{EFTPC}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel^j C_{open}: open probability of channel^j V_{rev}: voltage membrane E_{rev}: reversal potential for species of ions which flows through channel^j g_{max,j}: maximal conductance of channel^j g_{max,j} * (1 - 50% of inhibition of a drug for channel^j) IC₅₀: 50% of inhibition of a drug for channel^j Drug concentration (EFTPC for example) n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀endo - APD₅₀epi where APD₅₀ = APD₅₀with - APD₅₀without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}</p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>			
	Summary	<p>Loperamide x-fold EFTPC_{max} vs. IC₅₀</p>		
References	<ol style="list-style-type: none"> www.toxportal.com and www.godrugbank.com Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 Kramer J et al. (2013) Sci. rep. 3: 2100 Wosley RL (2015) www.CredibleMeds.org CPA (2016) www.bioextra.org/bes/science/Cardiac/CiPA/Project Wiśniewska B et al. (2017) Drug discovery today 22: 10-16 O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061,8 Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 96: 15-26 			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₅₀ 50% AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL} + I_{CaT} + I_{NaL} + I_{NaI} + I_{K1}, RMP: resting membrane potential, RUD: reverse use dependence, T_{50,60}: APD₅₀ - APD₆₀ or APD₅₀ - APD₆₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

Safe Cardiac Action Potential Test



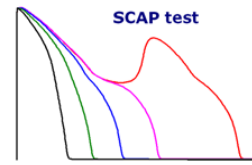
Drug	<h2 style="color: red;">Manidipine</h2> <p>Voltage-gated L-type Ca²⁺ channel (Ca_v1.2) blocker used to treat hypertension</p>			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 0.447 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 2.692 μM (1.0) I_{Nal}: 10.715 μM (1.0) I_{Na}: 8.511 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0001 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: not reported CiPA⁽⁵⁾: not reported WP⁽⁶⁾: not reported</p>	
<p>In silico cardiac action potential study (ORd model)⁽⁷⁾</p>				
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾</small></p> $\theta_j = \theta_{max,j} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50,j}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O_{max,j}: 50% of maximal conductance of channel⁽⁹⁾ IC_{50,j}: 50% of inhibition of a drug for channel⁽⁹⁾ n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀mid - APD₉₀epi <p>where APD₆₀ = APD₆₀ with - APD₆₀ without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL+AFCaL)/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>				
Results	<p>Human epicardial myocytes</p>			
				<p style="text-align: center;">Transmural dispersion of repolarisation</p>
	<p style="text-align: center;">Human midmyocardial myocytes</p>			
<p>Reverse use dependence on midmyocardial myocytes</p>				
			<ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
Summary	<p>Manidipine x-fold EFTPC_{max} vs. IC_{50s}</p>			
References	<ol style="list-style-type: none"> Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118: 107213 Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58: 32-45 Kramer J et al. (2013) <i>Sci rep</i> 3: 2100 Woolley RL (2015) www.CredibleMeds.org CiPA (2016) www.bioextra.org/bas/science/cardiac/cipa/Project Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput Biol</i> 7: e1002061,8 Mirams GR et al. (2011) <i>Cardiovasc Res</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₄₀₋₉₀: AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{CaT}+I_{CaB}+I_{CaX}+I_{CaY}, RMP: resting membrane potential, RUD: reverse use dependence, T_{CaL}: APD₉₀-APD₆₀ or APD₆₀ (*triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{50%}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

Safe Cardiac Action Potential Test



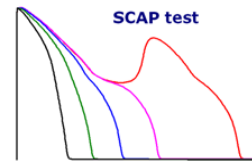
Drug	Maprotiline Noradrenaline reuptake inhibitor, α_1 - and α_2 -adrenoceptor antagonist used as antidepressant to treat depressive illness, major depressive and bipolar disorders or anxiety		
Raw data	IC_{50s} (slope) ⁽¹⁾ I_{CaL} : 4.266 μ M (1.0) I_{to} : ---- μ M (---) I_{Kr} : 2.455 μ M (1.0) I_{NaL} : 2.042 μ M (1.0) I_{Na} : 1.148 μ M (1.0) I_{K1} : ---- μ M (---) I_{Ks} : ---- μ M (---)	EFTPC_{max} ⁽¹⁾ 0.130 μ M	TdP risk Redfern ⁽²⁾ : numerous TdP reports (class 3) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible TdP risk (class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 4/0 (TdP+/TdP-)
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<div style="display: flex; justify-content: space-between;"> <div data-bbox="320 584 686 757"> <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 [Ca²⁺]_o: 1.8 [K⁺]_o: 5.4 Cycle length: 1000 msec Beat number: 100 </div> <div data-bbox="686 584 1029 757"> <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion})$ $O_j = \frac{O_{j,max}}{1 + \left(\frac{EFTPC_{max}}{IC_{50j}}\right)^n}$ <p><small>g_j: maximal conductance of channel / $O_{j,max}$: open probability of channel / E_{ion}: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / $O_{j,max}$: maximal conductance of channel / $O_{j,max}$: 50% of maximal conductance of channel / IC_{50}: 50% of inhibition of a drug for channel / n: drug cooperativity (EFTPC for example) / n: Hill slope</small></p> </div> <div data-bbox="1029 584 1423 757"> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀ mid - APD₆₀ epi (at CL of 1000 msec) RUD = APD₆₀ epi - APD₆₀ endo <p>where APD₆₀ = APD₆₀ with - APD₆₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾: IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the IC_{50s}, IC_{50L} and IC_{50C}</p> </div> </div>			
Human epicardial myocytes 		Transmural dispersion of repolarisation 	
Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
Human endocardial myocytes 			
Summary			
References	<ol style="list-style-type: none"> Watt ED et al. (2022) <i>J Pharmacol Toxicol Methods</i> 118: 107213 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woolsey RL (2015) www.CredibleMeds.org CPA (2016) www.ilsiextra.org/hesi/science/cardiacc/cipa/Project Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	AP: action potential, APA: AP amplitude, APD ₆₀ to APD ₉₀ : AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I _{CaL} + I _{Kr} + I _{Ks} + I _{NaL} + I _{Na} , RMP: resting membrane potential, RUD: reverse use dependence, T _{APD,60} : APD ₆₀ - APD ₆₀ or APD ₆₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{min} : minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second		

Safe Cardiac Action Potential Test



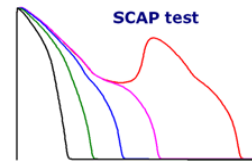
Drug	<h2 style="color: red;">Mepivacaine</h2> <p>Voltage-gated Na⁺ (Na_v1.5) channel blocker used for local or regional analgesia and anesthesia</p>		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 156.0 μM (0.89) I_{NaL}: ---- μM (---) I_{Na}: 81.4 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>12.7868 μM</p> <p>De Alwis D et al. (2024) www.hesjalab.org/crdatabase</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: not reported CiPA⁽⁵⁾: not reported Wp⁽⁶⁾: not reported</p>
<p>In silico cardiac action potential study (ORd model)⁽⁷⁾</p>			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: Cooper probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{max}: maximal conductance of channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug for channel⁽⁹⁾ C: drug concentration (EFTPC for example) n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ epi - APD₅₀ endo <p><small>where APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x</small></p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr / ((AFNaL + AFCL) / 2)) * 100</p> <p><small>where AFKr, AFNaL and AFCL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</small></p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary			
References	<ol style="list-style-type: none"> 1. www.tan-onal.com and www.gd-nghenik.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woodley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.tlsixtra.org/hesi/science/cardiac/cipa/Project 6. Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 95: 15-26 		
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₅₀ to APD₉₀: AP duration at 40, 60 or 90 % of APA, APD₅₀: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL} + I_{Na} + I_{NaL} + I_{CaT} + I_{CaB}, RMP: resting membrane potential, RUD: reverse use dependence, T₉₀: APD₅₀ - APD₉₀ or APD₅₀ - APD₉₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{max}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>		

Safe Cardiac Action Potential Test



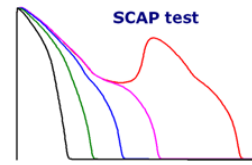
Drug	<h2 style="color: red;">Mesoridazine</h2> <p>Dopamine D₂ and serotonin 5-HT_{2A} receptor antagonist used as antipsychotic to treat schizophrenia, organic brain disorders, alcoholism and psychoneuroses no longer marketed in USA ⁽⁴⁾</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: 16.218 μM (1.0) I_{TO}: ---- μM (---) I_{Kr}: 0.347 μM (1.0) I_{NaL}: 4.467 μM (1.0) I_{Na}: 7.943 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>2.483 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: no published report of TdP (class 5) Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: known TdP risk (class 1) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 3/1 (TdP+/TdP-)</p>
<p>In silico cardiac action potential study (ORd model) ⁽⁷⁾</p>			
<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]_o: 140 - [Ca²⁺]_o: 1.8 - [K⁺]_o: 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾</small></p> $g_j = g_{jcontrol} \left[1 + \left(\frac{EFTPC}{IC_{50j}} \right)^n \right]^{-1}$ <p><small>g_{jcontrol}: maximal conductance of channel⁽⁹⁾ EFTPC: effective therapeutic plasma concentration of drug for channel⁽⁹⁾ IC_{50j}: 50% of inhibition of a drug for channel⁽⁹⁾ n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀endo - APD₅₀epi <p>where APD₅₀P_i = APD₅₀with - APD₅₀without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}</p>			
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound
	<p>Human endocardial myocytes</p>		
	<p>Summary</p>		
References	<ol style="list-style-type: none"> 1. Watt ED et al. (2022) <i>J Pharmacol. Toxicol. Methods</i> 118: 107213 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.bioextra.org/bioscience/Cardiac/CiPA/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol. Toxicol. Methods</i> 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀60-90 : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaT} + I_{CaL} + I_{NaT} + I_{NaL} + I_{NaP}, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP,50} : APD₅₀ or APD₅₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



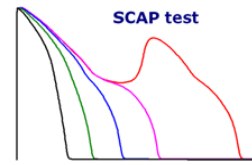
Drug	<h2 style="color: red;">Metoclopramide</h2> <p>Dopamine D₂ antagonist used as antiemetic to treat gastroesophageal reflux disease, to prevent nausea and vomiting or to stimulate gastric emptying</p>			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{T0}: ---- μM (---) I_{Kr}: 5.4 μM (0.95) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0957 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: conditional risk of TdP (class 3) CiPA⁽⁵⁾: not reported WP⁽⁶⁾: not reported</p>	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
	<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 	<p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾</small></p> $g_j = g_{jmax} / [1 + (EFTPC_{max} / IC_{50})^n]^{-1}$ <p><small>g_{jmax}: maximal conductance of channel⁽⁹⁾ EFTPC_{max}: 50% of inhibition of a drug for channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug for channel⁽⁹⁾ n: drug concentration (EFTPC for example) n: Hill slope</small></p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀APD₅₀ (at CL of 1000 msec) <p>where APD₆₀P_i = APD₆₀with - APD₆₀without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL+AFCaL)/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ca}, I_{NaL} and I_{CaL}</p>	
Results	<p>Human epicardial myocytes</p>	<p>Transmural dispersion of repolarization</p>		
	<p>Human midmyocardial myocytes</p>	<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 		
	<p>Human endocardial myocytes</p>			
	<p>Summary</p>			
References	<ol style="list-style-type: none"> www.toxportal.com and www.go.drugbank.com Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 Kramer J et al. (2013) Sci. rep. 3: 2100 Woolley RL (2015) www.CredibleMeds.org CiPA (2016) www.hi.strova.org/hi/strova/center/cipa/Project Wisniewska B et al. (2017) Drug discovery today 22: 10-16 O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061,8 Mirama GR et al. (2011) Cardiovasc. Res. 91: 53-61 Christophe B et al. (2019) J. Pharmacol. Toxicol. Methods 96: 15-26 			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₆₀ : AP duration at 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, I_{Ca} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{CaT}+I_{NaL}+I_{NaT}+I_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T₆₀ : APD₆₀APD₅₀ or APD₆₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

Safe Cardiac Action Potential Test



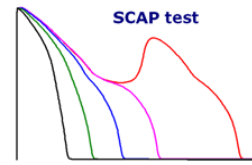
Drug		Mizolastine Histamine H ₁ receptor antagonist used to treat chronic allergic rhinitis and chronic idiopathic urticaria				
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 0.35 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)		EFTPC_{max}⁽¹⁾ 0.0087 μM		TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 2/1 (TdP+/TdP-)	
	In silico cardiac action potential study (ORd model)⁽⁷⁾					
Simulation conditions: • 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		Effect of drugs on AP⁽⁸⁾: • channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC _{max} and IC _{50s} $I_j = g_j O(V - E_{ion})$ $g_j = g_{j,control} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50s}} \right)^n \right]^{-1}$ where: g _j : maximal conductance of channel ⁽⁹⁾ O: open probability of channel ⁽⁹⁾ V: voltage membrane E _{ion} : reversal potential for species of ions which flows through channel ⁽⁹⁾ g _{j,control} : maximal conductance of channel ⁽⁹⁾ EFTPC _{max} : drug-dependent maximal conductance of channel ⁽⁹⁾ IC _{50s} : 50% of inhibition of a drug for channel ⁽⁹⁾ n: drug concentration (EFTPC for example) nH1: slope		TDR and RUD estimation: • TDR = APD ₆₀ mid - APD ₆₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ APD ₁₀₀ / APD ₉₀ APD ₁₀₀ where APD ₆₀ P _i = APD ₆₀ with - APD ₆₀ without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr)(AFNaL+AFCaL/2)*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I _{Ca} , I _{NaL} and I _{CaL}		
Results	Human epicardial myocytes 		Transmural dispersion of repolarization 			
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 			
	Human endocardial myocytes 					
	Summary 					
References	1. Pearlstein RA et al. (2016) <i>Curr. Top. Med. Chem.</i> 16 : 1792-1818 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 59 : 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100		4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2015) www.hiastest.org/html/science/credic/ciipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16		7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7 : e1002061.8 8. Miramis GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96 : 15-26	
Abbreviations	AP : action potential, APA : AP amplitude, APD ₆₀₋₉₀₋₁₀₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{CaT} +I _{NaL} +I _{NaT} , RMP : resting membrane potential, RUD : reverse use dependence, T ₆₀₋₉₀ : APD ₆₀ -APD ₉₀ or APD ₉₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second					

Safe Cardiac Action Potential Test



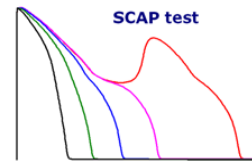
Drug	<h2 style="color: red;">Nifekalant</h2> <p>Potassium voltage-gated cardiac channel (K_v11.1) blocker under evaluation (clinical trial NCT03855826) as class III antiarrhythmic to treat cardiac arrhythmia</p>			
Raw data	<p>IC₅₀s (slope)⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{To}: ---- μM (---) I_{Kr}: 7.9 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.6517 μM*</p> <p><small>*Zhang M et al (2013) J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 938: 105-110</small></p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: known TdP risk (class 1) CiPA⁽⁵⁾: not reported WP⁽⁶⁾: not reported</p>	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug for channel⁽⁹⁾ Drug concentration (EFTPC for example) n: Hill slope</small></p> $\theta_j = \theta_{max,j} \left[1 + \left(\frac{D}{IC_{50}} \right)^n \right]^{-1}$ <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₆₀epi/APD₆₀epi <p>where APD₆₀epi = APD₆₀ with - APD₆₀ without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL/2)) * 100</p> <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>			
	Summary	<p>Nifekalant x-fold EFTPC_{max} vs. IC₅₀</p>		
References	<ol style="list-style-type: none"> Polak S et al. (2009) J. Appl. Toxicol. 29: 183-206 Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 Kramer J et al. (2013) Sci. rep. 3: 2100 Woolley RL (2015) www.CredibleMeds.org CiPA (2016) www.nature.com/scientificreports/CiPA/Project Wisniewska B et al. (2017) Drug discovery today 22: 10-16 O'Hara T et al. (2011) PLoS Comput. Biol. 7: e10020618 Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 96: 15-26 			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}+I_{Kr}+I_{NaL}+I_{Na}+I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₆₀ : APD₄₀-APD₆₀ or APD₆₀-APD₉₀ (*triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

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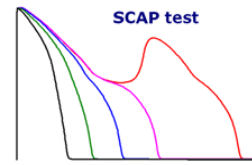
Drug	<h2 style="color: red;">Nilvadipine</h2> <p>Voltage-gated L-type Ca²⁺ channel (Ca_v1.2) blocker used to treat arterial hypertension</p>			
Raw data	<p>IC₅₀s (slope)⁽¹⁾</p> <p>I_{CaL}: 0.004 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 19.953 μM (1.0) I_{NaL}: 2.291 μM (1.0) I_{Na}: 0.955 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0005 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: not reported CiPA⁽⁵⁾: not reported WP⁽⁶⁾: not reported</p>	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
<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 - [Ca²⁺]_o 1.8 - [K⁺]_o 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel g_{max,j}: maximal conductance of channel IC_{50,j}: 50% of inhibition of a drug for channel C: drug concentration (EFTPC for example) n: Hill slope</small></p> $g_j = \frac{g_{max,j}}{1 + \left(\frac{C}{IC_{50,j}}\right)^n}$ <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₉₀mid - APD₉₀epi <p>where APD₅₀ = APD₅₀with - APD₅₀without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL+AFCaL)/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <p>1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound</p>	
	<p>Human endocardial myocytes</p>			
	<p>Summary</p>			
References	<p>1. Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118: 107213 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilisixtra.org/hesi/science/cardiac/cipa/Project 6. Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₄₀₋₉₀: AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{CaT}+I_{CaS}+I_{CaX}+I_{CaY}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD50}: APD₅₀-APD₉₀ or APD₅₀ (~triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V₅₀: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

Safe Cardiac Action Potential Test



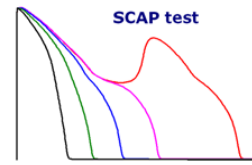
Drug	<h2 style="color: red;">Nortriptyline</h2> <p>Noradrenaline and serotonin reuptake inhibitor used as antidepressant to treat depression</p>			
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: 3.467 μM (1.0) I_{to}: ---- μM (---)</p> <p>I_{Kr}: 3.020 μM (1.0) I_{Nal}: 2.692 μM (1.0)</p> <p>I_{Na}: 0.871 μM (1.0) I_{K1}: ---- μM (---)</p> <p>I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.053 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported</p> <p>Kramer ⁽³⁾: not reported</p> <p>CredibleMeds ⁽⁴⁾: possible risk of TdP (class 2)</p> <p>CIPA ⁽⁵⁾: not reported</p> <p>WP ⁽⁶⁾: 2/1 (TdP+/TdP-)</p>	
In silico cardiac action potential study (ORd model) ⁽⁷⁾				
	<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 	<p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j \cdot O(V - E_{ion})$ $g_j = \beta_{channel} \cdot \left(1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right)^{-1}$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel β_{channel}: maximal conductance of channel IC₅₀: 50% of inhibition of a drug for channel n: drug concentration (EFTPC for example) nHill slope</small></p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p>where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFK_r((AFN_L-AFCL)/2))*100</p> <p>where AFK_r, AFN_L and AFCL = active fraction (%) of the I_{CaL}, I_{CaT} and I_{Ca}</p>	
Results	<p>Human epicardial myocytes</p>	<p>Transmural dispersion of repolarization</p>		
	<p>Human midmyocardial myocytes</p>	<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 		
	<p>Human endocardial myocytes</p>			
	<p>Summary</p>			
References	<ol style="list-style-type: none"> 1. Wath ED et al. (2022) <i>J Pharmacol. Toxicol. Methods</i> 118: 107213 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.lisixtra.org/hesi/science/cardiac/cipa/Project 6. Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol. Toxicol. Methods</i> 95: 15-26 			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₅₀ 60 or 90%: AP duration at 60 or 90% of APA, APD_P: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{CaT}+I_{Ca}+I_{Ca}+I_{Ca}, RMP: resting membrane potential, RUD: reverse use dependence, T_{AP,50}: APD₅₀-APD₉₀ or APD₅₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{max}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

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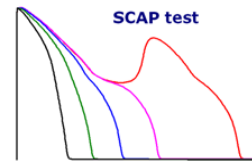
Drug	<h2 style="color: red;">Oseltamivir</h2> <p>Neuraminidase inhibitor used to treat influenza</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: 4263 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 231 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: 3545 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}[*]</p> <p>0.12067 μM</p> <p>[*] www.go.drugbank.com</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: not classified with TdP risk (class 4) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: not reported</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel</small></p> $g_j = g_{jmax} / [1 + (EFTPC_{max} / IC_{50})^n]^{-1}$ <p><small>g_{jmax}: maximal conductance of channel EFTPC_{max}: drug-dependent maximal conductance of channel IC₅₀: 50% of inhibition of a drug for channel n: drug concentration (EFTPC for example) nHil slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₉₀APD₁₀₀ / APD₆₀APD₁₀₀ where APD₉₀APD₁₀₀ = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Effect (%)</p> <p>APD₉₀ - APD₁₀₀ (msec)</p>		
References	<p>1. Kambayashi R et al. (2021) <i>Front. Pharmacol.</i> 12: 593021 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woolsey RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ciipa.org/has/science/cardiac/cipa/Project 6. Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061,8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>		
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₄₀₋₉₀: AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{CaT}, RMP: resting membrane potential, RUD: reverse use dependence, T₄₀₋₆₀: APD₉₀-APD₆₀ or APD₆₀ (*triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{50%}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>		

Safe Cardiac Action Potential Test



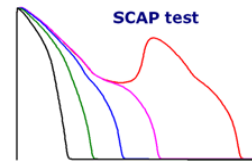
Drug	<h2 style="color: red;">Pitolisant</h2> <p>Histamine H₃ antagonist and inverse agonist used to treat narcolepsy in adult</p>		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 9.5 μM (1.0) I_{to}: 11.4 μM (1.0) I_{Kr}: 1.3 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: 26.4 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} *</p> <p>0.1604 μM</p> <p>*www.go.drugbank.com</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: possible risk of TdP (Class 2) CiPA⁽⁵⁾: not reported Wp⁽⁶⁾: not reported</p>
<h3>In silico cardiac action potential study (ORd model)⁽⁷⁾</h3>			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} / (1 + (EFTPC_{max} / IC_{50j})^n)$ <p><small>g_j: maximal conductance of channel / g_{j,max}: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_{j,max}: drug free maximal conductance of channel / IC_{50j}: 50% of inhibition of a drug for channel / n: drug concentration (EFTPC for example) / nHill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ epi - APD₅₀ endo <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100</p> <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ca}, I_{Na} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Pitolisant x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<ol style="list-style-type: none"> 1. Ligneau et al. (2017) <i>Br J Pharmacol</i>. 174: 4449-4463 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woolley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.ilisixtra.org/hesi/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₅₀₋₉₀: AP duration at 40, 60 or 90 % of APA, APD₉₀: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL} + I_{Kr} + I_{Ks} + I_{NaL} + I_{CaT}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD}: APD₅₀ - APD₉₀ or APD₅₀ - APD₉₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{max}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>		

Safe Cardiac Action Potential Test



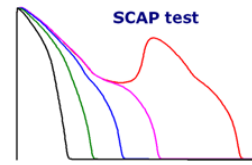
Drug	Procaine Voltage-gated Na ⁺ (Na _v 1.5) channel blocker used as local anaesthetic to manage anaesthesia, peripheral or spinal nerve block		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{Kr} : 23.442 μM (1.0) I _{Na} : 128.825 μM (1.0) I _{Ks} : ---- μM (---) I _{to} : ---- μM (---) I _{Nal} : 151.356 μM (1.0) I _{K1} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 9.945 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : not reported
In silico cardiac action potential study (ORd model)⁽⁷⁾			
	Simulation conditions: • 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	Effect of drugs on AP⁽⁸⁾: • channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC _{max} and IC _{50s} $f_j = g_j \cdot O(V - E_{ion})$ $g_j = \beta_{channel} \cdot \left(1 + \left(\frac{EFTPC_{max}}{IC_{50s}} \right)^n \right)^{-1}$ <small> g_j: maximal conductance of channel O: Cooper probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel β_{channel}: maximal conductance of channel IC_{50s}: 50% of inhibition of a drug for channel n: drug concentration (EFTPC for example) nHill slope </small>	TDR and RUD estimation: • TDR = APD ₅₀ mid - APD ₅₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ mid - APD ₉₀ epi where APD ₅₀ = APD ₅₀ with - APD ₅₀ without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr / (AFNaL + AFCL / 2)) * 100 where AFKr, AFNaL and AFCL = active fraction (%) of the I _{CaL} , I _{Kr} and I _{CaL}
Results	Human epicardial myocytes 	Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 	Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
	Human endocardial myocytes 		
	Summary		
References	<ol style="list-style-type: none"> 1. Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118: 107213 2. Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci rep</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilsestra.org/hesi/science/cardiac/cipa/Project 6. Wiñosińska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput Biol</i> 7: e1002061 8. Mirams GR et al. (2011) <i>Cardiovasc Res</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{40, 50, 90} : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{Kr} +I _{Ks} +I _{K1} +I _{K1L} , RMP : resting membrane potential, RUD : reverse use dependence, T _{40, 60} : APD ₄₀ -APD ₆₀ or APD ₆₀ -APD ₄₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{max} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second		

Safe Cardiac Action Potential Test



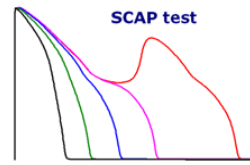
Drug	<h2 style="color: red;">Promethazine</h2> <p>H₁ receptor antagonist used to treat allergic conditions, nausea, vomiting and motion sickness</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 1.46 μM (1.07) I_{NAL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.00541 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: possible risk of TdP (Class 2) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 2/1 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORD model) ⁽⁷⁾			
<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 drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} / (1 + (EFTPC_{max} / IC_{50j})^n)$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel g_{j,max}: maximal conductance of channel IC_{50j}: 50% of inhibition of a drug for channel n: drug concentration (EFTPC) to example nHill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ mid - APD₅₀ epi <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ca}, I_{Na} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Promethazine x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<ol style="list-style-type: none"> 1. www.tox-portal.com and www.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilseixtra.org/hesi/science/cardiac/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{50, 90, 100} : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{CaT}, I_{Na}, I_{NaP}, I_{NaL}, I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP, 50} : APD₅₀-APD₅₀ or APD₅₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



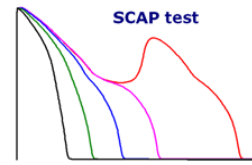
Drug	<h2 style="color: red;">Ribociclib</h2> <p>Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor used to treat HR+, HER2- advanced or metastatic breast cancer</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 8.511 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: 66.069 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.547 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: possible risk of TdP (class 2) CIPA ⁽⁵⁾: not reported WP ⁽⁶⁾: not reported</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 - [Ca²⁺]_o: 1.8 - [K⁺]_o: 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion}) \cdot \frac{1}{1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n}$ <p><small>g_j: maximal conductance of channel / Open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flow through channel / O: maximal conductance of channel / n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ epi - APD₅₀ endo (at CL of 1000 msec) <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL - AFCL)/2)) * 100 where AFKr, AFNaL and AFCL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>			
Summary	<p>Ribociclib x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<ol style="list-style-type: none"> Wah ED et al. (2022) <i>J Pharmacol Toxicol Methods</i> 118: 107213 Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58: 32-45 Kramer J et al. (2013) <i>Sci Rep</i> 3: 2100 Woolsey RL (2015) www.CredibleMeds.org CIPA (2016) www.lisixtra.org/hes/science/cardiac/cipa/Project Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput Biol</i> 7: e1002061.8 Mirams GR et al. (2011) <i>Cardiovasc Res</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 95: 15-26 		
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₅₀₋₉₅: AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{CaT}, RMP: resting membrane potential, RUD: reverse use dependence, T_{50,90}: APD₅₀-APD₉₀ or APD₉₀-APD₅₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>		

Safe Cardiac Action Potential Test



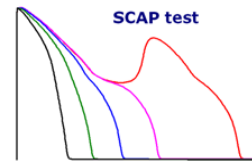
Drug	Ropivacaine Voltage-gated Na ⁺ (Na _v 1.5) channel blocker used for local or regional anesthesia during surgery and for short-term management of acute pain			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{CaT} : ---- μM (---) I _{Kr} : 15.488 μM (1.0) I _{NaL} : 10.000 μM (1.0) I _{Na} : 12.882 μM (1.0) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.612 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CiPA ⁽⁵⁾ : not reported Wp ⁽⁶⁾ : not reported	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
Simulation conditions: <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 - [Ca²⁺]_o 1.8 - [K⁺]_o 5.4 Cycle length : 1000 msec Beat number: 100 Effect of drugs on AP⁽⁸⁾: <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} / (1 + (EFTPC_{max} / IC_{50})^n)$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{j,max}: maximal conductance of channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug for channel⁽⁹⁾ n: drug concentration (EFTPC for example) nHill slope</small></p> TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p>where APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x</p> IC index calculation⁽⁹⁾: $IC\ index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ca}, I_{Na} and I_{CaL}</p>				
Results	Human epicardial myocytes 		Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
	Human endocardial myocytes 			
	Summary 			
References	<ol style="list-style-type: none"> Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118: 107213 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woosley RL (2015) www.CredibleMeds.org CPA (2016) www.ilseitra.org/hesi/science/cardiac/cipa/Project Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	AP : action potential, APA : AP amplitude, APD ₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APD ₅₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{CaT} +I _{NaL} +I _{Na} +I _{K1} , RMP : resting membrane potential, RUD : reverse use dependence, T _{AP,90} : APD ₉₀ -APD ₅₀ or APD ₅₀ -APD ₉₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V ₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second			

Safe Cardiac Action Potential Test



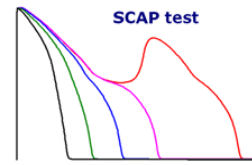
Drug	<h2 style="color: red;">Rilpivirine</h2> <p>Non-nucleoside reverse transcriptase inhibitor used to treat human immunodeficiency virus type 1 (HIV)</p>			
Raw data	<p>IC₅₀s (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{Kr}: 0.687 μM (1.0) I_{Na}: ---- μM (---) I_{Ks}: ---- μM (---)</p> <p>I_{to}: ---- μM (---) I_{Nal}: ---- μM (---) I_{K1}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.006741 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: possible risk of TdP (Class 2) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 0/1 (TdP+/TdP-)</p>	
<p>In silico cardiac action potential study (ORd model) ⁽⁷⁾</p>				
<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 - [Ca²⁺]_o 1.8 - [K⁺]_o 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel</small></p> $g_j = g_{j,control} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_{j,control}: maximal conductance of channel EFTPC_{max}: drug free maximal conductance of channel IC₅₀: 50% of inhibitor of a drug for channel n: drug collaboration (EFTPC for example) in ORd model</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ EFTPC_{max} APD₅₀ where APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL/2))*100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{CaL} and I_{CaT}</p>				
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>			
	<p>Summary</p>			
References	<ol style="list-style-type: none"> www.tox-portal.com and www.godnugbank.com Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci.rep.</i> 3: 2100 Woosley RL (2015) www.CredibleMeds.org CiPA (2016) www.ilisextra.org/hes/science/cardiac/cipa/Project Wanioswska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061,8 Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀ or 90 : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mv : millivolt, qNet : integration sum of I_{CaL}+I_{CaT}+I_{Kr}+I_{Ks}+I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD} : APD₅₀-APD₉₀ or APD₉₀ ("triangulation"), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{1/2} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>			

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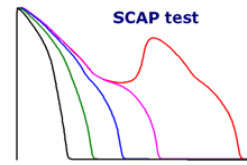


Drug	<h2 style="color: red;">Roxithromycin</h2> <p>Antibiotic used to treat various bacterial infections</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: --- μM (---) I_{to}: --- μM (---) I_{Kr}: 36.5 μM (1.16) I_{Nal}: --- μM (---) I_{Na}: --- μM (---) I_{K1}: --- μM (---) I_{Ks}: --- μM (---)</p>	<p>EFTPC_{max}</p> <p>1.314 μM</p> <p>Britzi et al. (2015) <i>Ther Drug Monit</i> 37: 512-515</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: known risk of TdP (class 1) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 2/0 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel / g_j: maximal conductance of channel / O: open probability of channel / V: voltage membrane / E_{ion}: reversal potential for species of ions which flows through channel /</small></p> $\theta_j = \theta_{max,j} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right]^{-1}$ <p><small>n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀mid - APD₆₀epi (at CL of 1000 msec) RUD = APD₆₀epi/APD₆₀epi <p>where APD₆₀ = APD₆₀ with - APD₆₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr / (AFNaL + AFCaL/2)) * 100</p> <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}</p>			
Results	<p>Human epicardial myocytes</p>	<p>Transmural dispersion of repolarization</p>	
	<p>Human midmyocardial myocytes</p>	<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
	<p>Human endocardial myocytes</p>		
	Summary		
References	<ol style="list-style-type: none"> 1. www.tox.portal.com and www.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2015) www.fda.gov/oc/ohrt/ohrt-report-cardiac-safety-project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061 8. Miram E et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₆₀₋₉₅ : AP duration at 60, 90 or 95 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC₅₀ : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL} + I_{CaT} + I_{NaL} + I_{NaT}, RMP : resting membrane potential, RUD : reverse use dependence, T₆₀₋₉₀ : APD₆₀/APD₉₀ or APD₉₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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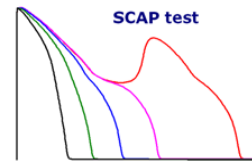


Drug	Semtilide Potassium voltage-gated cardiac channel (K _v 11.1) blocker used as class III antiarrhythmic to treat cardiac arrhythmia			
Raw data	IC_{50s} (slope) ⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 25.0 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max} ⁽¹⁾ 4.449 μM	TdP risk Redfern ⁽²⁾ : class IA or III antiarrhythmic (class 1) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 2/0 (TdP+/TdP-)	
In silico cardiac action potential study (ORd model) ⁽⁷⁾				
Simulation conditions: <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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length : 1000 msec Beat number: 100 Effect of drugs on AP ⁽⁸⁾: <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} \left(1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right)^{-1}$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel g_{j,max}: maximal conductance of channel IC_{50j}: 50% of inhibition of drug for channel n: drug concentration (EFTPC) or example n: Hill slope</small></p> TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ mid - APD₉₀ epi <p>where APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x</p> IC index calculation ⁽⁹⁾: $IC\ index = (AFK_r / (AFN_aL + AFCaL / 2)) * 100$ <p>where AFK_r, AFN_{aL} and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaT}</p>				
Results	Human epicardial myocytes 		Transmural dispersion of repolarization 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
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	Summary			
References	<ol style="list-style-type: none"> 1. Pearlstein RA et al. (2016) <i>Curr. Top. Med. Chem.</i> 15: 1792-1818 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.ilixtra.org/hes/science/clinical/cipa/Project 6. Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 			
Abbreviations	AP : action potential, APA : AP amplitude, APD ₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APD ₇₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{CaT} +I _{NaL} +I _{NaT} +I _{K1} , RMP : resting membrane potential, RUD : reverse use dependence, T _{40,50} : APD ₄₀ -APD ₅₀ or APD ₅₀ -APD ₄₀ (triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V ₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second			



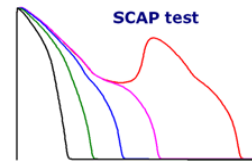
Drug	<h2 style="color: red;">Sibutramine</h2> <p>Noradrenaline, serotonin and dopamine reuptake inhibitor used to assist with weight loss in obesity no longer marketed worldwide (Onakpoya et al (2016) BMC Med. 14: 10)</p>		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 3.755 μM (1.0) I_{Nal}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.000161 μM</p> <p>De Alwis D et al. (2024) www.hesiglobal.org/cctdatabase</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: no risk of TdP but special risk for patients with long QT CiPA⁽⁵⁾: not reported WP⁽⁶⁾: 2/0 (TdP+/TdP-)</p>
<p>In silico cardiac action potential study (ORd model)⁽⁷⁾</p>			
	<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]_o, 1.8 - [K]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s}. $I_j = g_j O (V - E_{ion})$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel</small></p> $g_j = g_{jcontrol} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_{jcontrol}: maximal conductance of channel EFTPC_{max}: drug maximal conductance of channel IC₅₀: 50% of inhibition of a drug for example n: Hill slope</small></p>		<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₅₀ EFTPC_{max} - APD₅₀ EFTPC_{max} where APD₅₀ EFTPC_{max} = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFK_r((AFNaL + AFCaL)/2))¹⁰⁰ where AFK_r, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{Ks} and I_{CaL}</p>
Results	<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarization</p>
	<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound
	<p>Human endocardial myocytes</p>		
	Summary	<p>x-fold EFTPC_{max} vs. IC_{50s}</p> <p>APD₅₀ (msec) vs. IC index (a.u.)</p>	
References		<ol style="list-style-type: none"> Polak S et al. (2009) J. Appl. Toxicol. 29: 183-206 Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 Kramer J et al. (2013) Sci Rep. 3: 2100 Woodsley RL (2015) www.CredibleMeds.org CiPA (2016) www.hesiglobal.org/hesiglobal.org/cipa/Project Wisniewska B et al. (2017) Drug discovery today 22: 110-116 O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061.8 Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 95: 15-26 	
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀ : AP duration at 50 or 90 % of APA, APD₉₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{CaT}, I_{Kr}, I_{Ks}, I_{Na}, I_{to}, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD} : APD₅₀ - APD₉₀ or APD₅₀ ("triangulation"), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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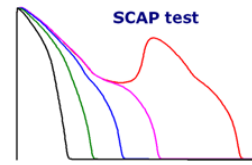
Drug	<h2 style="color: red;">Sulpiride</h2> <p>Dopamine D₂ receptor antagonist used to treat chronic and acute schizophrenia</p>		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{to}: ---- μM (---) I_{Kr}: 805 μM (1.0) I_{Nal}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.7082 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: known risk of TdP (Class 1) CiPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 1/0 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORD model) ⁽⁷⁾			
<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]_o, 1.8 - [K]_o, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP ⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flow through channel</small></p> $g_j = g_{jmax} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right]^{-1}$ <p><small>g_{jmax}: drug free maximal conductance of channel IC_{50j}: 50% of inhibition of a drug for channel n: drug concentration (EFTPC) to example n Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ epi - APD₉₀ epi <p>where APD₅₀ = APD₅₀ with - APD₅₀ without compound at CL x</p> <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFK_r / (AFN_{aL} + AFCa_L / 2)) * 100</p> <p>where AFK_r, AFN_{aL} and AFCa_L = active fraction (%) of the I_{CaL}, I_{Kr} and I_{CaL}</p>			
Results	<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> <ol style="list-style-type: none"> CL 1000 msec without compound CL 4000 msec without compound CL 1000 msec with compound CL 4000 msec with compound
	<p style="text-align: center;">Human endocardial myocytes</p>		
Summary			
References	<p>1. www.tox-portal.com and www.gd.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.ilseixtra.org/hesi/science/cardiacc/cipa/Project 6. Wisniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061,8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B et al. (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC_{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{Kr}, I_{Ks}, I_{Na}, I_{NaCa}, I_{NaP}, I_{NaK}, I_{NaKATPase}, RMP : resting membrane potential, RUD : reverse use dependence, Td₅₀₋₉₀ : APD₅₀-APD₉₀ or APD₅₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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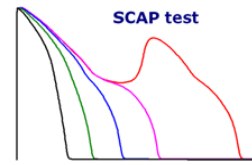
Drug	Telithromycin Ketolide used as antibiotic to treat community acquired pneumonia of mild to moderate severity			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 56.21 μM (0.7) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max} 0.5283 μM Javiscas LH et al (2010) J. Vet. Pharmacol. Ther. 33 : 383-388	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible risk of TdP (class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 1/1 (TdP+/TdP-)	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
	Simulation conditions: • 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	Effect of drugs on AP⁽⁸⁾: • channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC _{max} and IC _{50s} $I_j = g_j O(V - E_{ion}) \left(\frac{1}{1 + \left(\frac{EFTPC_{max}}{IC_{50s}} \right)^n} \right)^{-1}$ <small> g_j: maximal conductance of channel O: open probability of channel V: voltage membrane E_{ion}: reversal potential for species of ions which flow through channel n: Hill slope EFTPC_{max}: drug free maximal conductance of channel IC_{50s}: 50% of inhibition of a drug for channel O: drug concentration (EFTPC for example) </small>	TDR and RUD estimation: • TDR = APD ₅₀ mid - APD ₅₀ epi (at CL of 1000 msec) • RUD = APD ₅₀ endo - APD ₅₀ epi where APD ₅₀ P _i = APD ₅₀ with - APD ₅₀ without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I _{Ca} , I _{Na} and I _{CaL}	
Results	Human epicardial myocytes 	Transmural dispersion of repolarization 		
	Human midmyocardial myocytes 	Reverse use dependence on midmyocardial myocytes 		
	Human endocardial myocytes 			
	Summary 			
References	<ol style="list-style-type: none"> 1. www.tsc-central.com and www.gx-fdn.genbank.com 2. Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 3. Kramer J et al. (2013) Sci. rep. 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.ilisixtra.org/hesi/science/cardiac/cipa/Project 6. Wiśniowska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061.8 8. Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 95: 15-26 			
Abbreviations	AP: action potential, APA: AP amplitude, APD ₅₀₋₉₅ : AP duration at 40, 60 or 90 % of APA, APDP: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I _{CaL} +I _{CaT} +I _{Na} +I _{NaP} +I _{CaL} , RMP: resting membrane potential, RUD: reverse use dependence, T _{AP,50} : APD ₅₀ -APD ₉₀ or APD ₅₀ -APD ₉₅ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{min} : minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second			

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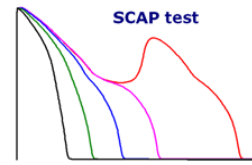
Drug	<h2 style="color: red;">Tetracaine</h2> <p>Voltage-gated Na⁺ (Na_v1.5) channel blocker used as local anaesthetic to induce local analgesia in the eyes and skin during medical procedures</p>		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 83.176 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 6.310 μM (1.0) I_{Nal}: 1.950 μM (1.0) I_{Na}: 1.023 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.270 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: not reported CIPA⁽⁵⁾: not reported WP⁽⁶⁾: not reported</p>
In silico cardiac action potential study (ORd model)⁽⁷⁾			
<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 - [Ca²⁺]_o, 1.8 - [K⁺]_o, 5.4 Cycle length: 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{max,j}: maximal conductance of channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug for channel⁽⁹⁾ C: drug concentration (EFTPC for example) n: Hill slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀ epi (at CL of 1000 msec) RUD = APD₉₀ epi - APD₉₀ mid <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ca}, I_{Na} and I_{CaL}</p>			
<p>Human epicardial myocytes</p>		<p>Transmural dispersion of repolarisation</p>	
<p>Human midmyocardial myocytes</p>		<p>Reverse use dependence on midmyocardial myocytes</p> <ol style="list-style-type: none"> 1 - CL 1000 msec without compound 2 - CL 4000 msec without compound 3 - CL 1000 msec with compound 4 - CL 4000 msec with compound 	
<p>Human endocardial myocytes</p>		<p>Summary</p>	
References	<ol style="list-style-type: none"> 1. Wath ED et al. (2022) <i>J Pharmacol. Toxicol. Methods</i> 118: 107213 2. Redfern WS et al. (2003) <i>Circulation</i>. Res. 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.lisixtra.org/hesi/science/cardiac/cipa/Project 6. Wiśniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Circulation</i>. Res. 108: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 95: 15-26 		
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD₅₀ to APD₉₀: AP duration at 40, 60 or 90 % of APA, APD₅₀: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNet: integration sum of I_{CaL}, I_{CaT}, I_{Na}, I_{NaP}, I_{NaL}, I_{CaL}, RMP: resting membrane potential, RUD: reverse use dependence, T_{AP,50}: APD₅₀-APD₉₀ or APD₅₀ (~triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>		

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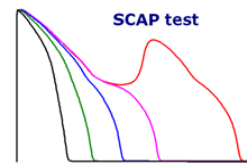
Drug	<h2 style="color: red;">Trimipramine</h2> <p>Noradrenaline and serotonin reuptake inhibitor used to treat depression</p>			
Raw data	<p>IC₅₀s (slope)⁽¹⁾</p> <p>I_{CaL}: ---- μM (---) I_{T0}: ---- μM (---) I_{Kr}: 2.7 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}</p> <p>0.02035 μM</p> <p>https://e-lactancia.org/media/papers/Trimipramine-DS-APharma2010.pdf</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: not reported CredibleMeds⁽⁴⁾: possible risk of TdP (class 2) CiPA⁽⁵⁾: not reported WP⁽⁶⁾: 1/1 (TdP+/TdP-)</p>	
In silico cardiac action potential study (ORd model)⁽⁷⁾				
<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 - [Ca²⁺]_o 1.8 - [K⁺]_o 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC₅₀ $I_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} \left[1 + \left(\frac{EFTPC_{max}}{IC_{50}} \right)^n \right]^{-1}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: charge probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{j,max}: drug free maximal conductance of channel⁽⁹⁾ IC₅₀: 50% of inhibition of a drug on channel⁽⁹⁾ n: drug concentration (EFTPC for example) in nH slope</small></p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₆₀ mid - APD₆₀ epi (at CL of 1000 msec) RUD = APD₆₀ EFTPC_{max} - APD₆₀ EFTPC_{max} where APD₆₀ P_i = APD₆₀ with - APD₆₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr((AFNaL+AFCaL)/2))¹⁰⁰ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}</p>				
Results	Human epicardial myocytes		Transmural dispersion of repolarization	
	Human midmyocardial myocytes			
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Summary				
References	<p>1. www.tox-portal.com and www.go.drugbank.com 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CPA (2016) www.lisextra.org/hasi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>			
Abbreviations	<p>AP: action potential, APA: AP amplitude, APD_{40, 60 or 90}: AP duration at 40, 60 or 90% of APA, APD_P: APD prolongation, a.u.: arbitrary unit, CL: cycle length, DA: depolarization abnormalities, EAD: early afterdepolarization, EFTPC_{max}: maximal effective free therapeutic plasma concentration, endo: endocardial myocyte, epi: epicardial myocyte, IC index: ion channel inhibition index, IC₅₀: 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mv: millivolt, qNet: integration sum of I_{CaL}+I_{Kr}+I_{Ks}+I_{NaL}+I_{Na}, RMP: resting membrane potential, RUD: reverse use dependence, T_{APD}: APD₆₀-APD₁₀₀ or APD₉₀ (triangulation), TdP: torsade de pointes, TDR: transmural dispersion of repolarization, V_m: membrane voltage, V_{max}: maximal rate of AP rise, V_{min}: minimal rate of AP decrease at EAD take-off voltage, V/s: volt per second</p>			

Safe Cardiac Action Potential Test



Drug	Venlafaxine Noradrenaline and serotonin reuptake inhibitor used to treat major depression, generalized or social anxiety disorder and panic disorder			
Raw data	IC_{50s} (slope)⁽¹⁾ <i>I</i> _{CaL} : ---- μM (---) <i>I</i> _{Kr} : 69.183 μM (1.0) <i>I</i> _{Na} : 158.489 μM (1.0) <i>I</i> _{Ks} : ---- μM (---) <i>I</i> _{to} : ---- μM (---) <i>I</i> _{NAL} : ---- μM (---) <i>I</i> _{K1} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.081 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible risk of TdP (class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 2/1 (TdP+/TdP-)	
In silico cardiac action potential study (ORD model)⁽⁷⁾				
Simulation conditions: <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]_o, 1.8 - [K]_o, 5.4 Cycle length : 1000 msec Beat number: 100 Effect of drugs on AP⁽⁸⁾: <ul style="list-style-type: none"> channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $f_j = g_j O(V - E_{ion})$ $g_j = g_{j,max} \left(1 + \left(\frac{EFTPC_{max}}{IC_{50j}} \right)^n \right)^{-1}$ <p><small>g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: voltage membrane E_{ion}: reversal potential for species of ions which flows through channel⁽⁹⁾ g_{j,max}: maximal conductance of channel⁽⁹⁾ IC_{50j}: 50% of inhibition of a drug for channel⁽⁹⁾ n: drug concentration (EFTPC for example) nHill slope</small></p> TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀ epi (at CL of 1000 msec) RUD = APD₉₀ 1000 - APD₉₀ 1000 <p>where APD₉₀P_i = APD₉₀ with - APD₉₀ without compound at CL x</p> IC index calculation⁽⁹⁾: IC index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100 where AFKr, AFNaL and AFCaL = active fraction (%) of the I _{CaL} , I _{NaL} and I _{CaL}				
Results	Human epicardial myocytes 		Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes 	
	Human endocardial myocytes 			
	Summary 			
References	1. Watt ED et al. (2022) <i>J Pharmacol Tox Methods</i> 118 : 107213 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58 : 32-45 3. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.isixtra.org/hesi/science/cardiac/cipa/Project 6. Wiñówska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7 : e1002061.8 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96 : 15-26			
Abbreviations	AP : action potential, APA : AP amplitude, APD ₄₀₋₉₀ or 90 : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} , I _{CaT} , I _{NaL} , I _{NaT} , I _{K1} , I _{Kr} , I _{Ks} , I _{K1} , RMP : resting membrane potential, RUD : reverse use dependence, T _{AP,90} : APD ₉₀ -APD ₁₀₀ or APD ₉₀ (~triangulation), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V ₅₀ : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second			

Safe Cardiac Action Potential Test



Class I (Known TdP risk) [§]	# I _{Kr}	# I _{CaL}	# I _{Na}	# I _{NaL}	## APA	## V _{max}	## APD ₉₀	## T ₆₀	## TDR	## RUD	## V _{min}	## IC _{index}	EAD [£]
Amiodarone	*	*	*								•	98.0	
Astemizole	***	*	*				•••	•••	•••	1	•••	32.0	x 36
Azithromycin	***			***			•••	•••	•••	1	•••	50.6	
Bepidil	****	****	***		o	oooo	•••	•••	•	1	•••	10.6	
Chloroquine	***						•••	•••	•••	1	•••	33.9	x 85
Chlorpromazine	***	**	***			oo	•••	•••	••	•••	•••	29.5	
Cilostazol	**	*	*			o	•	••	•	••	••	55.1	
Ciprofloxacin	***						•••	•••	•••	1	•••	31.6	x 61
Cisapride	***	*	*				•••	•••	•••	1	•••	31.7	x 15
Citalopram	***	*	*			o	•••	•••	•••	1	•••	33.2	
Clarithromycin	***						•••	•••	•••	1	•••	31.6	x 48
Disopyramide	***	*	*			o	•••	•••	•••	1	•••	31.4	x 48
Dofetilide	***	*	*				•••	•••	•••	1	•••	32.1	x 29
Domperidone	***		*				•••	•••	•••	1	•••	33.1	x 13
Donepezil	**	*	*				•	•	•	••	••	70.3	
Dronedarone	***	**	**			o	•••	•••	•••	1	•••	29.2	
Droperidol	***	*	*				•••	•••	•••	1	•••	33.6	x 8
Erythromycin	***						•••	•••	•••	1	•••	33.7	x 10
Flecainide	***	*	**			ooo	•••	•••	•••	1	•••	29.7	x 7
Fluconazole	***						•••	•••	•••	1	•••	31.7	x 7
Gatifloxacin	***						•••	•••	•••	1	•••	32.0	x 7
Grepafloxacin	***						•••	•••	•••	1	•••	31.6	x 37
Halofantrine	***	**	*				•••	•••	•••	1	•••	25.8	x 7
Haloperidol	***	*	*				•••	•••	•••	1	•••	32.2	x 20
Hydrochloroquine	****	**					•••	•••	•••	1	•••	35.4	x 12
Ibutilide	***	*	*				•••	•••	•••	1	•••	33.7	x 0.3
Ivabradine	**	*	*				•	••	•	•	••	73.3	
Levofloxacin	***						•••	•••	•••	1	•••	32.2	x 30
Mesoridazine	***	*	*	*		o	•••	•••	•••	1	•••	35.0	x 0.4
Methadone	***	*	*			o	•••	•••	•••	1	•••	31.3	x 17
Moxifloxacin	****	****	**		o	ooo	•••	••	=	•••	•••	14.8	
Nifekalant	***						•••	•••	•••	1	•••	31.8	x 27
Ondansetron	***	**		**			•••	•••	•••	1	•••	30.6	x 14
Pentamidine	*						•	•••	••	o	=	99.5	
Pimozide	***	*	*				••	••	••	••	•••	45.6	
Procainamide	****	****	****		2	2	2	2	2	2	2	8.7	
Quinidine	***	**	*			o	•••	•••	•••	1	•••	27.4	x 0.8
Roxithromycin	***						•••	•••	•••	1	•••	31.6	x 55
Sertindole	***	*	*				•••	•••	•••	•••	•••	32.2	x 31
Sotalol	****	****	*		o	o	••	••	oo	•••	•••	23.7	
Sparfloxacin	****	**	*				•••	•••	•••	1	•••	18.9	
Sulpiride	*						=	=	=	=	•	91.9	
Terfenadine	***	*	*				•••	•••	•••	1	•••	31.6	x 12
Terodiline	***	**	*			o	•••	•••	•••	1	•••	26.7	x 16
Thioridazine	***	*	**			ooo	•••	•••	•••	1	•••	36.9	x 2
Vandetanib	***						•••	•••	•••	1	•••	34.2	x 8

§ : Crediblemeds classification of compound TdP risk (08/2024)

: Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***) and 80 to 99.9 % (*). Absence of (*) in case of an active fraction of 100 %.

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: -5 to 5 % (=), -5 to -20 % (°), -20 to -40 % (°°), -40 to -60 % (°°°), > -60 % (°°°°), 5 to 20 % (•), 20 to 40 % (••), 40 to 60 % (•••) and > 60 % (••••)

€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

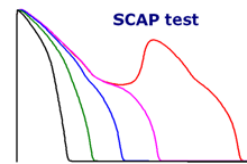
£ : First EFTPC_{max}/IC_{50s} ratio (x-fold) inducing an EAD

¹ EAD observed at CL of 4000 msec preventing the RUD calculation

² Depolarisation abnormality

Red color: Compounds described in the present zenodo file, other compounds already described in a previous zenodo file (doi: 10.5281/zenodo.7541554)

Safe Cardiac Action Potential Test



Class II (Possible TdP risk) [§]	# I _{Kr}	# I _{CaL}	# I _{Na}	# I _{NaL}	## APA	## V _{max}	## APD ₉₀	## T ₆₀	## TDR	## RUD	## V _{min}	## IC _{index}	EAD [£]
Alfuzosin	*	*	*									99.8	
Asenapine	*						•	•	•	•	••	81.1	
Atomoxetine	**						••	••	•	••	••	68.0	
Bedaquiline	***						•••	•••	•••	1	•••	33.3	
Bosutinib	***						•••	•••	•••	1	•••	32.1	x 29
Ceritinib	***						•••	•••	•••	1	•••	33.0	x 15
Clozapine	***	***	**		o	oo	•••	••	••	•••	•••	37.6	
Crizotinib	*						•	•	•	•	••	81.7	
Dasatinib	*	*	*				•			•	••	91.0	
Desipramine	****	****	****		2	2	2	2	2	2	2	20.2	
Dolasetron	****		**			oo	•••	•••	•••	1	•••	32.7	x 35
Granisetron	*	**					•	•			•	93.0	
Imatinib	**						••	••	••	••	••	51.2	
Imipramine	***	***	***			oooo	•••	•••	••	•••	•••	33.9	
Isradipine	*	****	*	*	o	•	oo		o		oo	189	
Ketanserin	***						•••	•••	•••	1	•••	31.8	x 78
Lapatinib	***	*	*				•••	•••	•••	1	•••	31.9	x 55
Lopinavir	****	****			o	•	•••	•••	••	1	•••	7.1	
Maprotiline	****	**	****	****	2	2	2	2	2	2	2	83.0	
Nicardipine	****	****	***		oo	ooo	•••	•	oo	•••	•••	30.4	
Nilotinib	***	*	*				•••	•••	•••	1	•••	29.5	x 17
Nortriptyline	**	**	****	****	2	2	2	2	2	2	2	99.1	
Ofloxacin	**						••	••	•	•	••	62.0	
Paliperidone	****	*	*				•••	•••	•••	1	•••	32.9	x 25
Palonosetron	*	*	*				•	•	•	•	••	81.1	
Pitolisant	***	*	*				••	••	••	••	••	48.3	
Promethazine	**						•	•	•	•	••	74.3	
Ribociclib	***		**			o	•••	•••	•••	1	•••	32.7	x 33
Rilpivirine	**						••	••	••	••	••	50.5	
Saquinavir	**	****	***		o	ooo	•	o	oooo	o	••	111	
Sunitinib	***	*	*				••	••	••	••	••	48.7	
Tamoxifen	***						•••	•••	•••	1	•••	31.7	x 94
Telithromycin	**						••	••	••	••	••	51.1	
Tolterodine	***		*				•••	•••	•••	1	•••	32.0	x 28
Trimipramine	**						••	••	••	••	••	57.0	
Vardenafil	*	*	*									100	
Venlafaxine	*		*				•	•			•	89.5	
Vernakalant	****	****	****	****	2	2	2	2	2	2	2	44.8	

§ : Crediblemeds classification of compound TdP risk (08/2024)

: Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***), 50 to 80 % (**), and 80 to 99.9 % (*). Absence of (*) in case of an active fraction of 100 %.

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: -5 to 5 % (=), -5 to -20 % (°), -20 to -40 % (oo), -40 to -60 % (ooo), > -60 % (oooo), 5 to 20 % (•), 20 to 40 % (••), 40 to 60 % (•••) and > 60 % (••••)

€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

£ : First EFTPC_{max}/IC_{50s} ratio (x-fold) inducing an EAD

¹ EAD observed at CL of 4000 msec preventing the RUD calculation

² Depolarisation abnormality

Red color: Compounds described in the present zenodo file, other compounds already described in a previous zenodo file (doi: 10.5281/zenodo.7541554)

Safe Cardiac Action Potential Test



Class III (Conditional TdP risk) [§]	# I _{Kr}	# I _{CaL}	# I _{Na}	# I _{NaL}	## APA	## V _{max}	## APD ₉₀	## T ₆₀	## TDR	## RUD	## V _{min}	## IC _{index}	EAD [£]
Amitriptyline	**	***	**	**	o	oo	••	••	•	o	•••	128	
Clomipramide	***	*	*		=	o	••••	••••	••••	1	••••	35.0	
Diltiazem	**	****	**		o	oo	••	•	oo	•	•••	101	
Diphenhydramine	**	*	*		=	o	••	••	•	•	•••	60.9	
Doxepin	**				=	=	••	••	•	••	•••	60.4	
Famotidine	*				=	=	=	=	=	=	=	98.6	
Fluoxetine	**	**	*		=	=	••	••	•	•	•••	67.1	
Fluvoxamine	****	****	**		o	oo	••••	•••	=	••••	••••	21.8	
Furosemide	**				=	=	••	•••	••	•••	•••	51.6	
Galantamine	*				=	=	=	=	=	=	=	99.6	
Hydroxyzine	****	*	***	*	=	oooo	••••	••••	••••	1	••••	34.4	x 90
Ketoconazole	****		*		=	o	••••	••••	••••	1	••••	32.5	x 43
Loperamide	*		*		=	=	•	=	=	•	•	89.3	
Metoclopramide	****				=	=	••••	••••	••••	1	••••	36.7	
Metronidazole	****	****	****		2	2	2	2	2	2	2	12.8	
Nelfinavir	**		*		=	o	••	••	•	••	•••	63.9	
Olanzapine	***		**		=	oo	••••	••••	••••	1	••••	33.1	x 1.4
Paroxetine	**	*	*		=	o	••	••	•	••	•••	65.9	
Piperacillin	****	****	****		2	2	2	2	2	2	2	4.8	
Propafenone	****	****	***	***	o	oooo	••••	•••	oo	••••	••••	34.5	
Quetiapine	****	****			o	•	••••	••••	••	1	••••	12.8	
Quinine	***	**	**	***	=	oo	••••	••••	••••	1	••••	44.9	x 5
Ranolazine	***			***	=	=	••••	••••	••••	1	••••	43.1	x 12
Risperidone	**	*	*		=	=	••	••	••	••	•••	56.9	
Sertraline	****	****	****		2	2	2	2	2	2	2	0.6	
Solifenacin	****	*	*		=	o	•••	•••	••	•••	•••	48.9	
Voriconazole	***	**	**		o	oo	•••	••	•	•	•••	58.1	
Ziprasidone	***		*		=	=	••••	••••	••••	•••	••••	31.6	x 72

§ : Crediblemeds classification of compound TdP risk (08/2024)

: Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***), 50 to 80 % (**), 80 to 99.9 % (*). Absence of (*) in case of an active fraction of 100 %.

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: -5 to 5 % (=), -5 to -20 % (e), -20 to -40 % (oo), -40 to -60 % (ooo), > -60 % (oooo), 5 to 20 % (•), 20 to 40 % (••), 40 to 60 % (•••) and > 60 % (••••)

€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

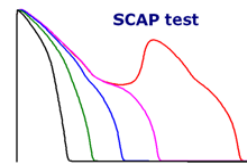
£ : First EFTPC_{max}/IC_{50s} ratio (x-fold) inducing an EAD

¹ EAD observed at CL of 4000 msec preventing the RUD calculation

² Depolarisation abnormality

Red color: Compounds described in the present zenodo file, other compounds already described in a previous zenodo file (doi: 10.5281/zenodo.7541554)

Safe Cardiac Action Potential Test



Class IV (No TdP risk) ^{ss}	# I _{Kr}	# I _{CaL}	# I _{Na}	# I _{NaL}	APA ##	V _{max} ##	APD ₉₀ ##	T ₆₀ ##	TDR ##	RUD ##	V _{min} ##	IC _{index} ##	EAD ^f
Ajmaline	****	*	**			oo	●●●	●●●	●●●	1	●●●	31.6	x 93
Alosetron	*						●	●		●	●	87.3	
Ambrisentan	*	*	*									97.7	
Amlodipine	****	****	***		oo	oooo	●●●	●	oo	●●●	●●●	26.3	
Aspirin	*											99.2	
Atenolol	*						●	●			●	91.4	
Bupivacaine	****	**	****	****	2	2	2	2	2	2	2	80.7	
Carbamazepine		**	**	****	o	oooo	o	o	oooo	oo	o	539	
Carvedilol	****						●●	●●	●●	●●	●●	49.9	
Cetirizine	*											97.7	
Chlorpheniramine	*							●			●	91.5	
Darifenacin	****	*	*			o	●●●	●●●	●●●	●●●	●●●	36.9	
Darunavir	**		***			ooo	●	●	●	●	●	77.4	
Dasabuvir	*											97.0	
Desvenfalaxine	****		***			oooo	●●	●●	●●	●●	●●	49.4	
Diazepam	*	*	*									101	
Digoxin	****						●●●	●●●	●●●	1	●●●	31.6	x 93
Doxorubicin	**						●●	●●	●●	●●	●●	68.3	
Duloxetine	**	**	*			o	●	●			●	91.1	
Eltrombopag	****		*				●●●	●●●	●●●	1	●●●	33.3	x 12
Everolimus	*		*									98.7	
Felodipine	*	***	*	*	o		o	o	oo	oo	o	164	
Fexofenadine	*						●	●	●		●	93.6	
Irbesartan	**						●●	●●	●●	●	●●	67.0	
Lacosamide	*	****	****		2	2	2	2	2	2	2	177	
Lamivudine	**	****	***		o	ooo	●●	o	oooo		●●	98.8	
Lamotrigine	****	**	****			oooo	●●●	●●●	●●●	1	●●●	41.4	x 14
Levocetirizine	*										●	94.1	
Lidocaine				****			o				o	197	
Linezolid	****	****	***		oo	oooo	●●●	o	oo	●●●	●●●	31.8	
Loratadine	*	*	*									99.9	
Mefloquine	**						●●	●●	●●	●●	●●	59.7	
Metoprolol	**	*	****	**		oooo		●	oo	oo		116	
Mexiletine				****			o				o	198	
Milrinone	*											96.4	
Mitoxantrone	*	**	*			o				oo		128	
Mizolastine	****						●●●	●●●	●●●	1	●●●	31.6	x 88
Nebivolol	**		*				●	●	●	●	●●	77.1	
Nifedipine	*	****	*		o		o	●	o	●●	●●	190	
Oseltamivir	*	*	*								●	95.2	
Oxybutynin	*	*										100	
Phenytoin	***	****	****		2	2	2	2	2	2	2	48.1	
Primidone	**		***			ooo	●●	●●	●	●●	●●	62.0	
Propranolol	*	*	*				●	●			●	91.2	
Raltegravir	*	**	*			o					●	103	
Ribavirin	****	****	**		o	ooo	●●	●●	o	●●	●●●	43.6	
Sildenafil	*	*	*				●	●	●	●	●	84.4	
Sildenafil	*	*	*				●	●		●	●	89.5	
Tadalafil	*	*	*			o	●	●	●	●	●	88.0	
Verapamil	****	****	*		o	o	●●●	●●●	o	●●●	●●●	7.7	

§ : Crediblemeds classification of compound TdP risk (08/2024)

: Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***) , 50 to 80 % (**) and 80 to 99.9 % (*). Absence of (*) in case of an active fraction of 100 %.

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: -5 to 5 % (=), -5 to -20 % (°), -20 to -40 % (°°), -40 to -60 % (°°°), > -60 % (°°°°), 5 to 20 % (•), 20 to 40 % (••), 40 to 60 % (•••) and > 60 % (••••)

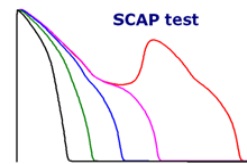
€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

£ : First EFTPC_{max}/IC_{50s} ratio (x-fold) inducing an EAD

¹ EAD observed at CL of 4000 msec preventing the RUD calculation, ² Depolarisation abnormality

Red color: Compounds described in the present zenodo file, other compounds already described in a previous zenodo file (doi: 10.5281/zenodo.7541554)

Safe Cardiac Action Potential Test



Class V (not reported) ^{ss}	# I _{Kr}	# I _{CaL}	# I _{Na}	# I _{NaL}	## APA	## V _{max}	## APD ₉₀	## T ₆₀	## TDR	## RUD	€ V _{min}	## IC _{index}	EAD ^f
Almokalant	****						●●●	●●●	●●●	1	●●●	31.9	x 48
Alvimopan	*	*	*							o		109	
Aprindine	***						●●●	●●●	●●●	1	●●●	32.5	x 2.1
Azimilide	****						●●●	●●●	●●●	1	●●●	31.6	x 13
Ceftriaxone	****	****	****		oo	oooo	●●●	•	oooo	●●	●●●	30.4	
Cibenzoline	****		*	**		o	●●●	●●●	●●●	1	●●●	36.2	x 8
Deferasirox	*	*	****			ooo		•				102	
Dobutamine ⁺	*	*	*				•	•	•	•	•	86.0	
Doripenem	****	****	****		2	2	2	2	2	2	2	82.6	
E-4031	****	*	*				●●●	●●●	●●●	1	●●●	37.6	x 7
Ebastine	*											98.1	
Encainide	****		**			oo	●●	●●	●	●●●	●●	47.0	
Etravirine	*		*									99.8	
Fenspiride	***						●●●	●●●	●●●	1	●●●	31.6	x 47
Gefitinib	****						●●●	●●●	●●●	1	●●●	32.5	x 26
Levosimendan	*	*	*					•			•	95.6	
Manidipine	*	*	*	*								101	
Maraviroc	**		*				•	•	•	•	●●	78.4	
Mepivacaine	****		***			oooo	●●●	●●●	●●●	1	●●●	36.3	x 24
Mibefradil	**	***	*		o		•	•	oo	o	●●	101	
Nilvadipine	*	****	*	*	o		o		o	o	●	188	
Nimodipine	*	**						o		oo	•	129	
Nisoldipine	*	*										106	
Nitrendipine	*	****	*		o		o	o	oo	o	•	173	
Omecamtiv mecarb	*	*	*			o	•	•	•	•	•	84.9	
Pentobarbital	**	***	*		o	o	•		o	oo	o	111	
Prenylamine	****	*	*			o	●●●	●●●	●●●	1	●●●	28.9	x 51
Procaine	***		**	**		oo	●●●	●●●	●●●	1	●●●	36.6	x 6
Ritonavir	****	****	****	****	o	•	●●●	●●●	o	●●●	●●●	65.4	
Ropivacaine	***		***	***		oooo	●●●	●●●	●●●	1	●●●	48.9	x 61
Rufinamide		****			o	•	o	•		•	●●	192	
Sematilide	***						●●●	●●●	●●●	1	●●●	31.9	x 13
Sibutramine ⁺	*											99.6	
Sitagliitin	**	**	*				•		•		•	90.2	
Tedisamil	****						●●●	●●●	●●●	1	●●●	34.0	x5.5
Telbivudine	****	***	***		o	oooo	●●●	●●	●●	●●●	●●●	27.9	
Tetracaine	****	**	****	****	2	2	2	2	2	2	2	46.1	
Vanoxerine	****	****	****	****	2	2	2	2	2	2	2	13.3	

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: Active fraction of I_{Kr}, I_{CaL}, I_{Na} or I_{NaL} cardiac current calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD: 0 to 20 % (****), 20 to 50 % (***), 50 to 80 % (**), and 80 to 99.9 % (*). Absence of (*) in case of an active fraction of 100 %.

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€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/IC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/IC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

£ : First EFTPC_{max}/IC_{50s} ratio (x-fold) inducing an EAD

¹ EAD observed at CL of 4000 msec preventing the RUD calculation

² Depolarisation abnormality

+ Compounds with special risk for patient with congenital long QT

Red color: Compounds described in the present zenodo file, other compounds already described in a previous zenodo file (doi: 10.5281/zenodo.7541554)



Introduction	page 2
Methods	pages 3-4
Classification of drugs	page 5

Drugs:

Alosetron	6	Digoxin	19	Manipine	32	Ribociclib	45
Aprindine	7	Doxepin	20	Maprotiline	33	Ropivacaine	46
Asenapine	8	Felodipine	21	Mepivacaine	34	Rilpivirine	47
Atomoxetine	9	Fenspiride	22	Mesoridazine	35	Roxithromycin	48
Bedaquiline	10	Fluconazole	23	Metoclopramide	36	Sematilide	49
Bosutinib	11	Furosemide	24	Mizolastine	37	Sibutramine	50
Bupivacaine	12	Galantamine	25	Nifekalant	38	Sulpiride	51
Carbamazepine	13	Granisetron	26	Nilvadipine	39	Telithromycin	52
Carvedilol	14	Grepafloxacin	27	Nortriptyline	40	Tetracaine	53
Ceritinib	15	Imatinib	28	Oseltamivir	41	Trimipramine	54
Clomipramide	16	Irbesartan	29	Pilotisant	42	Venlafaxine	55
Crizotinib	17	Isradipine	30	Procaine	43		
Dasabuvir	18	Loperamide	31	Promethazine	44		

Summary tables:

- Compounds with known TdP risk (Crediblemeds classification: Class 1), page 56
- Compounds with possible TdP risk (Crediblemeds classification: Class 2), page 57
- Compounds with conditional TdP risk (Crediblemeds classification: Class 3), page 58
- Compounds reviewed by Crediblemeds but no classified in class 1, 2 or 3 (Crediblemeds classification: Class 4), page 59
- Compounds not reported by Crediblemeds classification, page 60



Some of these data were also described in the following papers:

Christophe B. (2022)

Occurrence of early afterdepolarization under healthy or hypertrophic cardiomyopathy conditions in the human ventricular endocardial myocyte: *in silico* study using 109 torsadogenic or non-torsadogenic compounds.

Toxicol. Appl. Pharmacol., **438** : 115914

Christophe B. & Crumb W.J. Jr (2019)

Impact of disease state on arrhythmic event detection by action potential modeling in cardiac safety pharmacology

J. Pharmacol. Toxicol. Methods, **96** : 15-26

Christophe B. (2015)

In silico study of transmural dispersion of repolarisation in non-failing human ventricular myocytes: contribution to cardiac safety pharmacology

Br. J. Pharm. Res., **7** : 2, 88-101

Christophe B. (2013)

Simulation of early-afterdepolarisation in nonfailing human ventricular myocytes: can this help cardiac safety pharmacology ?

Pharmacol. Rep., **65** : 5, 1281-1293

The implementation of this database is still in progress: In addition to the 50 drugs described in this file, 150 other drugs were already described in the following zenodo file: (Christophe B. (2023) Safe cardiac action potential test (www.scaptest.com): a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization. doi:10.5281/zenodo.7541554)

New results are available at www.scaptest.com (please, create an account for free to see the results).

Comments/suggestions regarding this database are to be sent to bchristophe@scaptest.com

Electronic citation:

Christophe B. (2024) Safe cardiac action potential test (www.scaptest.com): a database describing the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization Part II: description of 50 additional drugs. doi:10.5281/zenodo.13913353