

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

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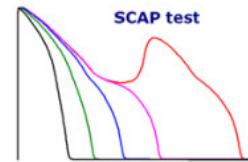
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January 2023 – version 1.0 – 150 drugs described

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Aim of the database

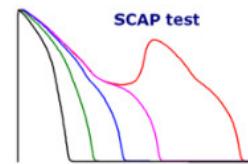
The aim of the present database is to describe the *in silico* cardiac safety profile of drugs and their propensity to induce early afterdepolarization. This is based on the study of the effects of drugs on the non-failing human ventricular myocyte (endo-, mid- and epicardial subtypes) action potential 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

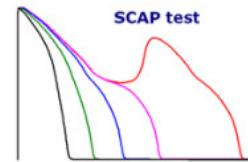
- Conductance of the channel (g_j) modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) determined from the tested EFTPC_{max}/IC_{50s} ratio.

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

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 = 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 (APD₉₅) from epi- and midmyocardial myocytes at CL of 1000 msec
- TDR = APD_{95mid} - APD_{95epi}

RUD estimation methodology

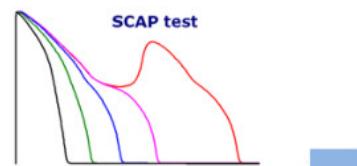
- Calculation of action potential duration prolongation (APD_{90P}) induced by a compound (vs. absence of compound) on the midmyocardial myocytes at CL of 1000 and 4000 msec
- RUD = APD_{90P4000}-APD_{90P1000} where

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

Calculation of the Ion Channel inhibition index

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

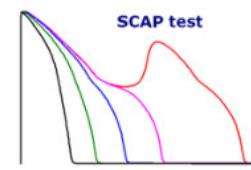
AF_{Kr}, AF_{NaL} and AF_{CaL} = active fraction (%) of I_{Kr}, I_{NaL} and I_{CaL} currents in the presence of compound calculated from each EFTPC_{max}/IC_{50s} ratio tested.



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

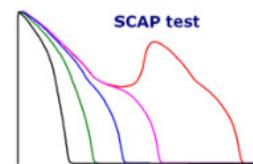
- **Redfern** TdP risk classification : (Cardiovasc Res 2003, 58 : 32-45)
 - Class 1 (class IA or III anti-arrhythmics with large but acceptable TdP risk)
 - Class 2 (compounds withdrawn from the market due to unacceptable TdP risk)
 - Class 3 (compounds with numerous TdP reports)
 - Class 4 (compounds 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.ilsiextra.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)
 - Class 1 (compounds with low risk)
 - Class 2 (compounds with intermediate risk)
 - Class 3 (compounds with high risk)

Safe Cardiac Action Potential Test



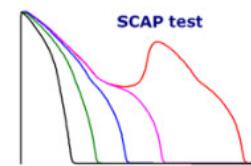
Drug	Ajmaline		
	Voltage-gated Na ⁺ channel (Na _v 1.5) blocker used as class IA antiarrhythmic to treat tachycardia		
Raw data	IC _{50s} (slope) ⁽¹⁾ I _{CaL} : 71.0 μM (1.0) I _{Kr} : 1.04 μM (1.0) I _{Na} : 8.2 μM (1.0) I _{Ks} : ---- μM (---)	EFTPC _{max} ⁽¹⁾ 0.025 μM	TdP risk Redfern ⁽²⁾ : large but acceptable TdP risk (class 1) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 8/0 (TdP+/TdP-)
	In silico cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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 F (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_f = g_f O(V - E_{\text{on}})$ <p>g_f = minimal conductance of channel⁽⁹⁾ O = open probability of channel⁽¹⁰⁾ V = membrane potential for species of ions which flows through channel⁽¹¹⁾ $\frac{d}{dx} \ln(g_f)$ = reversal potential for species of ions which flows through channel⁽¹²⁾ IC_{50s} = 50% of inhibition of drug/channel⁽¹³⁾ EFTPC_{max} = drug concentration EFTPC for example in Hill slope</p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{90, mid} - APD_{90, epi} (at CL of 1000 msec) RUD = APD_{90,endo}-APD_{90, mid} <p>where APD_{90,Pi} = APD₉₀ with - APD₉₀ without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr}/((\text{AFNaL}+\text{AFCaL})/2)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, 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> <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> <p>References</p> <ol style="list-style-type: none"> Ando H et al. (2017) <i>J Pharmacol Toxicol Methods</i> 84: 111-127 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 GPA (2016) www.lisextra.org/hesi/science/cardiac/cipa/Project Wiśniewski 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 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, APD_{90, 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qN : integration sum of I_{CaL}I_{Kr}I_{Na}I_{Ks}I_{Na,K}I_{Na,C}, RMP : resting membrane potential, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{m,0} : maximal rate of AP rise, V_{m,1} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>	

Safe Cardiac Action Potential Test



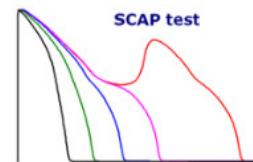
Drug	Alfuzosin		
α ₁ -adrenoceptor antagonist used to treat benign prostatic hypertrophy			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 199.5 μM (1.0) I _{to} : 1000.0 μM (1.0) I _{Kr} : 125.9 μM (1.0) I _{NaL} : --- μM (---) I _{Na} : 199.5 μM (1.0) I _{K1} : ---- μM (---) I _{Ks} : 125.9 μM (1.0)	EFTPC_{max}⁽¹⁾ 0.00463 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible TdP risk (class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/3 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	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} $I_j = g_j(V - E_{j,0})$ $\frac{g_j}{g_{j,control}} = \left[1 + \left(\frac{D}{IC_{50s}}\right)^n\right]^{-1}$ where g _j = maximal conductance of channel j V = voltage membrane E _{j,0} = reversal potential for species of ions which flows through channel j D = drug concentration (EFTPC for example) n = half slope	TDR and RUD estimation: • TDR = APD _{90,mid} - APD _{90,epi} (at CL of 1000 msec) • RUD = APD _{90,epi} /APD _{90,mid} where APD _{90,P} = APD ₉₀ with - APD ₉₀ without compound at CL x
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	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 midmyocardial myocytes 		
	Human endocardial myocytes 		
	Summary 		
	References 1. Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 70 :246-254 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.pharmaextraction.com/science/cardiac/cipa/Project 6. Wirschniak B et al. (2013) <i>Drug discovery today</i> 22 : 10-16 7. O'Hera 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 _{90,xx-xx} : AP duration at 40, 60 or 90 % of APA, APD _{xx} : APD prolongation, aau : arbitrary unit, CL : cycle lenght, DA : degenerarion abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, ende : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNef : integration sum of I _{NaL} , I _{Kr} , I _{Na} , I _{K1} , I _{Ks} , RMP : resting membrane potential, APA _{xx} : APD _{xx} -APD ₄₀ or APD _{xx} ("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



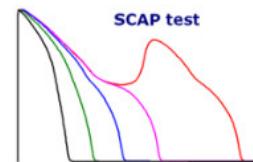
Drug	Almokalant		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	I_{CaL} : ---- μM (---) I_{Kr} : 3.66 μM (1.16) I_{Na} : ---- μM (---) I_K : ---- μM (---)		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	Simulation conditions: • Cell geometry, channel conductance, state variables and scaling factors for endo-, mid- and epicardial myocytes as described in ORD model • External ionic concentrations (mM): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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} $I_j = g_j(V - E_{jon})$ $E_{jon} = V_{rest} + \frac{g_{max}}{g_{max} + g_j} V_{infty}$ V_{infty} = reversal potential for species of ions which flows through channel g_{max} = maximal conductance of channel j = index of channel $g_j = 50\% \text{ inhibition of a drug for channel}$ IC_{50s} = 50% of inhibition of a drug for channel D = drug concentration ($EFTPC$ for example) x = full slope	TDR and RUD estimation: • TDR = $APD_{50, mid} - APD_{50, epi}$ (at CL of 1000 msec) • RUD = $APD_{50, Endo} - APD_{50, Mid}$ where $APD_{50, x} = APD_{50}$ with - APD_{50} without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes <ul 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 midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary			
References	1. Abi-Gerges N et al. (2011) <i>Br J Pharmacol</i> , 164 : 419-432 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.Isliefta.org/hesi/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		
Abbreviations	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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL} , I_{Kr} , I_{Na} , I_K , I_{NaP} , RMP : resting membrane potential, RUD : reverse use dependence, $T_{APD, 40}$: $APD_{40} - APD_{40}$ or APD_{40} ("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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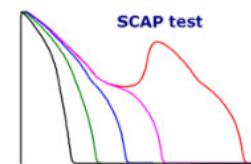
Drug	Alvimopan		
	μ -opioid receptor antagonist used to avoid postoperative ileus		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 5.012 \mu M (1.0)$ $I_{Kr} : 794.3 \mu M (1.0)$ $I_{Na} : 251.2 \mu M (1.0)$ $I_{Ks} : 50.12 \mu M (1.0)$	$I_{to} : \text{--- } \mu M (---)$ $I_{NaL} : \text{--- } \mu M (---)$ $I_{Kt} : \text{--- } \mu M (---)$	$0.01049 \mu M$ Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : not reported
	<i>In silico</i> 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} $I_f = g_f(V - E_{on})$ $g_f = g_{max} \cdot \frac{1}{1 + \left(\frac{V - V_{on}}{IC_{50s}}\right)^n}$ V_{on} = reversal potential for species of ions which flows through channel g_{max} = maximal conductance of channel n = slope of the sigmoidal curve of conductance of channel IC_{50s} = 50% of inhibition of a drug for a channel D = drug concentration (BP = EFTPC for example) in half-lapse 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{50, mid} - APD_{50, epi}$ (at CL of 1000 msec) $RUD = APD_{50, Endo} - APD_{50, Mid}$ where $APD_{50, P_i} = APD_{50}$ with - APD_{50} without compound at CL x IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks} , I_{NaL} and I_{CaL} .
Results	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p>		
	<p>Human midmyocardial myocytes</p>		
	<p>Human endocardial myocytes</p>		
	<p>Reverse use dependence on midmyocardial myocytes</p>		
Summary	<p>Alvimopan x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Alvimopan x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Effect (%)</p> <p>www.scaptest.com</p>		
	<p>Alvimopan Value (mV) vs. IC index (a.u.)</p> <p>Value (mV)</p> <p>www.scaptest.com</p>		
References	<ol style="list-style-type: none"> Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 70: 246-254 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Wooles RL (2015) www.CredibleMeds.org GPA (2016) www.Isliestra.org/heis/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 		
Abbreviations	<p>AP : action potential, APA : AP amplitude, $APD_{50, 40, 60, 90}$: 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{Kr}, I_{NaL}, I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 50}$: $APD_{50, Endo}$ or $APD_{50, Mid}$ ("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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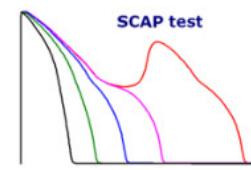
Drug	Ambrisentan		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 2511.9 \mu M (1.0)$ $I_{Na} : 251.2 \mu M (1.0)$ $I_Kr : 501.2 \mu M (1.0)$ $I_{NaL} : \text{---- } \mu M (\text{---})$ $I_{Na} : 1258.9 \mu M (1.0)$ $I_K1 : \text{---- } \mu M (\text{---})$ $I_Ks : 501.2 \mu M (1.0)$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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} $I_f = g_f(V - E_{f,0})$ (g_f: maximal conductance of channel f; V: membrane potential; $E_{f,0}$: reversal potential for species of ions which flows through channel f) $\beta_f = \frac{g_f}{g_f(\text{control})} = \left[1 + \left(\frac{\delta}{IC_{50s}}\right)^n\right]^{-1}$ (δ: drug concentration; n: slope of inhibition curve; IC_{50s}: 50% of inhibition of a drug for a channel f) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{50, \text{mid}} - APD_{50, \text{epi}}$ (at CL of 1000 msec) $RUD = APD_{50, \text{Epi}} - APD_{50, \text{Mid}}$ where $APD_{50,P_i} = APD_{50}$ with - APD_{50} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr / (AFNaL + AFCaL)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.</p>	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p> <p>Legend for plots: 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 midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Summary</p> <p>Effect (%)</p> <p>References</p> <ol style="list-style-type: none"> Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 70: 246-254 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Wooles RL (2015) www.CredibleMeds.org GPA (2016) www.Isliestra.org/hesi/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, $APD_{40, 60, 90}$: AP duration at 40, 60 or 90 % of APA, APD₅₀ : AP 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 $I_{CaL} + I_{NaL} + I_{Ks} + I_{K1}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{epi, 40}$: $APD_{40} - APD_{40}$ ("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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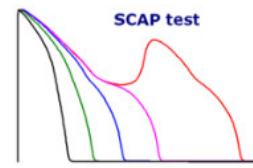
Drug	Amiodarone			
	Non-selective ionic channel blocker used as Class III antiarrhythmic to treat ventricular tachycardia			
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk	
	$I_{CaL} : 1.9 \mu M (0.69)$ $I_{Kr} : 0.86 \mu M (1.09)$ $I_{Na} : 15.9 \mu M (0.97)$ $I_Ks : --- \mu M (---)$	$I_{Na} : --- \mu M (---)$ $I_{Kr} : --- \mu M (---)$ $I_{CaL} : --- \mu M (---)$ $I_Ks : --- \mu M (---)$	$EFTPC_{max}$ ⁽¹⁾ 0.0008 μM	Redfern ⁽²⁾ : large but acceptable TdP risk (class 1) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 11/2 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	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): $[Na^+]_o = 140$, $[Ca^{2+}]_o = 1.8$, $[K^+]_o = 5.4$ 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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ $g_f = g_{f,0} \cdot \frac{1}{1 + \left(\frac{D}{IC_{50f}}\right)^n}$ $g_{f,0}$ = maximal conductance of channel f $E_{f,0}$ = reversal potential of species f which flows through channel f D = drug concentration (e.g. $100 \times EFTPC$ for example) n = half slope 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{mid} - APD_{epi}$ (at CL of 1000 msec) $RUD = APD_{endo} - APD_{epi}$ where $APD_{endo} = APD_{endo}$ without compound at CL x IC index calculation⁽⁹⁾: $IC\ index = (AFKr \cdot (AFNaL + AFCaL)/2) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr} , I_{NaL} and I_{CaL} in full slope	
	Human epicardial myocytes 			
	Transmural dispersion of repolarisation 			
	Reverse use dependence on midmyocardial myocytes 			
Summary	Human midmyocardial myocytes 			
	Human endocardial myocytes 			
References	<p>1. Kramer et al. (2013) <i>Science Reports</i> 3: 2100 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</p>			
	<p>4. Woosley RL (2015) www.CredibleMeds.org 5. GPa (2016) www.Isiextra.org/hesi/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, $APD_{40, 60, 90, 99}$: AP duration at 40, 60 or 90 % of APA, APD_{90} : 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{NaL} + I_{NaP} + I_K$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 40}$: $APD_{40} - APD_{40}$ or $APD_{90} - APD_{90}$ ("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</p>			

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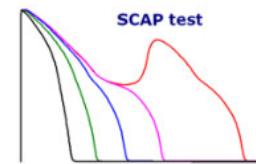
Drug	Amitriptyline Serotonin and noradrenaline reuptake inhibitor used to treat depressive illness		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	<p>I_{CaL}: 1.291 μM (1.0) I_{to}: 2.543 μM (0.4) I_{Kr}: 3.660 μM (1.0) I_{NaL}: 4.433 μM (0.5) I_{Na}: 5.760 μM (1.3) I_{K1}: ---- μM (---) I_{ks}: 2.737 μM (0.5)</p>		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ $g_f = g_{max} \cdot \min\left(1 + \left(\frac{D}{IC_{50s}}\right)^n, 1\right)$ D = open probability of channel V = membrane potential $E_f,0$ = reversal potential for species of ions which flows through channel IC_{50s} = 50% of inhibition of a drug for a channel D = drug concentration (EFTPC for example) in nM 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90,endo} - APD_{90, mid}$ where $APD_{90,P_i} = APD_{90}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFK_r \cdot (AFNaL_r + AFCaL_r)/2) * 100$ <p>where AFK_r, AFNaL_r and AFCaL_r = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL} in full scope</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>Human endocardial myocytes</p> <p>Summary</p> <p>Effect (%)</p> <p>AP/ADP₉₀ (msec)</p> <p>IC index (msec)</p>
References	<p>1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 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. GIPA (2016) www.IsiExtra.org/hesi/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, $APD_{90, 40, 60, 90}$: AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, au. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPCmax : 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 $i_{CaL} \cdot t_{CaL} + i_{NaL} \cdot t_{NaL} + i_{Ks} \cdot t_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{dp, 40}$: $APD_{90} - APD_{40}$ 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</p>		

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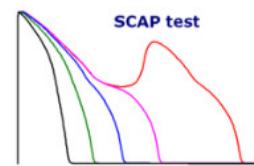
Drug	Amlodipine		
	L-type Ca ⁺⁺ channel (Ca _v 1.2) blocker used to treat hypertension or angina		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : 0.315 μM (1.00) I_{to} : ---- μM (---) I_{Kr} : 2.600 μM (1.33) I_{NaL} : ---- μM (---) I_{Na} : 5.942 μM (1.00) I_{K1} : ---- μM (---) I_{Ks} : 5.900 μM (1.65)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.105 μM</p>	<p>TdP risk</p> <p>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⁾ : 0/2 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 full inhibition which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_f = g_f (V - E_{\text{rest}})$ $g_f = g_{\text{control}} f \left[1 + \left(\frac{f}{IC_{50s}} \right)^{-1} \right]$ <p>g_f = intrinsic conductance of ion which flows through channel f V = voltage membrane g_{control} = reversal potential species of ion which flows through channel f f = drug concentration (EFTPC for example) IC_{50s} = 50% of inhibition of drug f channel TDR = Transmural dispersion of repolarisation</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀epi (at CL of 1000 msec) RUD = APD₉₀endo-APD₉₀mid where APD₉₀P = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (APKr / ((AFNaL + AFCaL)/2)) * 100 where AFKz, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in all sites</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>Human endocardial myocytes</p>		
	<p>Summary</p>		
References	<p>1. Passini E et al. (2019) Br J Pharmacol 176: 3819–3833 2. Redfern WS et al. (2003) Cardiovasc. Res. 58: 32–45 3. Kramer J et al. (2013) Sci. rep. 3: 2100</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.ilsexta.org/hses/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) Drug discovery today 22: 10–16</p> <p>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</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₉₀ : AP duration at 90%, APD₉₀ : AP duration at 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_{NaL}+I_{Kr}+I_{NaL}+I_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₆₀ : APD₉₀-APD₉₀ or APD₉₀ ("triangulation"), TDR : 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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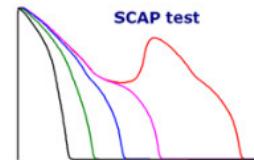
Drug	Aspirin				
Cyclooxygenase COX-1 and COX-2 inhibitor used to treat pain, fever, inflammation, migraine, or to prevent adverse cardiovascular events no longer marketed in UK, US, Hong Kong, Nigeria and Spain (Onakpoya et al (2016) <i>BMC Med</i> 14: 10)					
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: --- μM (---) I_{to}: --- μM (---) I_{Kr}: 100000 μM (1.0) I_{NaL}: --- μM (---) I_{Na}: --- μM (---) I_{K1}: --- μM (---) I_K: --- μM (---)</p>	<p>$EFTPC_{max}$⁽¹⁾</p> <p>7.7 μM</p>	TdP risk		
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾					
Results	<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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 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} $I_j = g_j O(V - E_{in})$ $\theta_j = \theta_{control} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ <p>where g_j: maximal conductance of channel⁽⁹⁾ O: open probability of channel⁽⁹⁾ V: membrane potential (mV) E_{in}: reversal potential for species of ions which flows through channel⁽⁹⁾ D: drug free maximal conductance of channel⁽⁹⁾ IC_{50s}: 50% inhibition concentration (RTD₅₀ for example) n: Hill slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $APD_{90, mid} = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, Epi}/APD_{90, mid}$ where $APD_{90, P_i} = APD_{90}$ with - APD_{90} 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_{Ko}, 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>Legend: 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>Aspirin x-fold $EFTPC_{max}$ vs. IC_{50s}</p> <p>www.scapttest.com</p>				
References	<p>1. Ugoz-Lorente J et al. (2020) <i>J Chem Inf Model</i> 60: 5172-5187 2. Redfern WS et al. (2003) <i>Cardiovasc Res</i> 57: 32-45 3. Kramer J et al. (2013) <i>Sci Rep</i> 3: 2100</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Icextra.org/heis/science/cardiac/cipa/Project 6. Widerńska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>7. O'Hara T et al. (2013) <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, $APD_{40, 60 \text{ or } 90}$: 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNET : integration sum of I_{CaL}, I_{NaL}, I_{K1}, I_K, I_{Na}, I_{Ca}, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 60}$: $APD_{90, 60}$ or APD_{90} ("triangulation"), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : membrane voltage, V_{min} : minimal rate of AP rise, V_{off} : volt per second</p>				

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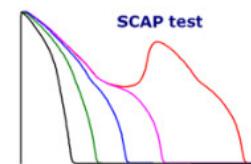
Drug	Astemizole		
	Histamine H ₁ -receptor antagonist used to treat allergy symptoms no longer marketed worldwide (onakpoya et al (2016) BMC Med. 14: 10)		
Raw data	IC _{50s} (slope) ⁽¹⁾ I _{CaL} : 1.1 μM (1.66) I _{Kr} : 0.004 μM (0.78) I _{NaL} : 3.0 μM (1.95) I _{Ks} : --- μM (---)		EFTPC _{max} ⁽¹⁾ 0.0003 μM
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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 10 (full inhibition) which is a function of a multiple of EFTPC_{max} and IC_{50s} $I_j = g_j O(V - E_{in})$ $\delta_j = g_{j,0} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ <p>g_j = maximal conductance of channel j O = open probability of channel j E_{in} = reversal potential for species of ions which flows through channel j g_{j,0} = drug-free maximal conductance of channel j D = drug concentration (0% to 100% for example) n = hill slope</p>
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes
	Human endocardial myocytes 		
	Summary 		
References	1. Kramer J et al. (2013) Sci. rep. 3: 2100 2. Redfern WS et al. (2003) Cardiovasc. Res. 58: 32-45 3. Kramer J et al. (2013) Sci. rep. 3: 2100 4. Worsley PL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Illustra.org/scientific/cardiac/cipa/Project 6. Winiarska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hearn T et al. (2014) PLoS Comput. Biol. 10: e1002861 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	AP : action potential, APA : AP amplitude, APD _{40,60 or 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 _{NaL} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{dp} : APD ₉₀ -APD ₅₀ or APD ₉₀ (triangulation), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{slope} : minimal rate of AP decrease at EAD take-off voltage, V _{slope} : volt per second		

Safe Cardiac Action Potential Test



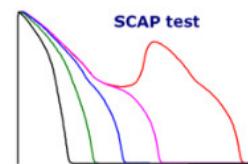
Drug	Atenolol				
	β_1 -adrenoceptor antagonist used to treat hypertension or chronic angina				
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk		
	I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 1500 μM (0.92) I_{Na} : --- μM (---) I_{Na} : --- μM (---) I_K : --- μM (---) I_K : --- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 1.156 μM	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/1 (TdP+/TdP-) not reported		
	<i>In silico</i> 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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 5.4 • Cycle length : 1000 msec • Beat number: 100	Effect of drugs on AP⁽⁸⁾: • Cell 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} $I_j = g_j(V - E_{jon})$ g_j = maximal conductance of channel E_{jon} = reversal potential of species of ions which flows through channel V_m =voltage membrane IC_{50s} = 50% of inhibition of a drug for a channel D = drug concentration (EF TPC_{max} for example) x = half slope	TDR and RUD estimation: • TDR = $APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) • RUD = $APD_{90, Epi}/APD_{90, Endo}$ where APD_{90, P_i} = APD_{90} without compound at CL x		
Results	Human epicardial myocytes 	Transmural dispersion of repolarisation 			
	Human midmyocardial myocytes 	Reverse use dependence on midmyocardial myocytes 			
	Human endocardial myocytes 				
Summary					
References	1. Passini E et al. (2019) Br J Pharmacol 176 : 3819–3833 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. CiPA (2016) www.pharmcentral.org/hes/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) Drug discovery today 22 : 10–16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7 : e1002061 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, $APD_{40, 60, 90, 99}$: AP duration at 40, 60 or 90 % of APA, APD_P : AP 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL} , I_{Na} , I_{Kr} , I_{NaP} , I_K , RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 90}$: APD_{90} - 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



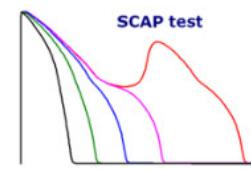
Drug	Azimilide		
Slow and rapid delayed rectifier K ⁺ voltage-gated (K _v 7.1 and K _v 11.1) channel blocker under clinical trials as Class III anti-arrhythmic (in USA , Drugbank on line)			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 0.4 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : --- μM (---) I_{K1} : --- μM (---) I_{Ks} : --- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.072 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : large but acceptable TdP risk (class 1) Kramer⁽³⁾ : not reported CredibleMeds⁽⁴⁾ : not reported but under review CIPA⁽⁵⁾ : high risk (class 1) WP⁽⁶⁾ : 6/0 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORD model)⁽⁷⁾			
Results	<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 and IC_{50s} $I_f = g_o(V - E_{f,0})$ (instantaneous conductance of channel) $P_{on} = \frac{1}{1 + \left(\frac{V - V_{50}}{IC_{50s}}\right)^n}$ (open probability of channel) V_{50} = reversal potential for species of ions which flows through channel IC_{50s} = 50% of inhibition of a drug for a channel IC_{50s} = 50% of inhibition of a drug for a channel IC_{50s} = drug concentration (BP) for example <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{90, mid} - APD_{90, epi} (at CL of 1000 msec) RUD = APD_{90, mid} - APD_{90, endo} where APD_{90, x} = APD₉₀ with - APD₉₀ 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} in full range</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> <p>Summary</p>	<p>References</p> <ol style="list-style-type: none"> Yamasaki et al. (2018) <i>J Pharmacol Sci</i>, 136: 249-256 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woolesley RL (2015) www.CredibleMeds.org GPA (2016) www.Ilextra.org/hesi/science/cardiac/cipa/project Winirowska 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 <p>Abbreviations</p> <p>AP : action potential , APA : AP amplitude, APD_{90, 40 or 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{EP} : APD₉₀-APD₄₀ 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



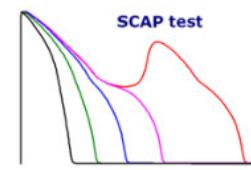
Drug	Azithromycin		
	Macrolide antibiotic used to treat a variety of bacterial infections		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : 88.764 μM (0.5) I_{Kr} : 70.796 μM (0.5) I_{NaL} : 189.128 μM (1.9) I_{Na} : --- μM (---) I_{K1} : --- μM (---) I_{Ks} : 470.131 μM (1.4)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>1.937 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⁾ : 5/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 and IC_{50s} $I_g = g_o(V - E_{\text{onset}})$ $\text{g} = \text{g}_{\text{max}} \cdot \text{probabilistic of channel}$ V=membrane potential E_{onset}= reversal potential for species of ions which flows through channel $g_{\text{max}} = \text{maximal conductance of channel}$ IC₅₀= 50% of inhibition of a drug for a channel D=drug concentration (EFTPC for example) <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{endo}-APD_{apo} where APD_{endo}=APD_{endo}with - APD_{endo}without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full range</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> <p>Summary</p> <p>Azithromycin x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Effect (%) - APD₉₀ - APD₅₀ (msec)</p> <p>IC index (a.u.)</p>	<p>1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 2. Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58: 32-45 3. Kramer J et al. (2013) <i>SciRep</i> 3: 2200 4. Woosley RL (2015) www.CredibleMeds.org 5. GPA (2016) www.Icteria.org/hscl/science/cardio/cipa/Project 6. Winirowska 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 (2013) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p> <p>References</p> <p>Abbreviations</p> <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_{to}*I_{NaL}*I_{K1}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP} : APD₉₀-APD₅₀ or APD₉₀ ("triangulation"), TDR : torsade de pointes , TDP : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{slope} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>

Safe Cardiac Action Potential Test



Drug	<p style="color: red; font-size: 1.5em;">Bepridil</p> <p>L-type Ca^{++} channel ($\text{Ca}_{v1.2}$) blocker used to treat angina and hypertension no longer marketed in USA (Onakpoya et al (2016) <i>BMC Med.</i> 14: 10)</p>		
Raw data	<p>IC_{50} (slope)⁽¹⁾</p> <p>$I_{\text{CaL}} : 1.00 \mu\text{M} (1.28)$ $I_{\text{to}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Kr}} : 0.16 \mu\text{M} (0.88)$ $I_{\text{NaL}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Na}} : 2.30 \mu\text{M} (1.26)$ $I_{\text{K1}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Ks}} : \text{--- } \mu\text{M} (\text{---})$</p>	<p>$\text{EFTPC}_{\text{max}}$⁽¹⁾</p> <p>0.035 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : numerous reports of TdP (class 3) Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : known risk of TdP (class 1) CIPA⁽⁵⁾ : High risk (class 1) WP⁽⁶⁾ : 15/0 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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): $[\text{Na}^+]: 140 - [\text{Ca}^{++}]: 1.8 - [\text{K}^+]: 5.4$ 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 $\text{EFTPC}_{\text{max}}$ and IC_{50} $I_j = g_j O(V - E_{\text{rest}})$ $O = \frac{1}{1 + \left(\frac{V - V_{\text{rest}}}{IC_{50}}\right)^{-1}}$ $V_{\text{rest}} = \text{reverse potential for species of ions which flows through channel}$ $g_j = \text{maximal conductance of channel}$ $IC_{50} = 50\% \text{ of inhibition of a drug for channel}$ D= drug concentration (SF PC for example) in full slope 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $\text{TDR} = \text{APD}_{\text{mid}} - \text{APD}_{\text{epi}}$ (at CL of 1000 msec) $\text{RUD} = \text{APD}_{\text{endo}}/\text{APD}_{\text{mid}}$ where $\text{APD}_{\text{P}} = \text{APD}_{\text{endo}}$ with - APD_{endo} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = \text{AFKr}/((\text{AFKr} + \text{AFCaL})/2) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.</p>
	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p>		
	<p>Human midmyocardial myocytes</p>		
	<p>Human endocardial myocytes</p>		
Reverse use dependence on midmyocardial myocytes			
Summary	<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>		
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.ilsextre.org/heis/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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. Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 95: 15-26</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, $\text{APD}_{\text{40-90-90}}$: 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, $\text{EFTPC}_{\text{max}}$: 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 $i_{\text{NaL}} + i_{\text{Ks}} + i_{\text{Na}} + i_{\text{K1}}$, RMP : resting membrane potential, RUD : reverse use dependence, $\text{Ta}_{\text{40-APD90-APD90}}$ or $\text{Ta}_{\text{40-TdP}}$ ("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>		

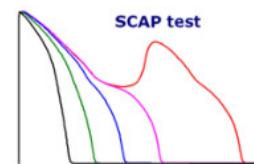
Safe Cardiac Action Potential Test



Drug	Ceftriaxone		
	Cephalosporin antibiotic used to treat various gram-negative bacterial infections		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 153.8 μM (1.0) I_{Ko} : ---- μM (---) I_{Kr}: 445.7 μM (1.0) I_{NaL} : ---- μM (---) I_{Na}: 555.9 μM (1.0) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>23.17 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not classified with TdP risk (class 4) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/3 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORd model)⁽⁷⁾		
Results	<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} $I_f = g_f(V - E_{\text{rest}})$ (V=membrane voltage) E_{rest}= reversal potential for species of ions which flows through channel g_f= maximal conductance of channel θ= scaling factor $\theta = \left(1 + \left(\frac{D}{EFTPC_{max}}\right)^n\right)^{-1}$ (D= drug concentration (EFTPC for example)) n=half slope <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p> <p>Summary</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{90, mid} - APD_{90, epi} (at CL of 1000 msec) RUD = APD_{90, Endo}-APD_{90, Mid} where APD_{90,P} = 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 AFGaL = active fraction (%) of the I_{Ko}, I_{NaL} and I_{CaL}.</p> <p>Human epicardial myocytes</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>References</p> <p>Abbreviations</p>	

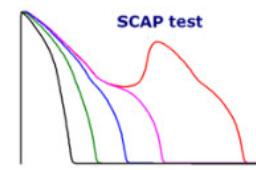
1. Kramer J et al. (2013) Sci. rep. **3**: 2100
2. Redfern WS et al. (2003) Cardiovasc. Res. **58**: 32-45
3. Kramer J et al. (2013) Sci. rep. **3**: 2100
4. Wooley RL (2015) www.CredibleMeds.org
5. CIPA (2016) www.Electra.org/hemis/science/cardiac/cipa/Project
6. Widłosińska B et al. (2017) Drug discovery today **22**: 10-16
7. O'Hearn T et al. (2011) PLoS Comput. Biol. **7**: e1002061-8
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- AP : action potential, APA : AP amplitude, APD_{90,e-w} : 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_{Ko}+I_{NaL}+I_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{end} : APD_{90, Endo}-APD_{90, Mid} ("triangulation"), TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_s : volt per second

Safe Cardiac Action Potential Test



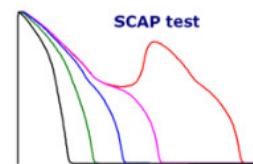
Drug	Cetirizine		
Histamine H ₁ receptor antagonist used to treat allergic rhinitis and chronic urticaria			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 240.0 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.056 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⁾ : 0/3 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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} $I_j = g_j(V - E_{jon})$ $\frac{g_j}{g} = \theta_{control} \left[1 + \left(\frac{\theta}{IC_{50s}} \right)^n \right]^{-1}$ <p>g = maximal conductance of channel j g_j = minimal conductance of channel j E_{jon} = reversal potential for species of ions which flows through channel j IC_{50s} = 50% of inhibition of a drug for channel j θ = drug concentration (EFTPC_{max} for example) n = half slope</p>	TDR and RUD estimation: • TDR = APD ₅₀ mid - APD ₅₀ epi (at CL of 1000 msec) • RUD = APD ₅₀ Endo - APD ₅₀ Mid where APD ₅₀ P ₀ = APD ₅₀ with - APD ₅₀ without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary			
References	1. Abi-Gerges N et al. (2011) Br J Pharmacol. 164 : 419-432 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. CIPA (2016) www.Isliefta.org/heis/science/cardiac/cipa/Project 6. Wiśniewska 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	AP : action potential, APA : AP amplitude, APD ₅₀ : AP duration at 50 % of APA, APD _{50,40,60} : AP duration at 40, 60 or 90 % of APA, APD ₅₀ 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 _{NaL} +I _{Kr} +I _{Na} +I _{K1} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{40,60} : APD ₅₀ -APD ₄₀ or APD ₅₀ -APD ₆₀ ("triangulation"), TdP : torsade de pointes , TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{m,Max} : maximal rate of AP rise, V _{m,Min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second		

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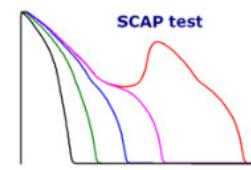
Drug	Chloroquine				
	Ferriprotoporphyrin IX complexing agent used to treat malaria no longer marked in Japan (Onakpoya et al (2016) <i>BMC Med.</i> 14 : 10)				
Raw data	IC _{50s} (slope) ⁽¹⁾ I _{CaL} : ---- μM (---) I _{Kr} : 6.889 μM (0.6) I _{NaL} : ---- μM (---) I _{K1} : 10.595 μM (0.8) I _{Ks} : ---- μM (---)	EFTP _{Cmax} ⁽¹⁾ 0.2495 μM	TdP risk Redfern ⁽²⁾ : isolated TdP reports (class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 3/3 (TdP+/TdP-)		
In silico cardiac action potential study (ORD model) ⁽⁷⁾					
Simulation conditions:	<p>Cell geometry, channel conductance, state variables and scaling factors for endo-, mid- and epicardial myocytes as described in ORD model</p> <p>External ionic concentrations (mM): [Na⁺]_o: 140 - [Ca²⁺]_o: 1.8 - [K⁺]_o: 5.4</p> <p>Cycle length : 1000 msec</p> <p>Beat number: 100</p>				
Results	<p>Human epicardial myocytes</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p>				
Summary	<p>Chloroquine x-fold EFTP_{Cmax} vs. IC_{50s}</p> <p>Chloroquine EAD at CL of 4000 msec</p>				
References	<p>1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 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 : www.Ilextra.org/hes/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>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, APD₉₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTP_{Cmax} : 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_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dP} : APD₉₀-APD₄₀ or APD₉₀ ("triangulation"), TDR : 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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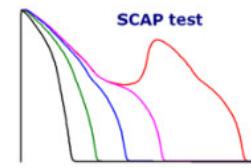
Drug	Chlorpheniramine		
	Histamine H ₁ -receptor antagonist used to treat upper respiratory allergies		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : ---- μM (---) I_{to} : ---- μM (---) I_{Kr} : 13.00 μM (1.00) I_{NaL} : ---- μM (---) I_{Na} : ---- μM (---) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.012 μM</p>	<p>TdP risk</p> <p>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⁾ : 0/2 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORd model)⁽⁷⁾		
Results	<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} <p>$I_j = g_j(V - E_{jon})$</p> <p>E_{jon} = reversal potential for species of ions which flows through channel^j</p> <p>g_j = maximal conductance of channel^j</p> <p>$\theta_j = \frac{g_j}{g_{j,control}}$</p> <p>$\theta_j = \left[1 + \left(\frac{\theta_j}{IC_{50s}}\right)^n\right]^{-1}$</p> <p>g = maximal conductance of channel^j</p> <p>θ = scaling factor for channel^j</p> <p>IC_{50s} = 50% of inhibition of a drug for channel^j</p> <p>D = drug concentration (EFTPC for example)</p> <p>n = half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀Endo - APD₅₀Mid where APD₅₀P_d = APD₅₀with - APD₅₀without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100</p> <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ks}, 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>		
	<p>Summary</p>		
References	<p>1. Llopis-Lorente J et al. (2020) <i>J Chem. Inf. Model</i> 60: 5172-5187 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.lsilextra.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, APD₅₀₋₉₀₋₉₀ : 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{Ks}+I_{NaL}+I_{CaL}+I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP-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, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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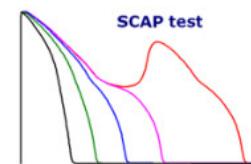
Drug	Chlorpromazine		
	Non selective dopamine and serotonin receptor antagonist used to treat nausea, vomiting, anxiety, schizophrenia and bipolar disorder		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 3.4 µM (1.73) I_{to} : ---- µM (---) I_{Kr}: 1.5 µM (1.4) I_{Na} : ---- µM (---) I_{Na}: 3.0 µM (1.14) I_{K1} : ---- µM (---) I_{Ks} : ---- µM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.038 µM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : numerous TdP reports (class 3) Kramer⁽³⁾ : torsadogenic drug (class 2) CredibleMeds⁽⁴⁾ : known risk of TdP (class 1) CIPA⁽⁵⁾ : intermediate risk (class 2) WP⁽⁶⁾ : 11/0 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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} $I_j = g_j(V - E_{jon})$ (V=membrane potential; E_{jon}= reversal potential for species of ions which flows through channel j) $\bar{g}_j = g_{j,control} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ (g_j= maximal conductance of channel j; D= drug concentration (EFTPC for example); n= half slope) IC_{50s} = 50% inhibition of a drug for a channel D= drug concentration (EFTPC for example) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{50, mid} - APD_{50, epi} (at CL of 1000 msec) RUD = APD_{50, Endo}-APD_{50, Mid} where APD_{50,P} = 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 AFGaL = active fraction (%) of the I_{Ks}, 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> <p>Summary</p>
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.ilsexta.org/hes/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. 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 _{50, 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 _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{K1} +I _{Ks} +I _{NaL} +I _{CaL} , RMP : resting membrane potential, RUD : reverse use dependence, T _{90, 50} : APD ₅₀ -APD ₉₀ or APD ₅₀ (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 /s : volt per second		

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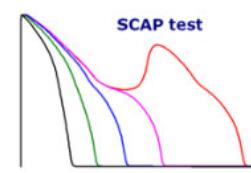
Drug	Cibenzoline		
	K _{ATP} channel (Kir 6.2) blocker used as Class IC antiarrhythmic to treat arrhythmia		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : --- μM (---) I _{Kr} : 2.097 μM (0.9) I _{Na} : 21.752 μM (1.2) I _{Ks} : --- μM (---) I _{to} : --- μM (---) I _{NaL} : 46.581 μM (0.6) I _{K1} : --- μM (---)	EFTPC_{max}⁽¹⁾ 0.673 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (Class 5) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/4 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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} $I_j = g_j(V - E_{j,0})^{1 - \frac{1}{1 + (\frac{g_j}{IC_{50s}})^n}}$ g _j = maximal conductance of channel E _{j,0} = reversal potential for species of ions which flows through channel IC _{50s} = 50% of inhibition of a drug for a channel n= drug concentration (EFTPC _{max} for example) x= full slope	TDR and RUD estimation: • TDR = AP _{mid} - AP _{Depi} (at CL of 1000 msec) • RUD = APD _{90mid} -APD _{90Depi} where APD ₉₀ =APD ₉₀ with - APD ₉₀ without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{CaL} and I _{CaL}
	Human epicardial myocytes Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary	 		
References	1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81 : 251-262 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.Illsieux.org/hsip/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		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{40, 60 or 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 _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{Kr} *I _{NaL} *I _{K1} *I _{CaL} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{dp} : APD ₉₀ -APD ₄₀ 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		

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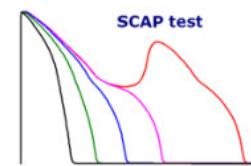
Drug	Cilostazol				
cAMP phosphodiesterase III (PDE _{3A}) inhibitor used as antiplatelet agent and vasodilator to treat intermittent claudication					
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 91.2 μM (1.0) I_{to} : ---- μM (---) I_{Kr}: 13.8 μM (0.91) I_{Na} : ---- μM (---) I_{Na}: 93.7 μM (1.0) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.128 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : known risk of TdP (class 1) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 3/0 (TdP+/TdP-)</p>		
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾					
Results	<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} $I_j = g_j(V - E_{jon})$ E_{jon} = reversal potential for species of ions which flows through channel g_j = maximal conductance of channel V = voltage membrane E_{50} = reversal potential for species of ions which flows through channel $IC_{50} = 50\% \text{ of inhibition of a drug for a channel}$ D_j = drug concentration (EFTPC for example) n = half slope $\theta_j = \theta_{control} \left[1 + \left(\frac{D_j}{IC_{50s}} \right)^n \right]^{-1}$	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀Endo - APD₅₀mid where APD₅₀P_i = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr / ((AFNaL + AFCaL)/2)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.</p>		
	<p>Human epicardial myocytes</p>				
	<p>Transmural dispersion of repolarisation</p>				
	<p>Human midmyocardial myocytes</p>				
Summary	<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>				
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Wooley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Ilextra.org/hsu/science/cardiac/cipa/Project 6. Włodziszka B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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>Pharmacol Toxicol Methods</i> 96: 15-26</p>				
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 $\int_{t_0}^{t_1} I_{Na} dt + \int_{t_0}^{t_1} I_{Ks} dt + \int_{t_0}^{t_1} I_{CaL} dt$, RMP : resting membrane potential, T_{AP} : AP duration, 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_s : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>				

Safe Cardiac Action Potential Test



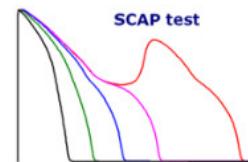
Drug	Ciprofloxacin		
	Fluoroquinolone antibiotic used to treat various bacterial infections		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 335.0 μM (1.00) I_{Na} : --- μM (---) I_{Na} : --- μM (---) I_K : --- μM (---) I_K : --- μM (---)</p>	<p>$EFTPC_{max}$ ⁽¹⁾</p> <p>12.072 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾ : isolated TdP reports (Class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : known TdP risk (Class 1) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 3/4 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 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} $I_j = g_j(V - E_{jon})$ $E_{jon} = V_{rest} + \frac{g_{max}}{g_{max} + g_{min}}(V - V_{rest})$ $E_{jrest} = V_{rest} + \frac{g_{min}}{g_{max} + g_{min}}(V - V_{rest})$ $\beta_j = \beta_{control} \left[1 + \left(\frac{\delta}{EFTPC_{max}} \right)^n \right]^{-1}$ $g_{max} = \text{maximal conductance of channel } j$ $g_{min} = \text{minimal conductance of channel } j$ $IC_{50s} = 50\% \text{ of inhibition of a drug for channel } j$ $\delta = \text{drug concentration (EFTPC for example)}$ $n = \text{half slope}$ <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>Human endocardial myocytes</p> <p>Summary</p>	<p>IC index calculation ⁽⁹⁾:</p> <p>IC index = $(AFKr/(AFNaL + AFCaL)/2) * 100$</p> <p>where</p> <p>AFKr, AFNaL and AFCaL = active fraction (%) of the I_K, I_{Na} and I_{CaL}.</p>	
References	<p>1. Passini E et al. (2019) <i>Br J Pharmacol</i> 176: 3819–3833 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.Isliefta.org/hesi/science/cardiac/cipa/ 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. 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, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPCmax : 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_{Na}, I_K, I_{Kr}, I_{NaP}, RMP : resting membrane potential, RUD : reverse use dependence, $TdP_{40,50}$: $APD_{40,50}$ or APD_{50} ("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



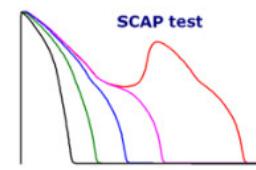
Drug	Cisapride		
	Serotonin 5-HT ₄ agonist used to treat gastroesophageal reflux disease no longer marketed worldwide (Onakpoya et al (2016) <i>BMC Med.</i> 14 : 10)		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 11.8 \mu M (1.0)$ $I_{Kr} : 0.02 \mu M (1.04)$ $I_{NaL} : 337.0 \mu M (1.0)$ $I_Ks : --- \mu M (---)$	$I_{To} : --- \mu M (---)$ $I_{NaL} : --- \mu M (---)$ $I_{K1} : --- \mu M (---)$	$0.003 \mu M$ <p>Redfern⁽²⁾ : unacceptable risk of TdP (class 2) Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : known risk of TdP (class 1) CIPA⁽⁵⁾ : intermediate risk of TdP (class 2) WP⁽⁶⁾ : 16/0 (TdP+/TdP-)</p>
Results	<i>In silico</i> 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} $I_j = g_j O(V - E_{in})$ $\delta_j = g_{control,j} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ <p>g_j = maximal conductance of channel j O = open probability of channel j E_{in} = reversal potential for species of ions which flows through channel j I_{rev} = reversal potential for species of ions which flows through channel j g_{control,j} = maximal conductance of channel j D = drug free maximal conductance of channel j n = Hill slope D = drug concentration (0% to 100% for example)</p>	TDR and RUD estimation: <ul style="list-style-type: none"> TDR = $APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) RUD = $APD_{90, mid}/APD_{90, epi}$ where $APD_{90,x} = APD_{90}$ with - APD₉₀ 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_{Kr} , I_{NaL} and I_{CaL} .
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	
	Human midmyocardial 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>
	Human endocardial myocytes 		
Summary			
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Ilsixtra.org/heis/science/cardiac/cipa/Project 6. Winirowska 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	AP : action potential, APA : AP amplitude, $APD_{90, 40/60/90}$: 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1}$, RMP : resting membrane potential, TdP : reverse use dependence, TE_{90} : $APD_{90} - APD_{40}$ or $APD_{90} - APD_{60}$ ("triangulation"), TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : volt per second		

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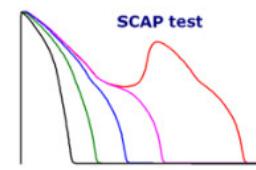
Drug	Citalopram		
	Serotonin reuptake (SSRI) inhibitor used to treat depression		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 38.0 μM (1.0) I_{to} : ---- μM (---) I_{Kr}: 1.1 μM (0.81) I_{NaL} : ---- μM (---) I_{Na}: 14.7 μM (1.0) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>$EFTPC_{max}$⁽¹⁾</p> <p>0.0271 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⁾ : 2/0 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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} $I_j = g_j(V - E_{jon})$ (j= maximal conductance of channel) E_{jon}= reversal potential for species of ions which flows through channel) E_{max}= maximum conductance of channel) E_{min}= minimum conductance of channel) IC_{50s}= 50% of inhibition of a drug for a channel) D= drug concentration (FEP_{max} for example) α= half slope <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, Endo} - APD_{90, Mid}$ where $APD_{90, P_i} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr / ((AFNaL + AFCaL)/2)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.</p>	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p>	<p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p>
Summary	<p>Citalopram x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Citalopram x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	1. Tox-Portal.com / PubChem 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. GIPA (2016) www.Isexta.org/hsic/science/cardiac/cipa/Project 6. Winiarska B et al. (2017) <i>Drug safety discovery</i> 22 : 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7 : e1002061_8 8. Mirans GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>Pharmacol Toxicol Methods</i> 96 : 25-26		
Abbreviations	AP : action potential , APA : AP amplitude, $APD_{90, mid, 90\%}$: 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, Endo : endocardial channel inhibition index, IC _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{to} + I_{NaL} + I_{K1} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, TE_{40-90} : $APD_{90} - APD_{40}$ 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		

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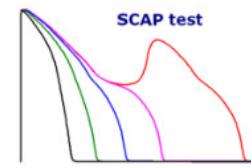
Drug	Clarithromycin				
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk		
	I_{CaL} : --- μM (---) I_Kr : 87.097 μM (1.0) I_{Na} : --- μM (---) I_Ks : --- μM (---)	I_{to} : --- μM (---) I_{NaL} : --- μM (---) I_K1 : --- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 4.011 μM	Redfern ⁽²⁾ : isolated TdP reports (class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : intermediate risk of TdP (class 2) WP ⁽⁶⁾ : 9/3 (TdP+/TdP-)	
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾				
Results	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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 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_{50} $I_j = g_j O(V - E_{on})$ $O = \frac{g_{max} (V - E_{on})}{g_{max} (V - E_{on}) + g_{min}}$ E_{on} = reversal potential for species of ions which flows through channel g_{max} = maximal conductance of channel V = voltage membrane E_{min} = reversal potential for species of ions which flows through channel IC_{50} = 50% of inhibition of a drug for a channel D = drug concentration (TFP for example) O = full slope	TDR and RUD estimation: • TDR = $APD_{50, mid} - APD_{50, epi}$ (at CL of 1000 msec) • RUD = $APD_{50, Endo} - APD_{50, Mid}$ where $APD_{50,P_i} = APD_{50}$ with - APD_{50} without compound at CL x		
	Human epicardial myocytes 	Transmural dispersion of repolarisation 			
	Human midmyocardial myocytes 				
	Human endocardial myocytes 				
	Reverse use dependence on midmyocardial myocytes 				
Summary					
References	1. Romano L et al. (2018) J Chem Inf Model. 58: 867-878 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.lisextra.org/heis/science/cardiac/cipa/Project 6. Wideniuska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hearn 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) Pharmacol Toxicol Methods 96: 15-26				
Abbreviations	AP : action potential, APA : AP amplitude, APD _{50-90%} : 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 $I_{CaL} + I_{Na} + I_{to} + I_{NaL} + I_{Ks}$, RMP : resting membrane potential, V _{max} : minimal rate of AP decrease at EAD take-off voltage, V _s : volt per second				

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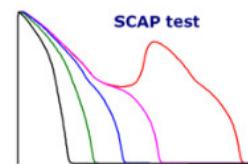
Drug	Clozapine		
Non-selective monoamine receptor (5-HT ₂ , D ₂ , α ₁ , β ₂ and H ₁) antagonist used to treat schizophrenia and risk of suicide no longer marketed in Finland, Singapore and Norway (Onakpoya et al (2016) BMC Med 14: 10)			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 3.6 μM (1.0) I _{Ko} : ---- μM (---) I _{Kr} : 2.3 μM (0.97) I _{NaL} : ---- μM (---) I _{Na} : 15.1 μM (1.14) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.071 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : possible risk of TdP (class 2) CiPA ⁽⁵⁾ : intermediate risk of TdP (class 2) WP ⁽⁶⁾ : 4/3 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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} $I_j = g_j O(V - E_{j,0})$ $\theta_j = \theta_{control,j} \left[1 + \left(\frac{D}{EFTPC_{max}} \right)^n \right]^{-1}$ <p>g_j= maximal conductance of channel j O= open probability of channel j D= drug concentration (μM) E_{j,0}= reversal potential for species of ions which flows through channel j n= drug free maximal conductance of channel j D= 50% of inhibition of drug for channel j D= drug concentration (μM) for example n= hill slope</p>	TDR and RUD estimation: • TDR = APD ₉₀ mid - APD ₉₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ endo-APD ₉₀ epi where APD ₉₀ = APD ₉₀ without compound at CL x
Human epicardial myocytes Transmural dispersion of repolarisation 			
Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes <ul 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	1. Kramer J et al. (2013) Sci. rep. 3: 2100 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. GPA (2016) www.lslextre.org/hes/science/cardiac/cipa/Project 6. Wiśniewska 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 (2013) J Pharmacol Toxicol Methods 66: 15-26		
Abbreviations	AP: action potential, APA: AP amplitude, APD ₄₀ to 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, epo: epicardial myocyte, IC index: ion channel inhibition index, IC _{50s} : 50% inhibition concentration, mid: midmyocardial myocyte, msec: millisecond, mV: millivolt, qNaL: integration sum of I _{NaL} +I _{K1} +I _{Ks} +I _{Kr} +I _{CaL} , RMP: resting membrane potential, RUD: reverse use dependence, 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 /s: volt per second		

Safe Cardiac Action Potential Test



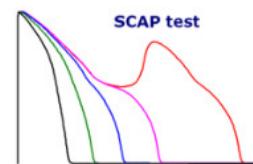
Drug	Darifenacin		
	Muscarinic M ₃ antagonist used to treat urinary incontinence		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 1584.9 μM (1.0) I_{to}: 12.59 μM (1.0) I_{Kr}: 0.079 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: 1.585 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: 19.95 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.00136 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⁾		
Results	<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} $I_j = g_j(V - E_{jon})$ (V=membrane voltage, E_{jon}= reversal potential for species of ions which flows through channel) $\bar{g}_j = g_j \left(1 + \left(\frac{D}{IC_{50s}}\right)^n\right)^{-1}$ (g_j= maximal conductance of channel j, D= drug concentration, n= slope of inhibition curve, IC_{50s}= 50% of inhibition of a drug for channel j) IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀P_{endo}-APD₅₀P_{endo} where APD₅₀P_e = APD₅₀with - APD₅₀without compound at CL x 	<p>Transmural dispersion of repolarisation</p> <p>Human epicardial myocytes</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial 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>Summary</p> <p>Graph showing Effect (%) vs AP parameters (RMP, APA, V_{max}, APD₅₀, APD₉₀, T_{dp}, T_{dp}, qNet, TDR) for Darifenacin at various concentrations (no drug, x3, x10, x30, x100).</p> <p>Graph showing APD₅₀ - APD₉₀ (msec) vs IC Index (μM) for Darifenacin, showing EAD at CL of 4000 msec.</p>
References	<p>1. Mirams GR et al. (2014) J.Pharmacol.Tox.Methods 70: 246-254 2. Redfern WS et al. (2003) Cardiovasc. Res. 52: 32-45 3. Kramer J et al. (2013) Circ. Res. 112: 2100 4. Woodley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Icextra.org/hsu/science/cardiac/cipa/Project 6. Wisiowska 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 (2013) J Pharmacol Toxicol Methods 65: 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{K1}+I_{Kr}+I_{NaL}+I_{Na}+I_{CaL}, RMP : resting membrane potential, T_{dp} : torsade de pointes , TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{slope} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



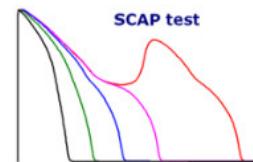
Drug	Darunavir		
HIV protease inhibitor used to treat human immunodeficiency virus (HIV) infection			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{Kr} : 158.5 μM (1.0) I _{Na} : 39.81 μM (1.0) I _{Ks} : 316.2 μM (1.0) EFTPC_{max}⁽¹⁾ 0.46338 μM	EFTPC_{max}⁽¹⁾ 0.46338 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : not reported
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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} $I_j = g_j(V - E_{jon})$ $\beta_j = \frac{g_j}{g_{j,control}} \left[1 + \left(\frac{\delta_j}{IC_{50s}} \right)^n \right]^{-1}$	TDR and RUD estimation: • TDR = APD _{50, mid} - APD _{50, epi} (at CL of 1000 msec) • RUD = APD _{50, Endo} -APD _{50, Mid} where APD _{50,P} = APD ₅₀ with - APD ₅₀ without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNal+AFCaL)/2)*100 where AFKr, AFNal, and AFGaL = active fraction (%) of the I _{Kr} , I _{Nal} , and I _{CaL} .
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
		Reverse use dependence on midmyocardial myocytes 	
Summary			
References	1. Mirams GR et al. (2014) J Pharmacol. Tox Methods 70: 246-254 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. CIPA (2016) www.Isliefta.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061 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	AP : action potential, APA : AP amplitude, APD _{50, 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 _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{Kr} +I _{Nal} +I _{Na} +I _{CaL} , RMP : resting membrane potential, RUD : reverse use dependence, T _{AP} : APD ₅₀ -APD ₄₀ or APD ₅₀ ("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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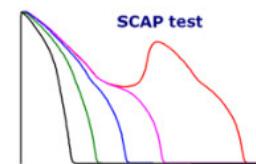
Drug	Dasatinib		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 81.1 \mu M (1.0)$ $I_{Kr} : 24.5 \mu M (1.16)$ $I_{Na} : 76.3 \mu M (1.43)$ $I_Ks : \text{---} \mu M (\text{---})$ $I_{to} : \text{---} \mu M (\text{---})$ $I_{NaL} : \text{---} \mu M (\text{---})$ $I_{K1} : \text{---} \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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} $I_j = g_j(V - E_{jon})$ (j= maximal conductance of channel) E_{jon}= reversal potential for species of ions which flows through channel) $\theta = \theta_{control} \left[1 + \left(\frac{\theta}{IC_{50s}} \right)^n \right]^{-1}$ (θ= maximal conductance of channel) IC_{50s}= 50% of inhibition of a drug for a channel) n= drug concentration (EFTPC for example) $\theta_{control}$: no slope 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, Endo} - APD_{90, Mid}$ where $APD_{90, P_i} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, 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>Legend: 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> <p>Dasatinib x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Dasatinib</p>
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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. GPa (2016) www.IsiExtra.org/hesi/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 : e1002618 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, $APD_{90, 40-90}$: 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, ende : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, Tdp_{90} : $APD_{90} - APD_{40}$ ("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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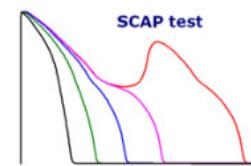
Drug	Deferasirox		
Iron chelator used to treat chronic iron overload caused by blood transfusions			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 1000.0 μM (1.0) I _{to} : 50.12 μM (1.0) I _{Kr} : 3981.1 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : 79.43 μM (1.0) I _{K1} : ----- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.995 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : not reported
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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} $I_j = g_j(V - E_{jon})$ $\frac{g_j}{g} = g_{jcontrol} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ <p>g = maximal conductance of channel E_{jon} = reversal potential for species of ions which flows through channel E_{rev} = reversal potential for species of ions which flows through channel IC_{50s} = 50% of inhibition of a drug for channel D = drug concentration (BP/PC for example) n = slope</p>	TDR and RUD estimation: • TDR = APD _{50, mid} - APD _{50, epi} (at CL of 1000 msec) • RUD = APD _{50, Endo} -APD _{50, Mid} where APD _{50,P} = APD ₅₀ with - APD ₅₀ without compound at CL x
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes
	Human endocardial myocytes 		
Summary	 		
References	1. Mirams GR et al. (2014) J Pharmacol. Toxicol. Methods 70: 246-254 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. CIPA (2016) www.Isliefta.org/heis/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061 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	AP : action potential, APA : AP amplitude, APD _{50, 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 _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{K1} +I _{NaL} +I _{Na} +I _{Kr} , RMP : resting membrane potential, RUD : reverse use dependence, T _{AP} : APD ₅₀ -APD ₄₀ or APD ₅₀ ("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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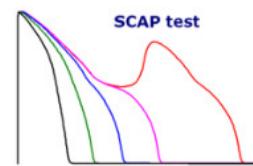
Drug	Desipramine		
	5-HT and noradrenaline reuptake inhibitor used to treat depression		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 1.709 \mu M (1.0)$ $I_{Kr} : 1.390 \mu M (1.0)$ $I_{Na} : 1.520 \mu M (1.0)$ $I_Ks : \text{---} \mu M (\text{---})$ $I_{to} : \text{---} \mu M (\text{---})$ $I_{NaL} : \text{---} \mu M (\text{---})$ $I_{K1} : \text{---} \mu M (\text{---})$	$0.108 \mu M$	Redfern ⁽²⁾ : isolated reports of TdP (class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible risk of TdP (class 2) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 3/6 (TdP+/TdP-)
Results	<i>In silico</i> 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} $I_j = g_j(V - E_{jon})$ $g_j = g_{j,control} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ $E_{j,control} = E_{j,control} + \frac{1}{2} \ln \left(\frac{g_{j,control}}{g_j} \right)$ $IC_{50s} = 50\% \text{ of inhibition of a drug for a channel}$ $D = \text{drug concentration (EFTPC for example)}$ $n = \text{half slope}$	TDR and RUD estimation: • $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) • $RUD = APD_{90, \text{endo}} - APD_{90, \text{mid}}$ where $APD_{90,D} = APD_{90}$ with - APD_{90} without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ where $AFKr, AFNaL$ and $AFCaL$ = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		Reverse use dependence on midmyocardial myocytes
Summary			
References	1. McMillan et al. (2017) <i>Tox. Rev.</i> 6 : 012-021. 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.intervra.org/hsis/science/cardiac/cipa/ Project. 6. Widońska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16. 7. O'Hearn T et al. (2011) <i>PLoS Comput. Biol.</i> 7 : e1003061. 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61. 9. Christophe B & Crumb WJ Jr (2019) <i>Pharmacol Toxicol Methods</i> 96 : 15-26.		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{90,90-90} : AP duration at 40, 50 or 90 % of APA, APD ₉₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPCmax : maximal effective free therapeutic plasma concentration, ende : endocardial myocyte, epi : epicardial myocyte, IC index : IC channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₅₀ : APD ₉₀₋₉₀ or APD ₅₀ ("triangulation"), TDR : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _s : volt per second		

Safe Cardiac Action Potential Test



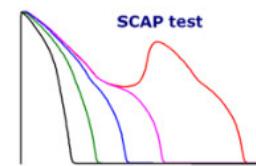
Drug	Desvenlafaxine		
	5-HT and noradrenaline reuptake inhibitor used to treat depression		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	I_{CaL} : $\text{--- } \mu\text{M} (\text{---})$ I_{Kr} : $251.19 \mu\text{M} (1.0)$ I_{Na} : $199.53 \mu\text{M} (1.0)$ I_K : $\text{--- } \mu\text{M} (\text{---})$ I_{Na} : $0.0 \mu\text{M} (\text{---})$ I_K : $0.0 \mu\text{M} (\text{---})$	$2.576 \mu\text{M}$	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
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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): $[Na^+]$: 140 - $[Ca^{2+}]$: 1.8 - $[K^+]$: 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_{50} $I_j = g_j(V - E_{jon})$ E_{jon} : reversal potential for species of ions which flows through channel g_j : maximal conductance of channel V : membrane potential E_{max} : reversal potential for species of ions which flows through channel IC_{50} : 50% of inhibition of a drug for a channel D: drug concentration (EFTPC for example) n: half slope	TDR and RUD estimation: • TDR = $APD_{50, \text{mid}} - APD_{50, \text{epi}}$ (at CL of 1000 msec) • RUD = $APD_{50, \text{endo}} - APD_{50, \text{mid}}$ where $APD_{50, P_i} = APD_{50}$ with - APD_{50} without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr} , I_{NaL} and I_{CaL} .
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary	Reverse use dependence on midmyocardial myocytes 		
References	1. Mirams GR et al. (2014) <i>J Pharmacol. Toxicol. Methods</i> 70: 246-254 2. Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 3. Kramer J et al. (2013) <i>Circ. Res.</i> 113: 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Ilextra.org/hsu/science/cardiac/cipa/ 6. Wisniowska 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 (2013) <i>J Pharmacol. Toxicol. Methods</i> 65: 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: 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, EFTPCmax : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Na} + I_K$, RMP : resting membrane potential, T_{AP50} : $APD_{50, \text{endo}} - APD_{50, \text{mid}}$ ("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



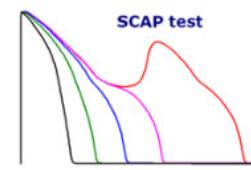
Drug	Diazepam				
Gamma aminobutyric acid (GABA _A) receptor antagonist used to treat panic disorders, severe anxiety, alcohol withdrawal and seizures					
Raw data	IC_{50s} (slope) ⁽¹⁾ I_{CaL} : 30.5 μM (0.89) I_{Ko} : ---- μM (---) I_{Kr} : 53.2 μM (1.07) I_{NaL} : ---- μM (---) I_{Na} : 306.4 μM (1.0) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 0.029 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/3 (TdP+/TdP-)		
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾					
Results	<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): $[Na^+]$: 140 - $[Ca^{2+}]$: 1.8 - $[K^+]$: 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} $I_j = g_j(V - E_{jon})$ (j= maximal conductance of channel) E_{jon}= reversal potential for species of ions which flows through channel⁽⁹⁾ $\beta_j = \beta_{control} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ (D= drug concentration (mM)) IC_{50s}= 50% of inhibition of a drug for a channel⁽¹⁰⁾ n= half slope 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, Endo} - APD_{90, Mid}$ where $APD_{90,P_i} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFKr / (AFNaL + AFCaL)/2) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ko}, 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>Diazepam x-fold EFTPC_{max} vs. IC_{50s}</p> <p>DIAZEPAM</p>	<p>DIAZEPAM</p>			
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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.Isliefta.org/hesi/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, $APD_{40, 60, 90}$: 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, ende : 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_{Kr}, I_{NaL}, I_{K1}, I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 60}$: $APD_{90, 60} - APD_{40}$ 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</p>				

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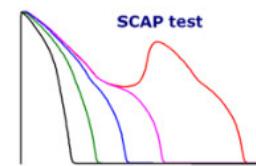
Drug	Diltiazem		
L-type slow Ca ⁺⁺ channel (Ca _v 1.2) blocker used to treat hypertension and chronic stable angina			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 0.76 μM (1.14) I _{Kr} : 13.2 μM (1.16) I _{Na} : 22.4 μM (1.29) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.122 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CIPA ⁽⁵⁾ : very low or no risk of TdP (class 3) WP ⁽⁶⁾ : 0/9 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	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 ⁺⁺] _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} $I_j = g_j(V - E_{jon})$ $E_{jon} = V_{rest} + \frac{RT}{4F} \ln \left(\frac{g_{max}}{g_j} \right)$ $\bar{g}_j = \text{maximal conductance of channel } j$ $V_{rest} = \text{resting membrane potential}$ $E_{jmax} = \text{reversal potential for species of ions which flows through channel } j$ $IC_{50} = 50\% \text{ of inhibition of a drug for a channel } j$ $D = \text{drug concentration (EFTPC for example)}$ $n = \text{half slope}$	TDR and RUD estimation: • TDR = APD _{90, mid} - APD _{90, epi} (at CL of 1000 msec) • RUD = APD _{90, Endo} -APD _{90, Mid} where APD _{90,P} = APD ₉₀ with - APD ₉₀ without compound at CL x
<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>Human endocardial myocytes</p>			
Summary	<p>Diltiazem</p>		
References	1. Kramer J et al. (2013) Sci. rep. 3: 2100 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. CIPA (2016) www.intervac.org/henri/science/cardio/cipa/Project 6. Widmowski B et al. (2017) Drug discovery today 22: 10-16 7. O'Hearn T et al. (2011) PLoS Comput. Biol. 7: e1003061-8 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 _{90,xx-xx} : 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 _{Ca,L} +I _{Kr} +I _{Na} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{dd} : APD ₉₀ -APD ₉₀ or APD ₉₀ ("triangulation"), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _s : volt per second		

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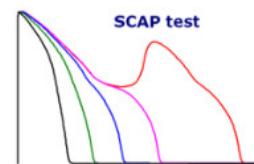
Drug	Diphenhydramine		
	Histamine H ₁ receptor antagonist used to treat seasonal allergies and various other allergic reactions		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 228.0 μM (1.0) I_{to} : ---- μM (--) I_{Kr}: 5.2 μM (1.0) I_{Na} : ---- μM (--) I_{Na}: 41.0 μM (1.0) I_{K1} : ---- μM (--) I_{Ks} : ---- μM (--)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.034 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⁾ : 3/5 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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> <p>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}</p> $I_j = g_j(V - E_{jon})$ <p>E_{jon} reversal potential for species of ions which flows through channel^j</p> $\beta_j = \frac{g_j}{g_{jcontrol}} \left[1 + \left(\frac{D_j}{IC_{50j}} \right)^n \right]^{-1}$ <p>g_j maximal conductance of channel^j E_{jon} reversal potential of channel^j IC_{50j} = 50% of inhibition of a drug for channel^j D_j drug concentration (EFTPC for example) n half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{50, mid} - APD_{50, epi} (at CL of 1000 msec) RUD = APD_{50, Endo}-APD_{50, Mid} where APD_{50, P} = 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 ACFaL = active fraction (%) of the I_{Ks}, 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>Human endocardial myocytes</p> <p>Summary</p> <p>Diphenhydramine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Diphenhydramine x-fold EFTPC_{max}, vs. IC_{50s}</p>
References	1. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 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.Isliefta.org/hesi/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. 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 _{50, 40-90} : AP duration at 40, 60 or 90 % of APA, APD ₅₀ : AP 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 _{Ks} +I _{NaL} +I _{CaL} +I _{K1} , RMP : resting membrane potential, RUD : reverse use dependence, T _{EP} : APD ₅₀ -APD ₄₀ or APD ₅₀ ("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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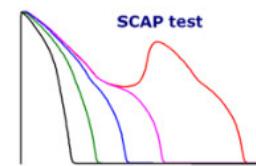
Drug	Disopyramide		
Raw data	IC_{50s} (slope) ⁽¹⁾ $I_{CaL} : 1036.7 \mu M (1.0)$ $I_{Kr} : 14.4 \mu M (0.91)$ $I_{Na} : 168.4 \mu M (1.09)$ $I_Ks : \text{--- } \mu M (\text{---})$	$EFTPC_{max}$ ⁽¹⁾ 0.742 μM	TdP risk Redfern ⁽²⁾ : large but acceptable TdP risk (class 1) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : high risk of TdP (class 1) WP ⁽⁶⁾ : 10/0 (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} $I_j = g_j(V - E_{jon})$ $E_{jon} = \text{ reversal potential for species of ions which flows through channel } j$ $g_j = \text{ maximal conductance of channel } j$ $\theta = \text{ reversal potential for species of ions which flows through channel } j$ $IC_{50s} = 50\% \text{ of inhibition of a drug for channel } j$ $D = \text{ drug concentration (EFTPC for example)}$ = full slope		TDR and RUD estimation: • $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) • $RUD = APD_{90, \text{endo}} - APD_{90, \text{mid}}$ where $APD_{90,P_i} = APD_{90,i}$ without compound at CL x
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>Human endocardial myocytes</p>		
Summary	<p>Disopyramide x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Disopyramide</p>		
References	1. Kramer J et al. (2013) Sci. rep. 3: 2100 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. CIPA (2016) www.intervac.org/hesi/science/cardiac/cipa/Project 6. Widłosińska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hearn T et al. (2011) PLoS Comput. Biol. 7: e1003061-8 8. Mirams GR et al. (2011) Cardiovasc. Res. 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 95: 1-26		
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{90, \text{endo}, \text{mid}, \text{epi}}$: AP duration at 40, 60 or 90 % of APA, APD ₉₀ : 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{Na} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{dP, \text{endo}}$: $APD_{90, \text{endo}} - APD_{90, \text{mid}}$, $T_{dP, \text{mid}}$: $APD_{90, \text{mid}} - APD_{90, \text{epi}}$, $T_{dP, \text{epi}}$: $APD_{90, \text{epi}} - APD_{90, \text{mid}}$, 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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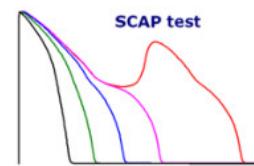
Drug	Dobutamine		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 55.147 \mu M (1.00)$ $I_{to} : \text{---- } \mu M (\text{---})$ $I_{Kr} : 15.0 \mu M (1.17)$ $I_{NaL} : \text{---- } \mu M (\text{---})$ $I_{Na} : 117.187 \mu M (1.00)$ $I_{K1} : \text{---- } \mu M (\text{---})$ $I_Ks : 53.571 \mu M (2.28)$		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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} $I_j = g_j O(V - E_{jon})$ $O = \frac{g_{max}}{g_{min}} \cdot \frac{V - V_{rev}}{V - V_{threshold}}$ $V_{rev} = \text{reversal potential for species of ions which flows through channel}$ $g_{max} = \text{maximal conductance of channel}$ $g_{min} = \text{minimal conductance of channel}$ $IC_{50s} = 50\% \text{ of inhibition of a drug or channel}$ $D = \text{drug concentration (EFTPC for example)}$ $n = \text{half slope}$	TDR and RUD estimation: • TDR = $APD_{50, mid} - APD_{50, epi}$ (at CL of 1000 msec) • RUD = $APD_{50, Endo} - APD_{50, Mid}$ where $APD_{50,P_i} = APD_{50,i}$ with - $APD_{50,i}$ without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	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	1. Passini E et al. (2019) Br J Pharmacol 176 : 3819–3833 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. GIPA (2016) www.iisextra.org/hesi/science/cardiac/gipa/Project 6. Wisiowska 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, $APD_{50, 40/60/90}$: 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of i_{CaL} , i_{Kr} , i_{NaL} , i_{Na} , i_{K1} , i_Ks , RMP : resting membrane potential, RUD : reverse use dependence, $TdP_{40/40}$: $APD_{50,40} - APD_{40,40}$ or $APD_{50,40}$ (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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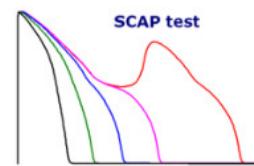
Drug	Dofetilide				
Potassium voltage-gated cardiac channel ($K_v11.1$) blocker used as class III antiarrhythmic to treat cardiac arrhythmia no longer marketed in Europe (Onalpoya et al (2016) <i>BMC Med.</i> 14 : 10)					
Raw data	IC_{50s} (slope) ⁽¹⁾ I _{CaL} : 26.7 μM (1.0) I _{to} : --- μM (---) I _{Kr} : 0.030 μM (1.2) I _{NaL} : --- μM (---) I _{Na} : 162.1 μM (1.0) I _{K1} : --- μM (---) I _{Ks} : --- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 0.002 μM	TdP risk Redfern ⁽²⁾ : class IA or III antiarrhythmics (class 1) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : high risk of TdP (class 1) WP ⁽⁶⁾ : 16/0 (TdP+/TdP-)		
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾					
Results	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 - $[Ca^{++}]$ _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 100 (full inhibition) which is a function of a multiple of EFTPC _{max} and IC _{50s} $I_f = g_f O(V - E_{open})$ $g_f = g_{control} f \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$	TDR and RUD estimation: • TDR = $APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) • RUD = $APD_{90, epi}/APD_{90, mid}$ where $APD_{90,x} = APD_{90}$ with - drug at CL x		
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	IC index calculation⁽⁹⁾: IC index = $(AFKr/(AFNaL + AFCaL)/2) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} .		
	Human midmyocardial myocytes 				
	Human endocardial myocytes 				
Summary	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> <p>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. Christope B & Crumb WJ Jr (2019) <i>Pharmacol Toxicol Methods</i> 96: 15-26</p>			
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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. GIPA (2016) www.Ilextra.org/hes/science/cardiac/cipa/Project 6. Wirsniowska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16				
Abbreviations	AP : action potential , APA : AP amplitude , APD _{90, 60 or 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 , IC ₅₀ : 50% inhibition concentration , mid : midmyocardial myocyte , msec : millisecond , mV : millivolt , qNf : integration sum of $i_{Ca,L}^n i_{Na,L}^n i_{K1,L}^n i_{Ks,L}^n$, RMP : resting membrane potential , RUD : reverse use dependence , T _{EP} : APD ₉₀ -APD ₄₀ 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				

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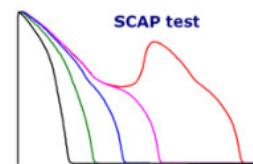
Drug	Dolasetron		
	Serotonin 5-HT ₃ receptor antagonist used as antinauseant and antiemetic no longer marketed in Germany (Onakpoya et al (2016) <i>BMC Med.</i> 14 : 10)		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{Kr} : 5.95 \mu\text{M} (1.0)$ $I_{NaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{K1} : 38.0 \mu\text{M} (1.0)$ $I_{Ks} : \text{--- } \mu\text{M} (\text{---})$	$I_{to} : \text{--- } \mu\text{M} (\text{---})$ $I_{NaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{K1} : \text{--- } \mu\text{M} (\text{---})$	$0.36 \mu\text{M}$ 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-)
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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 100 (full inhibition) which is a function of a multiple of $EFTPC_{max}$ and IC_{50s} $I_j = g_j O(V - E_{on})$ $\delta_j = g_{control,j} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, ep}$ (at CL of 1000 msec) $RUD = APD_{90, mid} / APD_{90, ep}$ where $APD_{90,x} = APD_{90}$ with - APD_{90} without compound at CL x IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / ((AFNaL + AFCaL) / 2)) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr} , I_{NaL} and I_{CaL} .
	Human epicardial myocytes 		
	Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes 		
Results	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	1. Ando H et al. (2017) <i>J Pharmacol. Tox. Meth</i> 84 : 111-127 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. GIA (2016) www.lslextrema.org/hes/science/cardiac/cipa/ 6. Wirschnowska 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, $APD_{90, 60 \text{ or } 90}$: 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, qN : integration sum of $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, TA_{90} : $APD_{90} - APD_{90, ep}$ or $APD_{90} - APD_{90, mid}$ ("triangulation"), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : 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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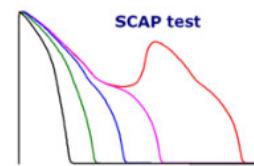
Drug	Domperidone		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 0.160 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : 5.6 μM (1.0) I_{K1} : --- μM (---) I_{Ks} : --- μM (---)		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 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} $I_j = g_j O(V - E_{j,0})$ $g_j = g_{j,0} P_j \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ <ul style="list-style-type: none"> $g_{j,0}$: maximal conductance of channel j O: open probability of channel j $E_{j,0}$: reversal potential for species of ions which flows through channel j D: drug concentration (e.g. 100 nM for channel j) n: Hill slope
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	Human midmyocardial 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>
	Human endocardial myocytes 		
Summary			
References	<ol style="list-style-type: none"> Ando H et al. (2017) J Pharmacol Toxicol Methods 84:111-127 Redfern WS et al. (2003) Cardiovasc Res. 58: 32-45 Kramer J et al. (2013) SciRep. 3: 2200 Worobey RL (2015) www.CredibleMeds.org CIPA (2016) www.Istepra.org/hses/science/cardioc/cipa/Project Winiarska B et al. (2017) Drug discovery today 22: 10-16 O'Hora T et al. (2014) PLoS Comput Biol. 10: e1002061 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, $APD_{40,60 \text{ or } 90}$: 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 $i_{CaL}^2, i_{NaL}^2, i_{K1}^2, i_{Ks}^2, i_{Kr}^2$, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP}^{max} : $APD_{40,60 \text{ or } 90}$ 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/V_s : volt per second</p>		

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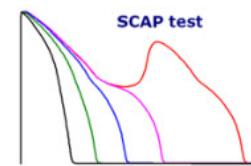
Drug	Donepezil		
Acetylcholinesterase enzyme inhibitor used to treat behavioural and cognitive effects of Alzheimer's disease or other type of dementia			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 34.3 μM (0.83) I _{to} : ---- μM (---) I _{Kr} : 0.70 μM (0.98) I _{Nal} : ---- μM (---) I _{Na} : 38.5 μM (1.0) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.003 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 2/2 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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} $I_j = g_j(V - E_{jon})$ $E_{jon} = V_{rest} + \frac{g_{max}}{g_{max} + g_{min}}(V - V_{rest})$ $E_{jrev} = reversal\ potential\ for\ species\ of\ ions\ which\ flows\ through\ channel\ j$ $\beta_j = \frac{g_j}{g_{control}} \left[1 + \left(\frac{\delta_j}{IC_{50s}} \right)^n \right]^{-1}$ $g_j = maximal\ conductance\ of\ channel\ j$ $g_{min} = minimal\ conductance\ of\ channel\ j$ $IC_{50s} = 50\% = inhibition\ of\ a\ drug\ for\ channel\ j$ $\delta_j = drug\ concentration\ (EFTPC\ for\ example)$ $n = half\ slope$	TDR and RUD estimation: • TDR = APD _{50, mid} - APD _{50, epi} (at CL of 1000 msec) • RUD = APD _{50, Endo} -APD _{50, Endo} where APD _{50, P_j} = APD _{50, 0} with - APD _{50, 0} without compound at CL x
<div style="display: flex; justify-content: space-around;"> <div style="width: 45%;"> Human epicardial myocytes </div> <div style="width: 45%;"> Transmural dispersion of repolarisation </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="width: 45%;"> Human midmyocardial myocytes </div> <div style="width: 45%;"> Reverse use dependence on midmyocardial myocytes </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="width: 45%;"> Human endocardial myocytes </div> <div style="width: 45%;"> </div> </div>			
Summary	Donepezil x-fold EFTPC_{max} vs. IC_{50s} 		
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Islsextra.org/hesi/science/cardiac/cipa/ 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. 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 _{50, 0-90} : 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 _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{K1} +I _{Ks} +I _{Kr} +I _{Na} +I _{CaL} , RMP : resting membrane potential, RUD : reverse use dependence, T _{EP, 50} : APD ₅₀ -APD ₄₀ or APD ₅₀ ("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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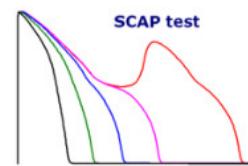
Drug	Doripenem		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 2.0 \mu M (1.0)$ $I_{to} : \text{---} \mu M (\text{---})$ $I_{Kr} : 5011.9 \mu M (1.0)$ $I_{NaL} : \text{---} \mu M (\text{---})$ $I_{Na} : 1584.9 \mu M (1.0)$ $I_{K1} : \text{---} \mu M (\text{---})$ $I_{Ks} : 316.2 \mu M (1.0)$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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} $I_j = g_j(V - E_{jon})$ ($j = Ca, Na, K, Kr, Ito, INa, IK, IKr, IKs$) $V_{mem} = V_{ext} + \frac{g_{Na}V_{Na} + g_{K}V_{K} + g_{Ca}V_{Ca} + g_{Kr}V_{Kr} + g_{Ito}V_{Ito} + g_{NaL}V_{NaL} + g_{K1}V_{K1} + g_{Ks}V_{Ks}}{g_{Na} + g_{K} + g_{Ca} + g_{Kr} + g_{Ito} + g_{NaL} + g_{K1} + g_{Ks}}$ $E_{jon} = \text{reverse potential for species of ions which flows through channel } j$ $g_{j} = \text{maximal conductance of channel } j$ $E_{Na} = \text{reverse potential for sodium channel}$ $IC_{50s} = 50\% \text{ of inhibition of a drug for a channel } j$ $D = \text{drug concentration (EFTPC for example)}$ $\eta = \text{half slope}$ <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>Human endocardial myocytes</p> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Mirams GR et al. (2014) J Pharmacol Toxicol Methods 70: 246-254 Redfern WS et al. (2003) Cardiovasc Res 58: 32-45 Kramer J et al. (2013) Sci Transl Med 5: 210 Woolesley RL (2015) www.CredibleMed.org GPA (2016) www.lituxtra.org/heis/science/cardiac/cipa/Project Widoniowska B et al. (2017) Drug discovery today 22: 10-16 O'Hearn 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) Pharmacol Toxicol Methods 96: 15-26 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, APD₉₀₋₅₀ : AP duration at 40, 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 : IC channel inhibition index, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{Na} + I_{NaL} + I_{K1} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₅₀ : APD₉₀-APD₅₀ or APD₉₀ : membrane voltage, V_{max} : maximal rate of AP rise, V_s : volt per second</p>		

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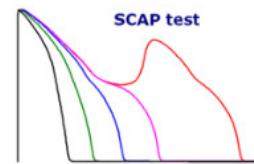
Drug	Doxorubicin Cytotoxic anthracycline antibiotic used to treat various cancer and Kaposi's sarcoma		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 1000.0 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : --- μM (---) I_{K1} : --- μM (---) I_{Ks} : 4.786 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>4.646 μM</p>	<p>TdP risk</p> <p>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⁾ : 0/2 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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} <p>$I_j = g_j(V - E_{j,0})$</p> <p>$\frac{g_j}{g_{j,control}} = \left[1 + \left(\frac{\delta}{IC_{50s}}\right)^n\right]^{-1}$</p> <p>g_j = maximal conductance of channel j V = voltage membrane E_{j,0} = reversal potential for species of ions which flows through channel j IC_{50s} = 50% of inhibition of a drug for channel j δ = drug concentration (EF-TCP_{max} for example) n = half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{depi} (at CL of 1000 msec) RUD = AP_{Depeo}-AP_{Dmid} where AP_{Dmid} = AP_{Depeo} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Romero L et al. (2018) J Chem Inf Model. 58: 867-878 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. CIPA (2016) www.lisextra.org/hesi/science/cardiac/cipa/Project 6. Wirsniowska 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	AP : action potential, APA : AP amplitude, APD ₄₀₋₅₀ : AP duration at 40, 50 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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 _{NaL} +I _{K1} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₅₀ : APD ₄₀ -APD ₅₀ or AP ₅₀ ("triangulation"), TDR : 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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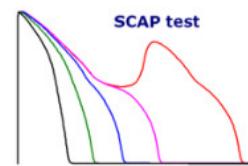
Drug	Dronedarone		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 0.4 \mu M (1.0)$ $I_{Kr} : 0.059 \mu M (1.0)$ $I_{Na} : 0.7 \mu M (1.0)$ $I_{Ks} : \text{---} \mu M (\text{---})$ $I_{to} : \text{---} \mu M (\text{---})$ $I_{Na} : \text{---} \mu M (\text{---})$ $I_{K1} : \text{---} \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 and IC_{50s} $I_f = g_f(V - E_{f,rest})$ (g_f: maximal conductance of channel ; $E_{f,rest}$: reversal potential for species of ions which flows through channel) $\frac{g_f}{g_{control}} = [1 + \left(\frac{D}{IC_{50s}}\right)]^{-1}$ (D: drug concentration ; IC_{50s}: 50% of inhibition of a drug for channel) $IC_{50s} = 50\% \text{ of inhibition of a drug for channel}$ (e.g. drug concentration (EFTPC for example) at half slope) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, endo}$ where $APD_{90,P_x} = APD_{90}$ with $P_x = APD_{90}$ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> $\text{IC index} = (AFKr/(AFNaL + AFCaL)/2) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{CaL} and I_{CaL} in half slope</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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Ando H et al. (2017) <i>J Pharmacol Toxicol Med</i> 84:111-127 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. GPA (2016) www.Ilextra.org/hesi/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		
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{40, 60, 90, 99}$: AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, au. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPCmax : 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 $I_{CaL} + I_{Kr} + I_{Na} + I_{Ks} + I_{to}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 40}$: $APD_{40} - APD_{40}$ or APD_{40} ("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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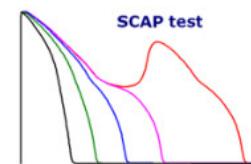
Drug	Droperidol		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 7.6 \mu M (1.16)$ $I_{to} : \text{--- } \mu M (\text{---})$ $I_{Kr} : 0.06 \mu M (1.10)$ $I_{NaL} : \text{--- } \mu M (\text{---})$ $I_{Na} : 22.7 \mu M (1.24)$ $I_{K1} : \text{--- } \mu M (\text{---})$ $I_{Ks} : \text{--- } \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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} $I_j = g_j O(V - E_{inj})$ $\delta_j = g_{control,j} \left[1 + \left(\frac{D}{IC_{50s,j}} \right)^n \right]^{-1}$ <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, Endo} - APD_{90, Mid}$ where $APD_{90,x} = APD_{90}$ with - AFC_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr / ((AFNaL + AFCaL)/2)) * 100$ <p>where</p> <p>$AFKr$, $AFNaL$ and $AFCaL$= active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}.</p>	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Reverse use dependence on midmyocardial myocytes</p>	
Summary	<p>Droperidol</p> <p>x-fold $EFTPC_{max}$ vs. IC_{50s}</p> <p>EFTPC_{max} vs. IC_{50s}</p> <p>APD₉₀ vs. IC_{50s}</p> <p>IC index vs. IC_{50s}</p>		
References	1. Kramer J et al. (2013) Sci. Rep. 3 : 2100 2. Redfern WS et al. (2003) Cardiovasc. Res. 58 : 32-45 3. Kramer J et al. (2013) Sci. Rep. 3 : 2100 4. Worsley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Illustra.org/hs/science/cardiac/cipa/Project 6. Winiarska B et al. (2017) Drug discovery today 22 : 10-16 7. O'Hearn T et al. (2014) PLoS Comput. Biol. 10 : e1002061 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	AP : action potential, APA : AP amplitude, $APD_{40,60 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APP : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{ER} : $APD_{90, Endo}$ or $APD_{90, Mid}$ (triangulation), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : 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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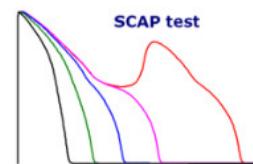
Drug	Duloxetine		
5-HT and noradrenaline reuptake inhibitor used to treat anxiety disorder, neuropathic pain, osteoarthritis and stress incontinence			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 2.8 μM (1.41) I_{to} : ---- μM (---) I_{Kr}: 3.8 μM (1.39) I_{NaL} : ---- μM (---) I_{Na}: 5.1 μM (1.66) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.016 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not classified with TdP risk (class 4) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/2 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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 and IC_{50s} <p>$I_j = g_j(V - E_{j,0})$</p> <p>$\beta_j = \frac{g_j}{g_{j,control}} \left[1 + \left(\frac{\delta_j}{[IC_{50s}]_j} \right)^{-1} \right]$</p> <p>g_j = maximal conductance of channel E_{j,0} = reversal potential of species of ions which flows through channel V = voltage membrane δ_j = reversal potential for species of ions which flows through channel IC_{50s} = 50% of inhibition of a drug for a channel δ = drug concentration (F/TPC for example) x = full slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀ epi (at CL of 1000 msec) RUD = APD₉₀endo - APD₉₀mid where APD₉₀s = 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 AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</p>	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p>
Summary	<p>Human midmyocardial myocytes</p> <p>Human endocardial 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>Duloxetine</p> <p>x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Effect (%)</p> <p>www.scaptest.com</p> <p>RMP APA V_{max} APD₄₀ APD₅₀ APD₉₀ T_{dp} T_{dp} qNet TDR</p> <p>APD90max - APD90min (msec)</p> <p>V_{dp} (mV)</p> <p>IC index (a.u.)</p> <p>RUD UD</p> <p>EAD threshold</p> <p>www.scaptest.com</p>
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Isiextra.org/hesi/science/cardiac/cipa/Project 6. Wiśnioska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, APD₅₀, APD₉₀ : 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_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{Kr}, I_{NaL}, I_{CaL}, I_{Ks}, I_{to}, I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dp}, T_{dp} : APD₉₀-APD₄₀ or APD₉₀ ("triangulation"), TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{dp} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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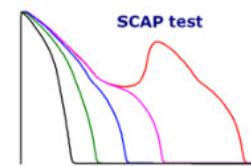
Drug	E-4031		
	Voltage-gated K ⁺ channel (Kv11.1) blocker used in Class III antiarrhythmic studies		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 713.7 μM (0.454) I_{to} : ---- μM (---) I_{Kr} : 0.026 μM (1.996) I_{NaL} : ---- μM (---) I_{Na} : 737.3 μM (0.334) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.00567 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⁾ : 1/0 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 10 (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_f = g_o(V - E_{f,0}) \left[1 + \left(\frac{g}{g_{max}} \right)^n \right]^{-1}$ <p>g_{max}= maximal conductance of channel V=membrane potential g= reversal potential for species of ions which flows through channel IC₅₀= 50% of inhibition of a drug for a channel D= drug concentration (F_f F_{PC} for example) n= half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{Depi} (at CL of 1000 msec) RUD = AP_{Dmid}-AP_{DDepi} where AP_D=AP_{Depi} with - AP_{Depi} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr}/(\text{AFNaL}+\text{AFCaL})/2)) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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>E-4031 x-fold EFTPC_{max} vs. IC_{50s}</p> <p>E-4031 APD₉₀ - APD₉₀ (msec)</p>		
References	<p>1. Okada J-I et al. Sci Adv. 1: e1400142 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Ilextra.org/hesi/science/cipa/ Project 6. Wisiowska 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, 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_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{EP} : APD₉₀-APD₄₀ 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



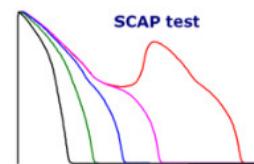
Drug	Ebastine		
Raw data	IC_{50s} (slope) ⁽¹⁾ I_{CaL} : --- μM (---) I_{Kr} : 0.724 μM (1.0) I_{Na} : --- μM (---) I_Ks : 0.794 μM (1.0)	$EFTPC_{max}$ ⁽¹⁾ 0.00014 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/3 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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} $I_f = g_f(V - E_{f,0})$ (g_f= maximal conductance of channel f; V=voltage membrane; $E_{f,0}$= reversal potential for species of ions which flows through channel f) $\beta_f = \frac{g_f}{g_f + g_{f,control}} \left[1 + \left(\frac{\delta}{IC_{50s}} \right)^n \right]^{-1}$ (g_f= maximal conductance of channel f; δ= IC_{50s} = 50% of inhibition of a drug for channel f; n= drug concentration (EFTPC for example); $n=1.5$ slope) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = $APD_{50, mid} - APD_{50, epi}$ (at CL of 1000 msec) RUD = $APD_{50, Endo} - APD_{50, Mid}$ where $APD_{50,P_i} = APD_{50}$ with - APD_{50} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFKr / (AFNaL + AFCaL)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}.</p>	
	Human epicardial myocytes	Transmural dispersion of repolarisation	Reverse use dependence on midmyocardial myocytes
Summary	x -fold $EFTPC_{max}$ vs. IC_{50s}	x -fold $EFTPC_{max}$ vs. IC_{50s}	x -fold $EFTPC_{max}$ vs. IC_{50s}
References	<p>1. Romero L et al. (2018) J.Chem.Inf.Model. 58: 867-878 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. GIPA (2016) www.Isiextra.org/hesi/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, $APD_{40, 60, 90}$: AP duration at 40, 60 or 90 % of APA, APDP : AP 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_Ks$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 60}$: $APD_{50, Endo} - APD_{50, Mid}$ ("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



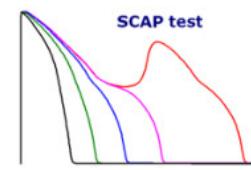
Drug	Eltrombopag				
	Thrombopoietin receptor agonist used to treat thrombocytopenia or aplastic anemia				
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (--) I_{to} : 1584.89 μM (1.0) I_{Kr} : 0.631 μM (1.0) I_{Na} : --- μM (---) I_{Na} : 158.49 μM (1.0) I_{K1} : --- μM (---) I_{Ks} : --- μM (--) I_{Net} : --- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.11481 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⁾				
Results	<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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ (g_f: maximal conductance of channel ; V: membrane potential ; $E_{f,0}$: reversal potential for species of ions which flows through channel ; f: open probability of channel ; I_f: current flowing through channel ; IC₅₀ = 50% of inhibition of a drug for a channel ; x: drug concentration (FETPC for example) in full scale) <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{epi} (at CL of 1000 msec) RUD = AP_{mid} - AP_{endo} - AP_{epi} where AP_{Dx} = AP_{D0} with - AP_{D0} 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_{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> <p>Summary</p> <p>Eltrombopag x-fold EFTPC_{max} vs. IC_{50s}</p> <p>APD₅₀ - APD₄₀ (msec)</p>			
References	<p>1. Mirams GR et al. (2014) <i>J.Pharmacol.Tox.Methods</i> 70: 246-254 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Illsieux.org/hscience/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, 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_{Kr}*I_{Na}*I_{CaL}*I_{NaP}*I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dP, 40} : APD₄₀-APD₄₀ 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



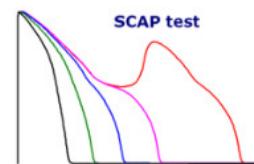
Drug	Encainide		
Voltage-gated Na^+ channel ($\text{Na}_v1.5$) blocker used to treat atrial or ventricular fibrillation, atrial flutter and ventricular tachycardia no longer marketed in UK (Onakpoya et al (2016) <i>BMC Med</i> 14: 10)			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>$I_{\text{CsL}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{to}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Kr}} : 5.42 \mu\text{M} (1.0)$ $I_{\text{NaL}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Na}} : 11.2 \mu\text{M} (1.0)$ $I_{\text{K1}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Ks}} : \text{--- } \mu\text{M} (\text{---})$</p>	<p>$\text{EFTPC}_{\text{max}}$⁽¹⁾</p> <p>0.061 μM</p>	TdP risk
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	<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): $[\text{Na}^+]_o = 140 - [\text{Ca}^{++}]_o = 1.8 + [\text{K}^+]_o = 5.4$ 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 $\text{EFTPC}_{\text{max}}$ and IC_{50s} $I_j = g_j O(V - E_{j,\text{rest}})$ $g_j = \text{minimal conductance of channel } j$ $O(x) = \frac{1}{1 + \left(\frac{x}{\text{IC}_{50s}}\right)^n}$ $n = \text{open probability of channel } j$ $E_{j,\text{rest}} = \text{reversal potential for species of ions that flows through channel } j$ $\text{g}_j = \text{minimal conductance of channel } j$ $\text{g}_{\text{dry}} = \text{dry free minimal conductance of channel } j$ $\text{g}_{\text{dry}} = \text{g}_j / (1 + \text{dry concentration of drug} / \text{IC}_{50s})$ $\text{dry concentration of drug} = 0.01 \text{ to } 1000$ <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $\text{RUD} = \text{APD}_{90,\text{mid}} - \text{APD}_{90,\text{epi}}$ (at CL of 1000 msec) $\text{RUD} = \text{APD}_{90,\text{endo}} - \text{APD}_{90,\text{mid}}$ where $\text{APD}_{90,\text{P}_x} = \text{APD}_{90} \text{ with } x = \text{APD}_{90} \text{ without compound at CL } x$ <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr} / ((\text{AFNaL} + \text{AFCaL}) / 2)) * 100$ <p>where $\text{AFKr}, \text{AFNaL}$ and AFCaL: active fraction (%) of the $I_{\text{Ks}}, I_{\text{NaL}}$ and I_{CsL}.</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>Human endocardial myocytes</p> <p>Summary</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>References</p> <ol style="list-style-type: none"> Abi-Gerges N et al. (2011) <i>Br J Pharmacol</i> 154: 419-432. (PMID 21480866) Redfern WS et al. (2003) <i>Cardiovasc Res</i> 52: 32-45 Kramer J et al. (2013) <i>Sci Rep</i> 3: 2100 Weissler RL (2015) www.CredibleMeds.org CIPA (2016) www.hellenicarrheis.gr/science/cardiac/cipa/Project Witiniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hare 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 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $\text{APD}_{90,60 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APP : APD prolongation, a.u. : arbitrary unit, CL : cycle length , DA : depolarization abnormalities, EAD : early afterdepolarization, $\text{EFTPC}_{\text{max}}$: 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 $I_{\text{CsL}} + I_{\text{NaL}} + I_{\text{K1}} + I_{\text{Ks}}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{EAD} : $\text{APD}_{90,\text{mid}} - \text{APD}_{90,\text{epi}}$ ("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



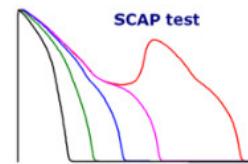
Drug	Erythromycin		
	Macrolide antibiotic used to treat various bacterial infections no longer marketed in France, Singapore, Greece, Denmark and Sweden (Onakpoya et al (2016) <i>BMC Med.</i> 14 : 10)		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{Kr} : 38.9 \mu\text{M (1.0)}$ $I_{NaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{K1} : \text{--- } \mu\text{M} (\text{---})$ $I_K : \text{--- } \mu\text{M} (\text{---})$	$I_{to} : \text{--- } \mu\text{M} (\text{---})$ $I_{NaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{K1} : \text{--- } \mu\text{M} (\text{---})$	$8.516 \mu\text{M}$ <p>Redfern⁽²⁾ : numerous TdP reports (class 3) Kramer⁽³⁾ : not reported CredibleMeds⁽⁴⁾ : known risk of TdP (class 1) CiPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 8/1 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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): $[Na^+]_o = 140 - [Ca^{2+}]_o = 1.8 - [K^+]_o = 5.4$ 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} $I_j = g_j O(V - E_{j,0})$ ($j = \text{Na}, \text{K}, \text{Ca}, \text{Cl}$) $\theta_j = g_{j,control} \left[1 + \left(\frac{2}{(IC_{50s})^{1/2}} \right)^{n_j} \right]^{-1}$ 	TDR and RUD estimation: <ul style="list-style-type: none"> $APD_{90, mid} = APD_{90, no comp} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, Epi} / APD_{90, mid}$ where $APD_{90, P} = APD_{90}$ with - APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / ((AFNaL + AFCaL) / 2)) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL}, I_{NaL} and I_{CaL}.</p>
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	
	Human midmyocardial 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>
	Human endocardial myocytes 		
Summary			
References	<ol style="list-style-type: none"> Uguz-Lorente J et al. (2020) <i>J Chem Inf Model</i> 60: 5172-5187 Redfern WS et al. (2003) <i>Cardiovasc Res</i> 57: 32-45 Kramer J et al. (2013) <i>Sci Rep</i> 3: 2100 Wessely RL (2015) www.CredibleMeds.org CiPA (2016) www.Icstar.org/heal/science/cardioc/cipa/Project Widmowska 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, $APD_{40, 60 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APPD : 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 $I_{CaL} + I_{NaL} + I_{K1} + I_K + I_{Cl}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{ER} : $APD_{90, Epi} / APD_{90, Mid}$ or $APD_{90, Epi} / APD_{90, Ende}$ ('triangulation'), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : 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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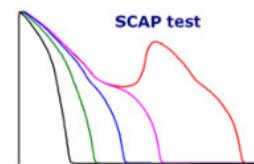
Drug	Etravirine		
	Non-nucleoside reverse transcriptase inhibitor used to treat HIV-1 infections		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : --- μM (---) I _{to} : 3162.3 μM (1.0) I _{Kr} : 158.49 μM (1.0) I _{NaL} : --- μM (---) I _{Na} : 501.19 μM (1.0) I _{K1} : --- μM (---) I _{Ks} : 1258.9 μM (1.0)	EFTPC_{max}⁽¹⁾ 0.00258 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⁾		
Results	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 and IC _{50s} $I_j = g_j(V - E_{j,0})^{1 - \frac{1}{1 + (\frac{EFTPC_{max}}{IC_{50s}})^n}}$ g _j = maximal conductance of channel j E _{j,0} = reversal potential for species of ions which flows through channel j n= exponent of inhibition (0 < n < 1) IC _{50s} = 50% of inhibition of a drug for channel j D= drug concentration (EF-TPC for example) x= full slope	TDR and RUD estimation: • TDR = APD _{mid} - APD _{epi} (at CL of 1000 msec) • RUD = APD _{mid} -APD _{epi} where APD _{mid} = APD _{mid} with - APD _{mid} without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} in full slope
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <p>Legend: 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 		
Summary	Etravirine x-fold EFTPC_{max} vs. IC_{50s} <p>Legend: Epi: Endocardial myocyte Mid: Midmyocardial myocyte Ende: Endothelial cell TDR: Transmural dispersion of repolarization no drug: Control x 100: 100x IC50s </p>		
References	1. Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 70 : 246-254 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.Isiextra.org/hesi/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		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{40,60 or 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 _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{Kr} *I _{NaL} *I _{CaL} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{EP,40} : APD ₄₀ -APD ₄₀ 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		

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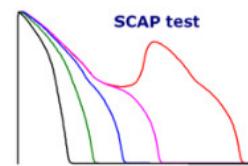
Drug	Everolimus		
	Mammalian target of rapamycin (mTOR) kinase inhibitor used to treat various types of malignancies		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_o : 10000.0 μM (1.0) I_{Kr} : 501.187 μM (1.0) I_{Na} : --- μM (---) I_{Na} : 630.957 μM (1.0) I_{K1} : --- μM (---) I_{Ks} : 100.00 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.068105 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>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 and IC_{50s} <p>$I_f = g_f(V - E_{on})$</p> <p>$\frac{g_f}{g} = \frac{1}{1 + \left(\frac{D}{IC_{50f}}\right)^n}$</p> <p>g = maximal conductance of channel V = voltage membrane E_{on} = reversal potential for species of ions which flows through channel D = drug concentration (EF-TPC for example)</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀mid - APD₅₀endo where APD₅₀P_a = APD₅₀without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100</p> <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full range</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>Legend: 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>	<p>APD₅₀ - APD₉₀ (msec)</p>	
References	<p>1. Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 70: 246-254 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. CPA (2016) www.ncbi.nlm.nih.gov/science/cardiopharmacology/ 6. Włodziszka 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</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀ or 90 : 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 $I_{CaL}I_{Kr} + I_{NaL}I_{Na} + I_{K1}I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{EA} : APD₅₀-APD₄₀ or APD₅₀ ("triangulation"), TDR : 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



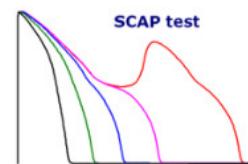
Drug	Famotidine		
Histamine H ₂ receptor antagonist used to treat duodenal ulcers, benign gastric ulcers or gastroesophageal reflux disease			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : --- μM (---) I _{to} : --- μM (---) I _{Kr} : 2325.3 μM (1.0) I _{NaL} : --- μM (---) I _{Na} : --- μM (---) I _{K1} : --- μM (---) I _{Ks} : --- μM (---)	EFTPC_{max}⁽¹⁾ 0.33 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/1 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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} $I_j = g_j(V - E_{jon})$ $E_{jon} = \text{ reversal potential for species of ions which flows through channel } j$ $g_j = \text{ maximal conductance of channel } j$ $\theta = \text{ reversal potential for species of ions which flows through channel } j$ $IC_50 = 50\% \text{ of inhibition of a drug for channel } j$ $D = \text{ drug concentration (BP/IC50 for example)}$ $\theta = \theta_{control} \left[1 + \left(\frac{D}{IC_50} \right)^n \right]^{-1}$	TDR and RUD estimation: • TDR = APD _{50, mid} - APD _{50, epi} (at CL of 1000 msec) • RUD = APD _{50, Endo} -APD _{50, Endo} where APD _{50,P} = APD ₅₀ with - APD ₅₀ without compound at CL x
	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	Famotidine x-fold EFTPC_{max} vs. IC_{50s} www.scaptest.com		 www.scaptest.com
References	1. Llopis-Lorente J et al. (2020) <i>J Chem. Inf. Model</i> 60 : 5172-5187 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.IsiExtra.org/heis/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. 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 _{50, 40, 60, 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, ende : 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 _{K1} +I _{Ks} +I _{NaL} +I _{Na} +I _{CaL} , RMP : resting membrane potential, RUD : reverse use dependence, T _{40, 50} : APD ₅₀ -APD ₄₀ or APD ₅₀ -TDR ("triangulation"), TDR : 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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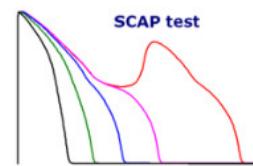
Drug	Fexofenadine		
	Histamine H ₁ receptor antagonist used to treat seasonal allergic rhinitis or chronic idiopathic urticaria		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	I_{CaL} : --- μM (---) I_{Kr} : 501.0 μM (1.0) I_{Na} : --- μM (---) I_{K1} : --- μM (---) I_{ks} : 20.4 μM (1.0)	I_{to} : --- μM (---) I_{NaL} : --- μM (---)	$0.345 \mu M$ Redfern ⁽²⁾ : isolated TdP reports (class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/3 (TdP+/TdP-)
	<i>In silico</i> 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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_f = g_f(V - E_{f,0})$ $\frac{g_f}{g} = \frac{1}{1 + \left(\frac{D}{IC_{50f}}\right)^n}$ g = maximal conductance of channel $E_f,0$ = reversal potential of species of ions which flows through channel IC_{50f} = 50% of inhibition of a drug for channel f D = drug concentration (FEP for example) in nM	TDR and RUD estimation: • TDR = $APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) • RUD = $APD_{90, mid} - APD_{90, end}$ where $APD_{90,P_s} = APD_{90}$ with - APD_{90} without compound at CL x
Results	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes <ul 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	Fexofenadine x-fold EFTPCmax vs. IC_{50s} 		
References	1. Abi-Gerges N et al. (2011) Br J Pharmacol. 164 : 419-432 (+ portocal.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. CiPA (2016) www.ciptextra.org/hses/science/cardiac/cipa/project 6. Winirowska 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	AP : action potential, APA : AP amplitude, $APD_{40, 60, 90, 99}$: 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $i_{CaL} + i_{Kr} + i_{NaL} + i_{K1} + i_{ks}$, RMP : resting membrane potential, RUD : reverse use dependence, TdP_{90} : $APD_{90} - APD_{40}$ 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		

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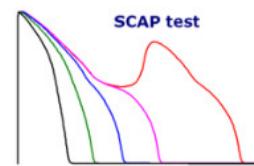
Drug	Flecainide		
Multichannel blocker used as Class IC antiarrhythmic to treat atrial fibrillation and paroxysmal supraventricular tachycardia			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 27.1 μM (0.97) I_{Ko} : ---- μM (---) I_{Kr}: 1.5 μM (0.88) I_{NaL} : ---- μM (---) I_{Na}: 6.2 μM (1.14) I_{K1} : ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.753 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : numerous reports of TdP (class 3) Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : known risk of TdP (class 1) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 8/1 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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 and IC_{50s} $I_j = g_j(V - E_{j,0}) \left[1 + \left(\frac{g_j}{IC_{50j}} \right)^n \right]^{-1}$ <p>g_j= maximal conductance of channel E_{j,0}= reversal potential for species of ions which flows through channel IC_{50j}= 50% of inhibition of a drug for channel j D= drug concentration (BP/EC50 for example) n= half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{Depi} (at CL of 1000 msec) RUD = AP_{Depi}-AP_{Dmid} where AP_{Dx}=AP_{Depi} with - AP_{Dmid} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ko}, I_{NaL} and I_{CaL} in full slope</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> <p>Summary</p>
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Illsieux.org/hesi/science/cardiac/cipa/ 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, 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_{Ko}+I_{NaL}+I_{CaL}+I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, TdP : torsade de pointes, TdP- : 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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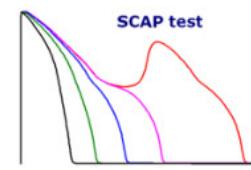
Drug	Fluoxetine				
	5-HT reuptake inhibitor used to treat bulimia, major depressive, obsessive compulsive premenstrual dysphoric, panic and bipolar disorders				
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk		
	$I_{CaL} : 2.82 \mu M (1.0)$ $I_{Kr} : 1.5 \mu M (1.0)$ $I_{NaL} : 39.4 \mu M (1.0)$ $I_{Ks} : \text{---} \mu M (\text{---})$ $I_{to} : \text{---} \mu M (\text{---})$ $I_{K1} : \text{---} \mu M (\text{---})$	0.011 μM	Redfern ⁽²⁾ : isolated reports of TdP (class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 3/2 (TdP+/TdP-)		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾				
Results	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 <p>Effect of drugs on AP⁽⁸⁾:</p> <p>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 and IC_{50s}</p> $I_j = g_j(V - E_{j,0})^{(1 + \left(\frac{D}{IC_{50s}}\right)^n)^{-1}}$ <p>where g_j = maximal conductance of channel $E_{j,0}$ = reversal potential for species of ions which flows through channel D = drug concentration (EFTPC for example) n = half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = AP_{90, \text{mid}} - AP_{90, \text{epi}}$ (at CL of 1000 msec) $RUD = AP_{90, \text{endo}} - AP_{90, \text{mid}}$ where $AP_{90, P_s} = AP_{90}$ with - AP_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr / (AFNaL + AFCaL)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p>		
Summary	<p>Fluoxetine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Fluoxetine</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>			
References	1. Yamasaki et al. (2018) J.Pharmacol.Sci. 136 : 249-256 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. GPA (2016) www.Isiextra.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska 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	AP : action potential , APA : AP amplitude, $AP_{90, 60 \text{ or } 90}$: 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Ks} + I_{to}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 60}$: $APD_{90} - APD_{40}$ ("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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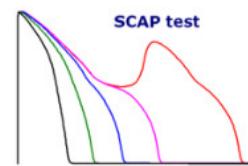
Drug	Fluvoxamine			
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk	
	$I_{CaL} : 4.90 \mu M (1.0)$ $I_{Kr} : 3.80 \mu M (1.0)$ $I_{Na} : 39.36 \mu M (1.0)$ $I_K : \text{----} \mu M (---)$	$I_{CaL} : \text{----} \mu M (---)$ $I_{Kr} : \text{----} \mu M (---)$ $I_{Na} : \text{----} \mu M (---)$ $I_K : \text{----} \mu M (---)$	$EFTPC_{max}^{(1)}$ 0.264 μM	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 1/3 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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 50 (full inhibition) which is a function of a multiple of $EFTPC_{max}$ and IC_{50s} $I_f = g_f O(V - E_{f,0})$ (open probability of channel f) $V_{inj} = V_{inj,0} e^{-\frac{V_{inj}-V_{inj,0}}{RT}}$ (reverse potential for series of ions which flows through channel f) $g_f = \text{minimal conductance of channel f}$ $g_{f,0} = \text{dry-state minimal conductance of channel f}$ $D_f = \text{Drug concentration (M)} / (\text{IC}_{50s} \times 100)$ (Drug concentration (M) / (IC_{50s} × 100)) in hill slope 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) $RUD = APD_{90, \text{apo}} - APD_{90, \text{apo}}$ where $APD_{90, \text{apo}} = APD_{90}$ with - APD₉₀ without compound at CL x 	
	Human epicardial myocytes 	Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes 	Reverse use dependence on midmyocardial myocytes 		
	Human endocardial myocytes 			
Summary				
References	1. McMillan et al. (2017) <i>Tox-Rep</i> 5 : 912-921 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.pharmcentral.org/scientific/cardioc/cipa/ 6. Wideröwska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16 7. O'Hearn T et al. (2011) <i>PLoS Comput. Biol.</i> 7 : e1002961-8 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, $APD_{40, 60 \text{ or } 90}$: 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_{Kr} , I_{Na} , I_{K1} , I_{K2} , RMP : resting membrane potential, RUD : reverse use dependence, T_{dP} : $APD_{90, \text{apo}} - APD_{90, \text{apo}}$ (triangulation), TDR : transmural dispersion of repolarization, V_{max} : membrane voltage, V_{min} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/V_s : volt per second			

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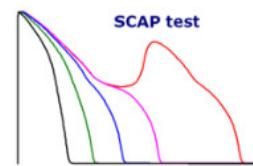
Drug	Gatifloxacin		
	Fluoroquinolone antibiotic used to treat a wide variety of bacterial infections no longer marketed in Europe and India (Onakpoya et al (2016) <i>BMC Med.</i> 14 : 10)		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{Kr} : 25.4 \mu\text{M} (1.0)$ $I_{Na} : \text{--- } \mu\text{M} (\text{---})$ $I_K : \text{--- } \mu\text{M} (\text{---})$ $I_{to} : \text{--- } \mu\text{M} (\text{---})$ $I_{NaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{K1} : \text{--- } \mu\text{M} (\text{---})$	9.0 μM	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) 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): $[\text{Na}^+]_o = 140 - [\text{Ca}^{++}]_o = 1.8 - [\text{K}^+]_o = 5.4$ • 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} $I_j = g_j O(V - E_{j,0})$ $g_j = g_{j,0} e^{-\frac{V}{V_{1/2,j}}}$ $\theta_j = g_{j,0} e^{-\frac{V}{V_{1/2,j}}} \left[1 + \left(\frac{2}{(IC_{50s})^{1/2}} \right)^{V_{1/2,j}} \right]^{-1}$	TDR and RUD estimation: • $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) • $RUD = APD_{90, \text{apo}} - APD_{90, \text{mid}}$ where $APD_{90,P_i} = APD_{90}$ with - APD_{90} without compound at CL x IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / ((AFNaL + AFCaL)/2)) * 100$ where $AFKr = AFK_r / (AFK_r + AFK_e)$ $AFNaL = AFN_aL / (AFN_aL + AFN_e)$ $AFCaL = AFCaL / (AFCaL + AFC_e)$
Results	Human epicardial myocytes Transmural dispersion of repolarisation Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes Human endocardial myocytes 		
Summary	 		
References	1. Ugoz-Lorente J et al. (2020) <i>J Chem Inf Model</i> 60 : 5172-5187 2. Redfern WS et al. (2003) <i>Cardiovasc Res</i> 57 : 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.Ictra.org/home/science/cardioc/cipa/ 6. Widnowska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16 7. O'Hara T et al. (2013) <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, $APD_{40, 60 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APPO : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_K + I_{to}$, RMP : resting membrane potential, RUD : reverse use dependence, TdP : $APD_{90} - APD_{90}$ or $APD_{90} - APD_{90}$ ('triangulation'), TDR : transmural dispersion of repolarization, V_{max} : 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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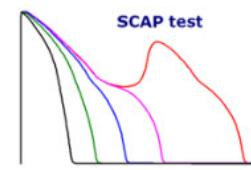
Drug	Gefitinib		
	Tyrosine kinase inhibitor used to treat non-small cell lung carcinoma		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 1.10 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : --- μM (---) I_{K1} : --- μM (---) I_{ks} : 23.8 μM (1.7)</p>	<p>$EFTPC_{max}$⁽¹⁾</p> <p>0.0913 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>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 and IC_{50s} $I_j = g_j \cdot (V - E_{j,rest}) \cdot \left[1 + \left(\frac{g_j}{IC_{50s}} \right)^n \right]^{-1}$ <p>g_j: maximal conductance of channel $E_{j,rest}$: reversal potential for species of ions which flows through channel n: cooperativity factor of inhibition of channel IC_{50s}: 50% of inhibition of a drug for a channel D: drug concentration (EFTPC for example) x: full slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, 0}$ where $APD_{90, 0}$ = APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFKr / (AFNaL + AFCaL)) * 100$ <p>where $AFKr$, $AFNaL$ and $AFCaL$ = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</p>	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p> <p>Human endocardial myocytes</p>
Summary			
References	1. Jie L-J et al. (2021) <i>Eur J Pharmacol</i> 910 : 174441 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. GPA (2016) www.lslextre.org/hesm/science/cardiac/cipa/Project 6. Winirowska 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 & Crunni WJ Jr (2019) <i>J. Pharmacol. Toxicol. Methods</i> 96 : 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{90, 60 \text{ or } 90}$: 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{to} + I_{NaL} + I_{K1}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{dP, 60}$: $APD_{60} - APD_{40}$ 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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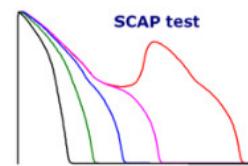
Drug	Halofantrine		
	Ferriprotoporphyrin IX complexing agent used to treat malaria		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: 1.9 μM (0.99) I_{Kr}: 0.38 μM (1.31) I_{Na}: 331.2 μM (1.0) I_{Ks}: ---- μM (---)</p> <p>I_{to} : ---- μM (---) I_{NaL} : ---- μM (---) I_{K1} : ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.172 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾ : numerous reports of TdP (class 3) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 9/0 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ (g_f: maximal conductance of channel; $E_f,0$: reversal potential of channel; f: species of channel) $\delta_f = \frac{g_f}{g_{f,0}} = \left[1 + \left(\frac{\delta}{IC_{50f}} \right)^n \right]^{-1}$ (δ: drug concentration (BP/EC₅₀ for example); n: Hill slope) IC₅₀ = 50% of inhibition of a drug for a channel D= drug concentration (BP/EC₅₀ for example) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP₉₀ mid - AP₉₀ epi (at CL of 1000 msec) RUD = AP₉₀ Endo - AP₉₀ Mid where AP₉₀P_x = AP₉₀ with - AP₉₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and ACFaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full scope</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>Human endocardial myocytes</p> <p>Summary</p>
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Illsieux.org/hesl/science/cardiac/cipa/ Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, 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_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dp,90} : APD₉₀-APD₄₀ 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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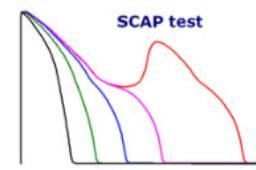
Drug	Haloperidol		
	Dopamine D ₂ receptor antagonist used to treat schizophrenia and other psychoses		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 1.3 μM (1.38) I_{to}: ---- μM (---) I_{Kr}: 0.04 μM (1.18) I_{Na}: ---- μM (---) I_{Na}: 4.3 μM (1.58) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.004 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : numerous reports of TdP (class 3) Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : known risk of TdP (class 1) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 11/0 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 and IC_{50s} $I_j = g_j(V - E_{j,0})$ $g_j = \text{maximal conductance of channel}$ $P_j = \text{open probability of channel}$ $V_m = \text{reverse potential for species of ions which flows through channel}$ $B_j = \frac{g_j}{g_{j,0}} \left[1 + \left(\frac{D_j}{IC_{50j}} \right)^n \right]^{-1}$ $D_j = \text{drug concentration (EFTPC for example)}$ $IC_{50j} = 50\% \text{ of inhibition of drug for channel}$ 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{mid} - APD_{endo} where APD_{endo} = APD_{endo} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full dose</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>Human endocardial myocytes</p> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Wooles RL (2015) www.CredibleMeds.org GPA (2016) www.Isiextra.org/hesi/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, 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 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, APD₄₀₋₉₀ : AP duration at 40, 60 or 90 % of APA, APD₄₀ : 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_{NaL}+I_{Kr}+I_{Na}+I_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, TdP₄₀₋₆₀ : APD₄₀-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>

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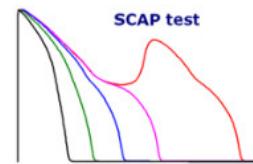
Drug	Hydroxychloroquine			
	Ferriprotoporphyrin IX complexing agent used to treat malaria			
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk	
	$I_{CaL} : 26.9 \mu M (1.0)$ $I_{Kr} : 5.62 \mu M (1.0)$ $I_{Na} : \text{---} \mu M (\text{---})$ $I_K : 9.33 \mu M (1.0)$	$I_{Io} : \text{---} \mu M (\text{---})$ $I_{NaL} : \text{---} \mu M (\text{---})$ $I_{KL} : \text{---} \mu M (\text{---})$	$EFTPC_{max}$ ⁽¹⁾ 1.22 μM	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : known TdP risk (class 1) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 2/0 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	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 <p>Effect of drugs on AP⁽⁸⁾:</p> <p>Cell 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_{50}</p> $I_j = g_j O(V - E_{j,0})$ $\frac{g_j}{g_{j,\text{control}}} = \left[1 + \left(\frac{D}{IC_{50j}} \right)^n \right]^{-1}$ <p>where: g_j = maximal conductance of channel j V = voltage membrane $E_{j,0}$ = reversal potential of species of ions which flows through channel j D = drug concentration (EFTPC_{max} for example) n = Hill slope</p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) $RUD = APD_{90, \text{endo}} - APD_{90, \text{epi}}$ where $APD_{90, P_x} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr / ((AFNal + AFCaL) / 2)) * 100$ <p>where $AFKr$, $AFNal$ and $AFCaL$: active fraction (%) of the I_{CaL}, I_{NaL} and I_{IoL}</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>Human endocardial myocytes</p> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Whittaker DG et al. (2021) <i>R. Soc. Open Sci.</i> 8: 210235 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.pharmaexperiments.org/scientific/cardiac/cipa/ 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> 95: 15-26 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $APD_{90, 40\%, 60\%, 90\%}$: 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $i_{Na} + i_{K} + i_{Ca} + i_{K1} + i_{NaL}$, RMP : resting membrane potential, RUD : reverse use dependence, $TdP_{40\%, 50\%, 90\%}$: APD₉₀-APD₄₀ 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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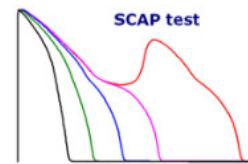
Drug	Hydroxyzine				
	Histamine H ₁ receptor antagonist used to treat anxiety, pruritus or chronic urticaria				
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 8.6 μM (1.0) I_{to}: 10.1 μM (1.0) I_{Kr}: 0.39 μM (1.0) I_{NaL}: 5.8 μM (1.0) I_{Na}: 0.3 μM (1.0) I_{K1}: >30 μM (--) I_{Ks}: >30 μM (--)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.01 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : no published report of TdP (class 5) 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: • 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> <p>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} $I_j = g_j(V - E_{jon})$ $E_{jon} = V_{rest} + \frac{g_{max}}{g_{max} + g_j} (V - V_{rest})$ $E_{jmax} = V_{rest} + \frac{g_{max}}{g_{max} + g_{jmax}} (V - V_{rest})$ $g_j = \text{maximal conductance of channel } j$ $g_{max} = \text{maximal conductance of all channels}$ IC₅₀ = 50% of inhibition of a drug for a channel D = drug concentration (EFTPC for example) n = half slope</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>Human endocardial myocytes</p>	<p>Human endocardial myocytes</p>			
Summary	<p>Hydroxyzine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Hydroxyzine</p>	<p>Hydroxyzine x-fold EFTPC_{max} vs. IC_{50s}</p>			
References	<p>1. Schiltz AF et al. (2017) <i>Pharm Res Per</i> 5: e00309 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</p> <p>4. Wessley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Istepra.org/HealthScience/cardiac/cipa/ 6. Widenowska C et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>7. O'Hearn T et al. (2011) <i>PLoS Comput Biol</i> 7: e1003061-8 8. Mirams GR et al. (2011) <i>Cardiovasc Res</i> 91: 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>Pharmacol Toxicol Methods</i> 96: 15-26</p>				
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀₋₉₀ : AP duration at 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 : IC 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 APD₅₀, 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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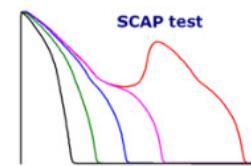
Drug	Ibutilide		
	Multichannel inhibitor used as Class III antiarrhythmic to treat atrial fibrillation and atrial flutter		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 62.5 \mu M (1.16)$ $I_{Kr} : 0.018 \mu M (1.53)$ $I_{Na} : 42.5 \mu M (1.03)$ $I_{Ks} : --- \mu M (---)$ $I_{to} : --- \mu M (---)$ $I_{NaL} : --- \mu M (---)$ $I_{K1} : --- \mu M (---)$	$0.14 \mu M$	Redfern ⁽²⁾ : class IA or III antiarrhythmics (class 1) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : high risk of TdP (class 1) VWP ⁽⁶⁾ : 11/0 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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} $I_j = g_j(V - E_{j,0})$ $\frac{g_j}{g_{j,control}} = \left[1 + \left(\frac{\delta}{IC_{50s}} \right)^n \right]^{-1}$ <p>g_j: maximal conductance of channel j g_{j,control}: maximal conductance of control channel j IC_{50s}: 50% of inhibition of a drug for channel j δ: drug concentration (BP TdP for example) n: Hill slope</p>	TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD_{90, mid} - APD_{90, epi} (at CL of 1000 msec) RUD = APD_{90, mid} - APD_{90, endo} where APD_{90, x} = APD₉₀ with - APD₉₀ without compound at CL x IC index calculation⁽⁹⁾: $IC\ index = (AFKr/(AFNaL+AFCaL)/2)) * 100$ <p>where AFKr, AFNaL and ACFaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full scope</p>
	Human epicardial myocytes 		
	Transmural dispersion of repolarisation 		
	Reverse use dependence on midmyocardial myocytes 		
Summary	EAD at 1-fold EFTPC_{max} vs. IC_{50s} on midmyocardial and endocardial myocytes 		
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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. Woodsley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.intervra.org/hesi/science/cardiac/cipa/Project 6. Widerowska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16 7. O'Hera 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, 60 or 90} : AP duration at 40, 60 or 90 % APA, APPD : AP 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 $i_{CaL}dt + i_{NaL}dt + i_{K1}dt + i_{Ks}dt$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{dP, 90}$: APD ₉₀ -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 decrease at EAD take-off voltage, V _s : volt per second		

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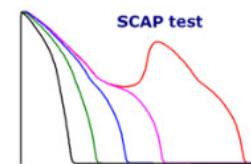
Drug	Imipramine		
	5-HT and noradrenaline reuptake inhibitor used to treat depression and childhood enuresis		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 8.1 \mu M (1.0)$ $I_{Kr} : 3.4 \mu M (1.0)$ $I_{Na} : 3.6 \mu M (1.0)$ $I_{Ks} : 0.0 \mu M (---)$ $I_{to} : 50.0 \mu M (1.0)$ $I_{NaL} : 0.0 \mu M (---)$ $I_{K1} : 0.0 \mu M (---)$	$0.106 \mu M$	Redfern ⁽²⁾ : isolated reports of TdP (class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible risk of TdP (class 2) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 6/4 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 10 (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_f = g_f(V - E_{f,rest})$: maximum conductance of channel f $P_f = \frac{g_f}{\sum g_i}$: open probability of channel f V_m : reversal potential for species of ions which flows through channel f $IC_{50} = 50\% \text{ of inhibition of a drug for a channel}$ IC_{50s}: 50% of inhibition of a drug for all channels Dn drug concentration (EFTPC for example) in full range 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90, Epi} - APD_{90, Mid}$ where $APD_{90, P_n} = APD_{90}$ without compound at CL x
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes
	Human endocardial myocytes 		
	Summary 		
References	1. McMillan et al. (2017) <i>Tox Rep</i> 5: 912-921 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.Iseuxtra.org/hesi/cardiac/cipa/Project 6. Wirschnowska 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, $APD_{90, \text{expt}}$: AP duration at 40, 60 or 90 % of APA, APD_{90} : 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_{50} : ion channel inhibition index, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, $qNet$: integration sum of $I_{CaL} + I_{Kr} + I_{Na} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{40-40} : $APD_{40} - APD_{40}$ or APD_0 ("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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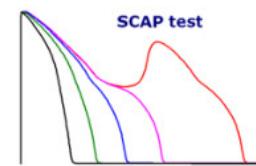
Drug	Ivabradine		
	Hyperpolarisation-activated, cyclic nucleotide-gated cation channels (HCN1-4) blocker used to treat stable symptomatic heart failure		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 34.09 \mu M (1.00)$ $I_{Kr} : 3.6 \mu M (0.99)$ $I_{Na} : 78.947 \mu M (1.00)$ $I_K : \text{--- } \mu M (\text{---})$ $I_{to} : \text{--- } \mu M (\text{---})$ $I_{NaL} : \text{--- } \mu M (\text{---})$ $I_{KrL} : \text{--- } \mu M (\text{---})$	0.014 μM	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-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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): $[Na^+]_o = 140$, $[Ca^{++}]_o = 1.8$, $[K^+]_o = 5.4$ • 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 and IC_{50s} $I_j = g_j(V - E_{j,0})$ $\frac{g_j}{g_{j,0}} = \frac{1 + \left(\frac{D}{IC_{50s}}\right)^n}{1 + \left(\frac{D}{IC_{50s}}\right)^n}$ $g_{j,0}$ = maximal conductance of channel D = drug concentration n = power law exponent of inhibition IC_{50s} = 50% of inhibition of a drug for a channel IC_{50s} = 50% of inhibition of a drug for a channel	TDR and RUD estimation: • TDR = $APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) • RUD = $APD_{90, \text{endo}} - APD_{90, \text{mid}}$ where $APD_{90,P_i} = APD_{90}$ with - APD_{90} without compound at CL x
	Human epicardial myocytes	Transmural dispersion of repolarisation	IC index calculation ⁽⁹⁾ : $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr} , I_{NaL} and I_{CaL} in full scope
	Human midmyocardial myocytes		
			Reverse use dependence on midmyocardial myocytes
	Human endocardial 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
Summary			
References	1. Passini E et al. (2019) <i>Br J Pharmacol</i> 176 : 3819–3833 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. GIPA (2016) www.Isiextra.org/hscience/cardiac/cipa/ 6. Wiśnioska 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, $APD_{90, 40\text{ or }60}$: 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, EFTPCmax : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{KrL}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{EP, 40}$: $APD_{90} - APD_{40}$ ("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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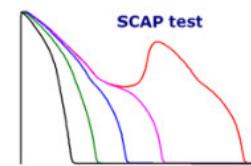
Drug	Ketanserin		
Serotonin 5-HT _{2A} receptor inverse agonist investigated to treat septic shock, severe sepsis and diabetic foot ulcer			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{Kr} : 0.75 μM (1.24) I_{Na} : --- μM (---) I_{K1} : --- μM (---) I_{ks} : --- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.018 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : isolated TdP reports (class 4) Kramer⁽³⁾ : not reported CredibleMeds⁽⁴⁾ : possible risk of TdP (class 2) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 3/2 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ (g_f= maximal conductance of channel ; $E_f,0$= reversal potential for species of ions which flows through channel) $B_f = g_f \text{Control} \left[1 + \left(\frac{D}{IC_{50f}} \right)^n \right]^{-1}$ (D= drug concentration (EFTPC for example) in nMage ; n= exponent probability of channel inhibition ; IC_{50f}= 50% of inhibition of a drug for channel) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{90, mid} - APD_{90,epi} (at CL of 1000 msec) RUD = APD_{90,epic}-APD_{90,mid} where APD_{90,P} = 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 AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p> <p>Summary</p>
References	<p>1. Abi-Gerges N et al. (2011) <i>Br J Pharmacol</i> 164: 419-432 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Illsieux.org/hesi/science/cardiac/cipa/ 6. Wiśnioska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, 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_{Kr}*I_{NaL}*I_{CaL}*I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dP} : APD₉₀-APD₄₀ or APD₁₀₀ ("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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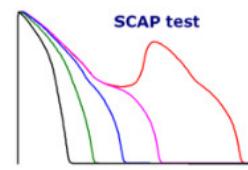
Drug	Ketoconazole		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : \text{--- } \mu\text{M} (\text{---})$ $I_{Kr} : 4.61 \mu\text{M} (1.53)$ $I_{NaL} : 44.9 \mu\text{M} (1.0)$ $I_K : \text{--- } \mu\text{M} (\text{---})$ $I_{KS} : \text{--- } \mu\text{M} (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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 <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} $I_j = g_j O(V - E_{j0})$ $\theta_j = g_{j0} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} / APD_{90, p100}$ where $APD_{90, p100} = APD_{90}$ with - drug at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr / ((AFNaL + AFCaL) / 2)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}.</p>		
	Human epicardial myocytes 		
	Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary	Ketoconazole 		
References	1. Abi-Gerges N et al. (2011) Br J Pharmacol. 164 : 419-432 (+21480866 PMID) 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. CIPA (2016) www.Isiextra.org/reviews/cardiac/cipa/project 6. Witkowskiwa B et al. (2017) Drug discovery today 22 : 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7 : e1002061 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, $APD_{40, 60 \text{ or } 90}$: 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_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qN : integration sum of $i_{CaL} + i_{Kr} + i_{NaL} + i_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{APD, 60}$: $APD_{90} - APD_{40}$ or APD_{90} ("triangulation"), TdP : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : membrane voltage, V_{Vm} : maximal rate of AP rise, V_{Vm} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second		

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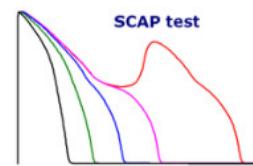
Drug	Lacosamide		
	Voltage-gated Na ⁺ channel (Na _v 1.5) blocker used to treat partial onset seizure in epilepsy		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 50.12 μM (1.0) I_{to}: --- μM (---) I_{Kr}: 50118.72 μM (1.0) I_{NaL}: --- μM (---) I_{Na}: 501.19 μM (1.0) I_{K1}: --- μM (---) I_{Ks}: 251.19 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>60.46 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⁾		
Results	<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> <p>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 and IC_{50s}</p> $I_j = g_j(V - E_{j,0}) \left[1 + \left(\frac{g_j}{IC_{50j}} \right)^n \right]^{-1}$ <p>g_j= maximal conductance of channel j V=membrane potential E_{j,0}= reversal potential for species of ions which flows through channel j IC_{50j}= 50% of inhibition of a drug for channel j x= drug concentration (EFTPC for example) n=tail slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{mid} - APD_{endo} <p>where APD_{endo} = APD_{endo} with - APD_{endo} without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 70: 246-254 Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58: 32-45 Kramer J et al. (2013) <i>Sci Rep</i> 3: 2100 Woooley RL (2015) www.CredibleMeds.org GPA (2016) www.Ilextra.org/heal/science/cardiac/cipa/Project Wisniewska 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 <p>Abbreviations</p> <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_{Kr}+I_{NaL}+I_{CaL}+I_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{EP,AP} : APD₉₀-APD₄₀ 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



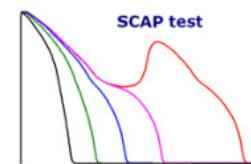
Drug	Lamivudine		
	Reverse transcriptase inhibitor used to treat HIV and hepatitis B infections		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 54.2 μM (0.89) I_{to}: ---- μM (---) I_{Kr}: 2054.0 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: 1571.4 μM (1.0) I_{K1}: ---- μM (--) I_{Ks}: ---- μM (--)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>19.54 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not classified with TdP risk (class 4) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/2 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 and IC_{50s} $I_j = g_j(V - E_{j,0})^{n_j}$ $g_j = \text{maximal conductance of channel } j$ $E_{j,0} = \text{reverse membrane potential for species of ions which flows through channel } j$ $n_j = \text{exponent probability of channel } j$ $IC_{50} = 50\% \text{ of inhibition of a drug for channel } j$ $x = \text{drug concentration (F/TPC for example)}$	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀epi (at CL of 1000 msec) RUD = APD₉₀mid-APD₉₀endo where APD₉₀s = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr}/(\text{AFNaL} + \text{AFCaL})/2) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full scope</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>Human endocardial myocytes</p>		
Summary	<p>Lamivudine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>APD90 - APD90epi (msec)</p>		
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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. GIPA (2016) www.Islieextra.org/heis/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. Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>	<p>AP : action potential, APA : AP amplitude, APD₉₀ : 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_{NaL}*I_{K1}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dp} : APD₉₀-APD₄₀ 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>	
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₉₀ : 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_{NaL}*I_{K1}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dp} : APD₉₀-APD₄₀ 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>	<p>in silico cardiac safety profile of drugs p 76</p>	

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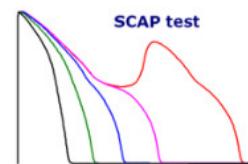
Drug	Lamotrigine		
	Voltage-gated Na ⁺ channel (Na _v 1.5) blocker used to treat some types of epilepsy and bipolar disorder		
Raw data	IC _{50s} (slope) ⁽¹⁾ I _{CaL} : 1584.89 μM (1.0) I _{Kr} : 251.19 μM (1.0) I _{Na} : 100.0 μM (1.0) I _{Ks} : 158.49 μM (1.0)	EFTPC _{max} ⁽¹⁾ 32.860 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/1 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 and IC _{50s} $I_f = g_o(V - E_{f,0})^{n_f}$ $\frac{g}{g_0} = \frac{1}{1 + \left(\frac{D}{IC_{50s}}\right)^{n_f}}$ g _f = maximal conductance of channel n_f = power law exponent of conductance of channel IC_{50s} = 50% of inhibition of a drug for channel D= drug concentration (F _f TPC for example) In this figure	TDR and RUD estimation: • TDR = AP _{mid} - AP _{epi} (at CL of 1000 msec) • RUD = AP _{mid} - AP _{endo} - AP _{epi} where $APD_{endo} = APD_{mid}$ without compound at CL x IC index calculation⁽⁹⁾: $IC\ index = (AFKr/(AFNaL+AFCaL)/2)*100$ where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} .
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes
	Human endocardial myocytes 		
Summary	 		
References	1. Mirams GR et al. (2014) <i>J.Pharmacol.Tox.Methods</i> 70 : 246-254 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. GIPA (2016) www.Ilextra.org/hesi/science/cardiac/cipa/Project 6. Wisiowska 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, 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, IC _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{Kr} *I _{NaL} *I _{CaL} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{EP} : APD ₄₀ -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		

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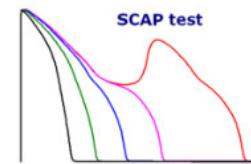
Drug	Lapatinib 4-anilinoquinazoline kinase inhibitor used to treat breast cancer				
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk		
	$I_{CaL} : 1995.3 \mu M (1.0)$ $I_{to} : \dots \mu M (\dots)$ $I_{Kr} : 1.0 \mu M (1.0)$ $I_{NaL} : \dots \mu M (\dots)$ $I_{Na} : 3162.3 \mu M (1.0)$ $I_{K1} : \dots \mu M (\dots)$ $I_{Ks} : 251.2 \mu M (1.0)$				
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾				
Results	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 <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 and IC_{50s} $I_j = g_j(V - E_{j,0})$ $\left[1 + \left(\frac{g_j}{IC_{50j}} \right)^n \right]^{-1}$ $\left(\frac{g_{max}}{g_j} \right)^n$ $\left(\frac{1}{1 + e^{(V - V_{1/2})/k}}} \right)$ $\left(\frac{1}{1 + e^{(V - V_{1/2})/k}}} \right)$ $\left(\frac{1}{1 + e^{(V - V_{1/2})/k}}} \right)$ g_{max} maximal conductance of channel n:open probability of channel $V_{1/2}$: reversal potential for species of ions which flows through channel k:IC₅₀ = 50% of inhibition of a drug for a channel IC_{50} = 50% of inhibition of a drug for channel D: drug concentration (EFTPC for example) <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{mid} - APD_{epi}$ (at CL of 1000 msec) $RUD = APD_{endo} - APD_{endo}$ where $APD_{endo} = APD_{endo}$ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> $IC\ index = (AFKr / (AFNaL + AFCaL)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}.</p>	Human epicardial myocytes Human midmyocardial myocytes Human endocardial myocytes 	Transmural dispersion of repolarisation Reverse use dependence on midmyocardial myocytes 		
Summary	 				
References	1. Mirams GR et al. (2014) <i>J Pharmacol. Toxicol. Methods</i> 70 : 246-254 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. GPA (2016) www.Ilextra.org/hesi/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				
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{40,60,90,99}$: 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, EFTPCmax : 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 $i_{CaL}^+ + i_{Kr}^- + i_{NaL}^+ + i_{NaL}^- + i_{K1}^+$, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD} : $APD_{40} - APD_{40}$ or $APD_{90} - APD_{90}$ ("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				

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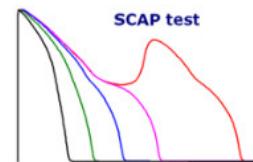
Drug	Levocetirizine			
	Histamine H ₁ receptor antagonist used to treat chronic allergic rhinitis and chronic idiopathic urticaria			
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk	
	I_{CaL} : --- μM (---) I_{Kr} : 100.0 μM (1.0) I_{Na} : --- μM (---) I_K : --- μM (---)	I_{to} : --- μM (---) I_{NaL} : --- μM (---) I_{K1} : --- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 0.063 μM	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
	<i>In silico</i> 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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 and IC_{50s} $I_j = g_j(V - E_{j,0})$ $\frac{g_j}{g_{j,0}} = \frac{1 + \left(\frac{E_{j,0}}{IC_{50s}}\right)^n}{1 + \left(\frac{E_{j,0}}{IC_{50s}}\right)^n}$ $E_{j,0}$ = reversal potential for species of ions which flows through channel n = maximal conductance of channel IC_{50s} = 50% of inhibition of a drug for a particular channel IC_{50s} = 50% of inhibition of a drug for channel • Drug concentration (BP-PC for example) in full range	TDR and RUD estimation: • TDR = $APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) • RUD = $APD_{90, mid} - APD_{90, endo}$ where $APD_{90, x} = APD_{90}$ with - APD_{90} without compound at CL x	
Results	Human epicardial myocytes 		Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes 	
	Human endocardial myocytes 			
	Summary 			
References	1. Ando H et al. (2017) J Pharmacol. Tox. Meth 84 :111-127 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. CiPA (2016) www.pharmacia.org/hesi/science/cardiac/cipa/Project 6. Wisiowska 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. Christope B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 96 : 15-26
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{90, 40, 60, 90}$: AP duration at 40, 60 or 90 % of APA, APD_{90} : 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 90}$: $APD_{90} - APD_{40}$ 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			

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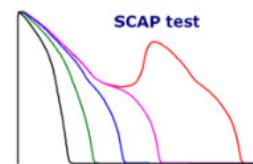
Drug	Levofloxacin		
	Fluoroquinolone antibiotic used to treat various bacterial infections		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_o : --- μM (---) I_Kr : 426.58 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : --- μM (---) I_K1 : --- μM (---) I_Ks : --- μM (---)</p>	<p>$EFTPC_{max}$⁽¹⁾</p> <p>30.932 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⁾ : 4/0 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 and IC_{50s} $I_j = g_j(V - E_{j,0})$ (j maximal conductance of channel) $g_j = g_{j,0} \cdot P_{inhibition}$ $P_{inhibition} = \frac{1}{1 + \left(\frac{[Drug]}{IC_{50j}}\right)^n}$ $n = 2$ (open probability of channel) IC_{50j} = 50% of inhibition of a drug for channel⁽⁹⁾ $[Drug]$ = drug concentration (EFTPC for example) $n = 2$ (slope) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{mid} - APD_{epi}$ (at CL of 1000 msec) $RUD = APD_{mid} - APD_{endo}$ where $APD_{endo} = APD_{mid}$ with - APD_{endo} without compound at CL x <p>IC index calculation⁽⁹⁾: $IC\ index = (AFKr / (AFNaL + AFCaL)) * 100$ where $AFKr$, $AFNaL$ and $AFCaL$ = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p> <p>Summary</p>
References	<p>1. Romero L et al. (2018) J.Chem.Inf.Model. 58: 867-878 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Illsieux.org/hesi/science/cardiac/cipa/project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, EFTPCmax : 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 $i_{CaL} \cdot t_{CaL} + i_{NaL} \cdot t_{NaL} + i_{Ks} \cdot t_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $TdP_{40,60}$: $APD_{40,60}$ - $APD_{40,60}$ ("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</p>		

Safe Cardiac Action Potential Test



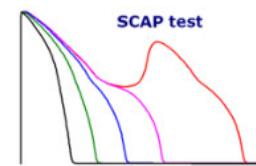
Drug	Levosimendan		
	Troponin C ligand inducing Ca^{++} sensitization used to treat acutely decompensated severe chronic heart failure		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 28.45 \mu M (1.00)$ $I_{Kr} : 22.00 \mu M (0.68)$ $I_{Na} : 85.714 \mu M (1.00)$ $I_{Ks} : --- \mu M (---)$ $I_{to} : --- \mu M (---)$ $I_{NaL} : --- \mu M (---)$ $I_{K1} : --- \mu M (---)$	$0.0028 \mu M$	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/1 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 <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 and IC_{50s} $I_f = g_f(V - E_{on})$ $\frac{g_f}{g_m} = \frac{1}{1 + \left(\frac{V - V_{50}}{IC_{50s}}\right)^n}$ <p>where g_m = maximal conductance of channel V = open probability of channel V_{50} = reversal potential for species of ions which flows through channel n = slope of inhibition curve IC_{50s} = 50% of inhibition of a drug for channel D = drug concentration (BP for example) x = full slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, TDR}$ where $APD_{90, P_s} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr \times AFNaL + AFCaL)/2) \times 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL} in full slope</p>	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Summary</p> <p>Levosimendan x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Levosimendan</p> <p>References</p> <ol style="list-style-type: none"> Passini E et al. (2019) <i>Br J Pharmacol</i> 176: 3819–3833 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32–45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woolesley RL (2015) www.CredibleMeds.org GPA (2016) www.IsiExtra.org/hesi/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: e1002061.8 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 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: 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_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{NaL} + I_{Ks} + I_{to}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{DR, 60}$: $APD_{90} - APD_{40}$ 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</p>

Safe Cardiac Action Potential Test



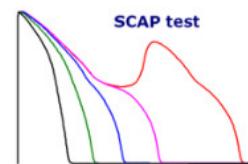
Drug	Lidocaine		
	Neural Na ⁺ channel blocker used as local anesthetic		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL} : ---- μM (---) I_{to} : ---- μM (---) I_{Kr} : ---- μM (---) I_{Na} : 10.79 μM (1.3) I_{Na} : ---- μM (---) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>2.5604 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⁾ : 0/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 and IC_{50s} $I_j = g_j(V - E_{jon}) \left[1 + \left(\frac{g_j}{IC_{50j}} \right)^n \right]^{-1}$ <p>g_j= maximal conductance of channel E_{jon}= reversal potential for species of ions which flows through channel n= reversal probability of channel IC_{50j}= 50% of inhibition of a drug for channel j D= drug concentration (BP for example) x= full dosage</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀ epi (at CL of 1000 msec) RUD = APD₉₀endo - APD₉₀mid where APD₉₀s = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> $IC\ index = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and ACFaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full dosage</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>Legend: 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>	<p>APD90s - APD90e (msec)</p>	<p>IC index (msec)</p>
References	<p>1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Isiextra.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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_{90,40 or 60} : 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_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP,40} : APD₉₀-APD₄₀ 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



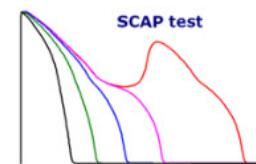
Drug	Linezolid		
	Oxazolidinone antibiotic used to treat aerobic gram-positive bacterial infections		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 105.4 μM (0.94) I_{to} : ---- μM (---) I_{Kr}: 1147.2 μM (1.0) I_{NaL} : ---- μM (---) I_{Na}: 2644.5 μM (1.0) I_{K1} : ---- μM (--) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>59.11 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not classified with TdP risk (class 4) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/2(TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 and IC_{50s} $I_j = g_j(V - E_{j,0})^{n_j}$ $\frac{g_j}{g_{j,0}} = \text{Control} \cdot \left[1 + \left(\frac{D}{IC_{50j}} \right)^{\alpha_j} \right]^{-1}$ <p>g_j = maximal conductance of channel j E_{j,0} = reversal potential for species of ions which flows through channel j D = drug concentration (F_jTPC for example) α_j = tail slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀epi (at CL of 1000 msec) RUD = APD₉₀endo-APD₉₀mid where APD₉₀s = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr}/(\text{AFNaL} + \text{AFCaL})/2) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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> <ul 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	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Illsieux.org/hsip/science/cardiac/cipa/project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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_{90,40,60,90} : 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, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dp} : APD₉₀-APD₄₀ 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



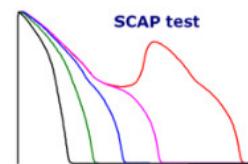
Drug	Lopinavir		
	HIV-1 protease inhibitor used to treat HIV infection		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 15.601 μM (1.0) I_{to} : ---- μM (---) I_{Kr}: 5.17 μM (1.2) I_{NaL} : ---- μM (---) I_{Na} : ---- μM (---) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.7037 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : not reported CredibleMeds⁽⁴⁾ : possible risk of TdP (class 2) (+ ritonavir) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : not reported</p>
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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} <p>$I_j = g_j(V - E_{j,0})$</p> <p>$E_{j,0} = V_{rest} + \frac{g_{max}}{g_{min}} \cdot \ln \left(\frac{V - V_{rest}}{V_{rest}} \right)$</p> <p>$\beta_j = \frac{g_j}{g_{max}}$</p> <p>$\beta_j = \frac{1}{1 + \left(\frac{IC_{50s}}{[D]} \right)^n}$</p> <p>g_j = maximal conductance of channel j V_{rest} = resting membrane potential E_{j,0} = reversal potential for species of ions which flows through channel j g_{max} = maximal conductance of channel j g_{min} = minimal conductance of channel j IC_{50s} = 50% of inhibition of a drug for channel j [D] = drug concentration (EFTPC for example) n = half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀Endo - APD₅₀Mid 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 AFGaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL}.</p>	
Summary	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p>		
References	<p>1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Isliefta.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, APD₅₀ : AP duration at 50 or 90 % of APA, APD₅₀ : 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, IC_{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{Ks}+I_{NaL}+I_{CaL}+I_{K1}, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP} : 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, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

Safe Cardiac Action Potential Test



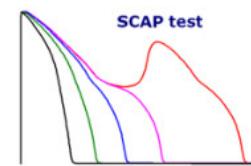
Drug	Loratadine		
	Histamine H ₁ receptor antagonist used to treat allergic rhinitis		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 11.4 \mu M (1.38)$ $I_{Kr} : 6.1 \mu M (1.44)$ $I_{Na} : 28.9 \mu M (1.64)$ $I_Ks : --- \mu M (---)$ $I_{to} : --- \mu M (---)$ $I_{NaL} : --- \mu M (---)$ $I_{K1} : --- \mu M (---)$	0.0004 μM	Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CIPA ⁽⁵⁾ : low or no risk of TdP (class 3) WP ⁽⁶⁾ : 0/7 (TdP+/TdP-)
	<i>In silico</i> 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): $[Na^+]_o = 140$ - $[Ca^{++}]_o = 1.8$ - $[K^+]_o = 5.4$ • 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 and IC_{50s} $I_j = g_j(V - E_{jon})$ $\frac{g_j}{g_{no\ compound}} = [1 + \left(\frac{\delta}{IC_{50s}}\right)^n]^{-1}$ $\delta = \text{open probability of channel}$ $V = \text{voltage membrane}$ $E_{jon} = \text{reverse potential for species of ions which flows through channel}$ $g_{max} = \text{maximal conductance of channel}$ $IC_{50s} = 50\% \text{ of inhibition of a drug for a channel}$ $n = \text{drug concentration (EF-TPC for example)}$ $\delta = \text{drug concentration}$	TDR and RUD estimation: • TDR = $APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) • RUD = $APD_{90, mid} - APD_{90, TDR}$ where $APD_{90, P_s} = APD_{90}$ without compound at CL x IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr/(AFNaL+AFCaL)/2)*100$ where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ks} , I_{NaL} and I_{CaL} in full scope
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>
Summary	<p>Loratadine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Loratadine 100-fold EFTPC_{max} vs. IC_{50s}</p>		
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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. GIPA (2016) www.Isiextra.org/hesi/science/cardiac/gipa/ 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	AP : action potential, APA : AP amplitude, $APD_{40, 60, 90, 99}$: 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, ende : endocardial myocyte, epi : epicardial myocyte, IC : ion channel inhibition index, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{NaL} + I_{Ks} + I_{to}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{EP, 90}$: $APD_{90} - APD_{40}$ 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		

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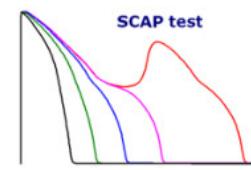
Drug	Maraviroc		
	Human chemokine CCR5 receptor antagonist used to treat HIV infection		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 39.81 μM (1.0) I_{Na} : --- μM (---) I_{Na} : 1000.0 μM (1.0) I_{K1} : --- μM (--) I_{Ks} : 63.096 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.10981 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⁾		
Results	<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 F (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_f = g_f(V - E_{f,0})$ $g_f = g_{control} \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ <p>g : maximal conductance of channel D : drug concentration IC_{50s} : 50% of inhibition of a drug for channel n : drug concentration (EF-TPC for example) CL : cycle length</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP₄₀₀mid - AP₄₀₀epi (at CL of 1000 msec) RUD = AP₄₀₀endo - AP₄₀₀mid where AP₄₀₀P_a = AP₄₀₀without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p>		
Summary	<p>Maraviroc x-fold EFTPC_{max} vs. IC_{50s}</p> <p>www.scapttest.com</p>	<p>Maraviroc</p> <p>www.scapttest.com</p>	
References	<p>1. Mirams GR et al. (2014) <i>J.Pharmacol.Tox.Methods</i> 70: 246-254 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GPA (2016) www.Issixtra.org/hesi/science/cipa/project 6. Wisiowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, APD₆₀, APD₉₀ : 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_{Kr}, I_{NaL}, I_{CaL}, I_{K1}, I_{Ks}, 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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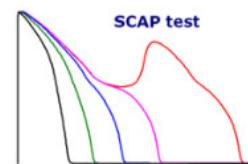
Drug	Mefloquine		
	Mechanism of action not fully understood, used to treat malaria		
Raw data	IC_{50s} (slope) ⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 14.1 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{ks} : 1.43 μM (1.0)	$EFTPC_{max}$ ⁽¹⁾ 0.0952 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⁾ : 2/2 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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 - $[Ca^{++}]$ _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_{50} $I_j = g_j O(V - E_{on})$ E_{on} : reversal potential for species of ions which flows through channel E_{max} : maximal conductance of channel V : membrane potential O : reversal potential for species of ions which flows through channel IC_{50} : 50% of inhibition of a drug for a channel D : drug concentration (EFTPC for example) \times : full slope	TDR and RUD estimation: • TDR = $APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) • RUD = $APD_{90, Endo} - APD_{90, Mid}$ where $APD_{90, D} = APD_{90}$ with - APD_{90} without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary			
References	1. Abi-Gerges N et al. (2011) <i>Br J Pharmacol</i> 164 : 419-432 (+PMID 21561091) 2. Redfern WS et al. (2003) <i>Cardiovasc Res</i> 58 : 32-45 3. Kramer J et al. (2013) <i>Circ Res</i> 112 : 2100 4. Woosley RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.Fluxtra.org/neuroscience/cardiac/cipa/ 6. Witsniewska 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 : e1002051-8 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	AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: 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 $I_{Ca,L} + I_{Na,L} + I_{K1,L} + I_{Ks,L}$, RMP : resting membrane potential, Tdp_{40} : $APD_{90} - APD_{90}$ ("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/V_s : volt per second		

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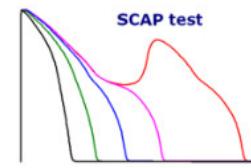
Drug	Methadone		
	Opioid κ and σ receptor antagonist used to treat severe pain		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 37.4 \mu M (1.67)$ $I_{Kr} : 3.5 \mu M (1.0)$ $I_{Na} : 31.8 \mu M (1.37)$ $I_K : \text{--- } \mu M (\text{---})$ $I_Ks : \text{--- } \mu M (\text{---})$	$0.507 \mu M$	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 6/0 (TdP+/TdP-)
	<i>In silico</i> 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} $I_j = g_j(V - E_{jon})$ $g_j = g_{j,control} \left[1 + \left(\frac{D}{IC_{50j}} \right)^n \right]^{-1}$ $g_{j,control}$ = maximal conductance of channel j E_{jon} = reversal potential for species of ions which flows through channel j IC_{50j} = 50% of inhibition of drug for channel j D = drug concentration (EF TPC_{max} for example) n = half slope	TDR and RUD estimation: • TDR = $APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) • RUD = $APD_{90, Endo} - APD_{90, P_{mid}}$ where $APD_{90,P_i} = APD_{90}$ with - APD_{90} without compound at CL x
Results	<p>Human epicardial myocytes</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p>	<p>Transmural dispersion of repolarisation</p>	<p>Reverse use dependence on midmyocardial myocytes</p>
Summary			
References	1. Kramer J et al. (2013) Sci Rep. 3: 2300 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. CiPA (2016) www.Istearta.org/hsis/science/cardiac/cipa/ Project 6. Weronika B et al. (2017) Drug discovery today 22: 10-16 7. O'Hearn T et al. (2011) PLoS Comput Biol. 7: e1003061.8 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	AP : action potential , APA : AP amplitude , $APD_{90,xx-xx}$: AP duration at 40, 60 or 90 % of APA , APD_{xx} : APD prolongation , a.u. : arbitrary unit , CL : cycle length , DA : depolarization abnormalities , EAD : early afterdepolarization , EF TPC_{max} : maximal effective free therapeutic plasma concentration , endo : endocardial myocyte , epi : epicardial myocyte , IC index : IC channel inhibition index , IC_{50} : 50% inhibition concentration , mid : midmyocardial myocyte , msec : millisecond , mV : millivolt , qNet : integration sum of $I_{CaL} + I_{Kr} + I_{Na} + I_{NaP} + I_{Ks}$, RMP : resting membrane potential , RUD : reverse use dependence , T_{40-60} : $APD_{40}-APD_{60}$ or APD_{40} : 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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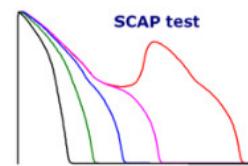
Drug	Metoprolol		
β_1 -adrenoceptor antagonist used to treat hypertension and angina, and to reduce mortality due to myocardial infarction			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>$I_{CaL} : 3280 \mu M (1.0)$ $I_{to} : \text{---- } \mu M (\text{---})$ $I_{Kr} : \text{---- } \mu M (\text{---})$ $I_{NaL} : 630.0 \mu M (1.0)$ $I_{Na} : 30.3 \mu M (1.0)$ $I_{K1} : \text{---- } \mu M (\text{---})$ $I_Ks : \text{---- } \mu M (\text{---})$</p>	<p>$EFTPC_{max}$⁽¹⁾</p> <p>1.80 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⁾ : low or no risk of TdP (class 3) WP⁽⁶⁾ : 0/1 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 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} $I_j = g_j(V - E_{jon})$ $g_j = g_{max} \cdot \min\left(1 + \left(\frac{D}{IC_{50s}}\right)^n, 1\right)$ <p>where g_{max} = maximal conductance of channel E_{jon} = reversal potential for species of ions which flows through channel IC_{50s} = 50% of inhibition of a drug for a channel D = drug concentration (EFTPC for example) n = half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90, Emax}/APD_{90, P_{100}}$ where $APD_{90, P_{100}} = APD_{90}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, 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>Human endocardial myocytes</p> <p>Summary</p> <p>Metoprolol x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Metoprolol</p>
References	1. Li Z et al. (2019) <i>Clin Pharmacol Ther</i> 105 : 466-475 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.IslExtra.org/hes/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 : 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> 95 : 15-26		
Abbreviations	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 ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL} , I_{Kr} , I_{NaL} , I_{K1} , I_K , RMP : resting membrane potential, RUD : reverse use dependence, $TdP_{+/-}$: $APD_{90, Emax}/APD_{90, P_{100}}$ ("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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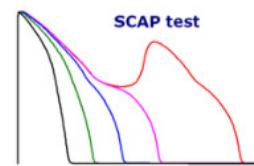
Drug	Metronidazole		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 177.9 \mu M (0.66)$ $I_{to} : \text{--- } \mu M (\text{---})$ $I_{Kr} : 1340.2 \mu M (1.0)$ $I_{NaL} : \text{--- } \mu M (\text{---})$ $I_{Na} : 2073.2 \mu M (1.0)$ $I_K : \text{--- } \mu M (\text{---})$ $I_Ks : \text{--- } \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	<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} $I_f = g_f(V - E_{f,0})$ (V:voltage membrane; $E_{f,0}$: reversal potential for species of ions which flows through channel); g_f: maximal conductance of channel; f: drug effect on channel $\theta = \left[1 + \left(\frac{D}{IC_{50s}} \right)^n \right]^{-1}$ (D: drug concentration (EFTPC for example); n: half slope; IC_{50s}: 50% of inhibition of a drug for a channel) 		
	<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			
References	1. Kramer J et al. (2013) Sci. rep. 3 : 2100 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.CredibleMed.org 5. CIPA (2016) www.intervra.org/henri/science/cardiac/cipa/ Project 6. Widłosińska B et al. (2017) Drug discovery today 22 : 10-16 7. O'Hearn 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, $APD_{50-90\%}$: 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, EFTPCmax : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_K + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{dP+} : $APD_{90} - APD_{50}$ or $APD_{90} - APD_{40}$, 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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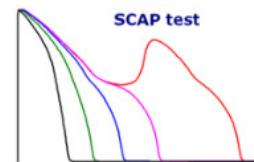
Drug	Mexiletine		
	Voltage-gated Na^+ channel blocker used as class IB antiarrhythmic to treat ventricular arrhythmia		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	I_{CaL} : ---- μM (---) I_{to} : ---- μM (---) I_{Kr} : ---- μM (---) I_{NaL} : 8.957 μM (1.4) I_{Na} : ---- μM (---) I_{Kt} : ---- μM (---) I_{Ks} : ---- μM (---)	2.5032 μM	Redfern ⁽²⁾ : isolated reports of TdP (class 4) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : low or no risk of TdP (class 3) WP ⁽⁶⁾ : 1/5 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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): $[\text{Na}^+]_o$, 140 - $[\text{Ca}^{++}]_o$, 1.8 - $[\text{K}^+]_o$, 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 and IC_{50s} $I_j = g_j(V - E_{j,\text{rest}})$ $\frac{g_j}{g_{\text{max}}} = \frac{\text{open probability of channel } j}{\text{open probability of channel } \text{max}}$ V_{rest} = reversal potential for species of ions which flows through channel $\beta_j = \left(1 + \left(\frac{\delta}{IC_{50s}}\right)^n\right)^{-1}$ IC_{50s} = 50% of inhibition of a drug for a channel δ = drug concentration (BP = EFTPC for example) n = tail slope	TDR and RUD estimation: • TDR = $APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) • RUD = $APD_{90, \text{endo}} - APD_{90, \text{mid}}$ where $APD_{90,P_i} = APD_{90}$ with - APD_{90} without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary			
References	1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81 : 251-262 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.Isiextra.org/hesi/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		
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{40, 40 \text{ or } 60}$: 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Na} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 40}$: $APD_{40} - APD_{40}$ or $APD_{60} - APD_{60}$ ("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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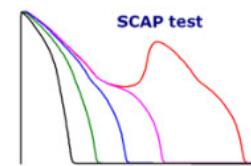
Drug	Mibepradil		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 0.51 \mu M (1.44)$ $I_{to} : \text{---} \mu M (\text{---})$ $I_{Kr} : 1.7 \mu M (1.38)$ $I_{NaL} : \text{---} \mu M (\text{---})$ $I_{Na} : 5.6 \mu M (1.53)$ $I_{K1} : \text{---} \mu M (\text{---})$ $I_K : \text{---} \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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): $[Na^+]_o = 140 - [Ca^{++}]_o = 1.8 + [K^+]_o = 4.5$ 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} $I_j = g_j O(V - E_{j,0})$ $g_j = \text{minimal conductance of channel } j$ $O(\cdot) = \text{open probability of channel } j$ $E_{j,0} = \text{reverse potential for species of ions which flows through channel } j$ $\theta_j = g_{control,j} \left[1 + \left(\frac{D}{[IC_{50s}]^{x_j}} \right)^{y_j} \right]^{-1}$ $g_{control,j} = \text{minimal conductance of channel } j$ $D = \text{dry weight minimal conductance of channel } j$ $x_j = \text{IC index (0.1 to 1000 for example)}$ $y_j = \text{hill slope}$ 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) $RUD = APD_{90, \text{Epi}}/APD_{90, \text{Endo}}$ where $APD_{90,P} = APD_{90} \text{ with } - P \text{ APD}_{90} \text{ without compound at CL } x$ IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / ((AFNaL + AFCaL)/2)) * 100$ where $AFKr = \text{AF}K_r / (\text{AF}K_r + \text{AF}C_a)$ $AFNaL = \text{AF}N_a / (\text{AF}N_a + \text{AF}C_a)$ $AFCaL = \text{AF}C_a / (\text{AF}N_a + \text{AF}C_a)$ active fraction (%) of the I_{CaL} , I_{NaL} and I_{CaL}
Summary	<p>Human epicardial myocytes</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Reverse use dependence on midmyocardial myocytes</p>		
References	1. Kramer J et al. (2013) Sci. rep. 3 : 2100 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.IAHA.org/hesi/science/cardiac/cipa/ Project 6. Widmowska B et al. (2017) Drug discovery today 22 : 10-16 7. O'Hearn 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	AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APP : 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 $I_{CaL} + I_{NaL} + I_{K1} + I_K + I_{Kr}$, RMP : resting membrane potential, 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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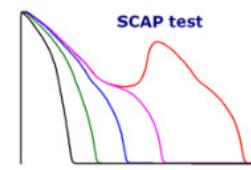
Drug	Milrinone		
	Phosphodiesterase PDE-III inhibitor used to treat acute decompensated heart failure		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : ---- μM (---) I _{to} : ---- μM (---) I _{Kr} : 1500.0 μM (0.85) I _{Na} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.316 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
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 and IC _{50s} $I_j = g_j(V - E_{j,0})^{1 + \left(\frac{g_j}{g_{j,0}}\right)^{-1}}$ g _j = maximal conductance of channel g _{j,0} = maximal conductance of channel without drug E _{j,0} = reversal potential for species of ions which flows through channel IC _{50s} = 50% of inhibition of a drug for channel D= drug concentration (EF-TPC for example) x= fold increase	TDR and RUD estimation: • TDR = APD ₉₀ mid - APD ₉₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ endo - APD ₉₀ mid where APD ₉₀ P _x = APD ₉₀ with - APD ₉₀ without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
	Summary 		
References	1. Passini E et al. (2019) Br J Pharmacol 176 : 3819-3833 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. CiPA (2016) www.pharmcentral.org/hesi/science/cardiac/cipa/project 6. Wisiowska 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. Christope B & Crumb WJ Jr (2019) J Pharmacol Toxicol Methods 96 : 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{90, 40 or 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, ende : 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 _{K1} *I _{Na} *I _{Na} *I _{Kr} *I _{CaL} , RMP : resting membrane potential, RUD : reverse use dependence, T _{EP, 90} : APD ₉₀ -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		

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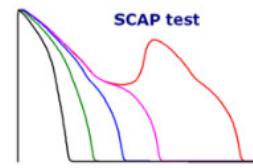
Drug	Mitoxantrone		
	DNA reactive agent used to treat multiple sclerosis		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 22.5 μM (0.64) I_{to}: --- μM (---) I_{Kr}: 539.4 μM (1.0) I_{NaL}: --- μM (---) I_{Na}: 93.5 μM (1.05) I_{K1}: --- μM (---) I_{Ks}: --- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.225 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not classified with TdP risk (class 4) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/3 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 and IC_{50s} $I_j = g_j(V - E_{j,0}) \left[1 + \left(\frac{g_j}{IC_{50j}} \right)^n \right]^{-1}$ <p>g_j = maximal conductance of channel j E_{j,0} = reversal potential for species of ions which flows through channel j V = voltage membrane n = reversal potential for species of ions which flows through channel j IC_{50j} = 50% of inhibition of a drug for channel j x = drug concentration (FEP_{max} for example) CL = cycle length</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₅₀ mid - APD₅₀epi (at CL of 1000 msec) RUD = APD₅₀endo - APD₅₀mid where APD₅₀x = APD₅₀ with - APD₅₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and ACFaL = active fraction (%) of the I_{Kr}, 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>		
	<p>Summary</p>		
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GPa (2016) www.Isiextra.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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. Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{50,40,60,90} : 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_{NaL}*I_{K1}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{EP,40} : 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, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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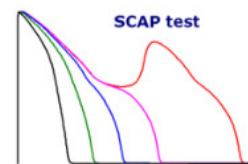
Drug	Moxifloxacin Fluoroquinolone antibiotic used to treat various bacterial infections		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 173.0 \mu M (1.0)$ $I_{to} : \text{---} \mu M (\text{---})$ $I_{Kr} : 86.2 \mu M (0.94)$ $I_{Na} : \text{---} \mu M (\text{---})$ $I_{Na} : 1112.0 \mu M (1.0)$ $I_K1 : \text{---} \mu M (\text{---})$ $I_Ks : \text{---} \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 <p>Effect of drugs on AP⁽⁸⁾:</p> $I_f = g_f(V - E_{f,0})$ $g_f = g_{max} \cdot \min\left(1 + \frac{\delta}{(IC_{50})^{n_f}}, 1\right)^{-1}$ <ul style="list-style-type: none"> g_{max}: maximal conductance of channel δ: open probability of channel n_f: reversal potential for species of ions which flows through channel IC_{50}: 50% of inhibition of a drug for a channel δ: drug concentration (BP for example) on full scale 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, TDR}$ where $APD_{90, P_s} = APD_{90}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFK_r \cdot (AFNa_L + AFCa_L)/2) * 100$ <p>where AFK_r, AFNa_L and AFCa_L = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full scope</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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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. GPA (2016) www.Ilextra.org/hesi/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		
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{90, 40 \text{ or } 90}$: 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, EFTPCmax : 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 $i_{CaL} \cdot t_{CaL} + i_{NaL} \cdot t_{NaL} + i_{Kr} \cdot t_{Kr}$, RMP : resting membrane potential, RUD : reverse use dependence, TdP_{40} : $APD_{90} - APD_{40}$ or $APD_{90} - qNet$ ("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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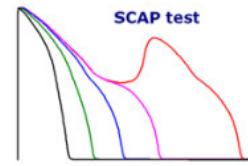
Drug	Nebivolol		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	I_{CaL} : --- μM (---) I_{to} : 50.119 μM (1.0) I_{Kr} : 0.316 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : 6.310 μM (1.0) I_{K1} : --- μM (---) I_K : 15.849 μM (1.0)		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <p>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}</p> $I_j = g_j(V - E_{jon})$ $g_j = \text{maximal conductance of channel } j$ $V = \text{voltage membrane}$ $E_{jon} = \text{reverse potential for species of ions which flows through channel } j$ $B_j = g_{jcontrol} \left[1 + \left(\frac{D}{IC_{50j}} \right)^n \right]^{-1}$ <p>$g_{jcontrol}$ = maximal conductance of channel j n = exponent of inhibition curve D = IC₅₀ = 50% of inhibition of a drug for a channel IC_{50j} = IC₅₀ of compound at CL 1000 msec D = drug concentration (BP/EC for example) x = full slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90, P_{endo}} - APD_{90, P_{mid}}$ where $APD_{90, P_i} = APD_{90}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, 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> <p>Summary</p> <p>Effect (%)</p> <p>References</p> <ol style="list-style-type: none"> Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 70: 246-254 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 GPA (2016) www.lisextra.org/hes/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, $APD_{40, 60 \text{ or } 90}$: 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1} + I_K$, RMP : resting membrane potential, APA : $APD_{90, 60}$ 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</p>

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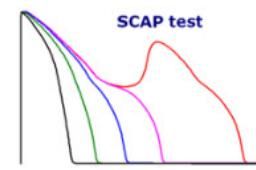
Drug	Nelfinavir		
	Viral protease inhibitor used to treat HIV infection		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : 5011.87 μM (1.0) I_{Kr} : 12.589 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : 79.433 μM (1.0) I_{K1} : --- μM (---) I_{Ks} : 79.433 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0710 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⁾ : 2/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORd model)⁽⁷⁾		
Results	<p>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 - [Ca²⁺]_o 1.8 - [K⁺]_o 5.4 • Cycle length : 1000 msec • Beat number: 100</p> <p>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} $I_j = g_j(V - E_{jon})$ $E_{jon} = \text{ reversal potential for species of ions which flows through channel } j$ $g_j = \text{ maximal conductance of channel } j$ $\theta = \text{ drug concentration}$ $\theta_{control} = \left[1 + \left(\frac{\theta}{IC_{50s}} \right)^n \right]^{-1}$ $IC_{50s} = 50\% \text{ inhibition of a drug for a channel } j$ D = drug concentration (EFTPC for example) n = half slope</p>	<p>TDR and RUD estimation: • TDR = APD₅₀mid - APD₅₀epi (at CL of 1000 msec) • RUD = APD₅₀P_{endo}-APD₅₀P_{endo} where APD₅₀P_e = APD₅₀with - APD₅₀without compound at CL x</p> <p>IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, 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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Mirams GR et al. (2014) <i>J Pharmacol. Toxicol. Methods</i> 20 : 246-254 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.Istepra.org/hesi/science/cardiac/cipa/Project 6. Wosiński 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 (2013) <i>J Pharmacol Toxicol Methods</i> 96 : 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, APD ₅₀ : AP duration at 50, 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, ende : endocardial myocyte, epi : epicardial myocyte, IC index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, m sec : millisecond, mV : millivolt, qMax : integration sum of I _{Kr} +I _{NaL} +I _{CaL} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, TdP : APD ₅₀ -APD ₅₀ 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 _s : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second		

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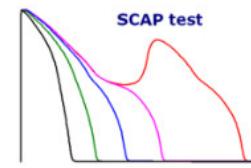
Drug	Nicardipine		
	Voltage-gated L-type Ca ⁺⁺ channel (Ca _v 1.2) blocker used to treat hypertension and chronic stable angina		
Raw data	IC _{50s} (slope) ⁽¹⁾	EFTPC _{max} ⁽¹⁾	TdP risk
	<p>I_{CaL}: 0.0097 μM (1.0) I_{to} : ---- μM (---)</p> <p>I_{Kr} : 0.3 μM (1.11) I_{Na} : ---- μM (---)</p> <p>I_{Na} : 1.02 μM (1.0) I_{K1} : ---- μM (---)</p> <p>I_{Ks} : ---- μM (---)</p>	0.014 μM	<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⁾ : 1/2 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 100 (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_f = g_f(V - E_{f,rest})$ (g_f= maximal conductance of channel ; V=voltage membrane ; $E_f,rest$= reversal potential for species of ions which flows through channel) $B_f = \frac{g_f}{g_f,control} \left[1 + \left(\frac{D_f}{IC_{50,f}} \right)^n \right]^{-1}$ (D_f= drug concentration (FPC for example) in full range ; $IC_{50,f}$= 50% of inhibition of a drug for channel) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{90, mid} - APD_{90,epi} (at CL of 1000 msec) RUD = APD_{90,epic}-APD_{90,mid} where APD_{90,P} = APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr}/(\text{AFNaL}+\text{AFCaL}))/2 * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full range</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>Legend: 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>Nicardipine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Nicardipine</p>		
References	<p>1. Passini E et al. (2019) <i>Br J Pharmacol</i> 176: 3819–3833 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. GPC (2016) www.Islsextra.org/hes/science/cardiac/cipa/Project 6. Wisińska 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_{90, 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_{K1}+I_{Kr}+I_{NaL}+I_{Na}+I_{CaL}, RMP : resting membrane potential, RUD : reverse use dependence, T_{40,60} : APD₉₀-APD₆₀ 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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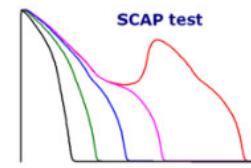
Drug	Nifedipine		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 0.012 \mu M (1.02)$ $I_{NaL} : 44.0 \mu M (0.80)$ $I_{K1} : 88.5 \mu M (0.71)$ $I_K : --- \mu M (---)$	$I_{NaL} : --- \mu M (---)$ $I_{K1} : --- \mu M (---)$	$0.008 \mu M$ <p>Redfern⁽²⁾ : isolated TdP reports (class 4) Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not classified with TdP risk (class 4) CiPA⁽⁵⁾ : low or no risk of TdP (class 3) WP⁽⁶⁾ : 0/7 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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 100 (full inhibition) which is a function of a multiple of $EFTPC_{max}$ and IC_{50s} $I_f = g_f O(V - E_{f,0})$ (g_f: maximal conductance of channel^(*)) $O(v) = \frac{1}{1 + e^{-\frac{v - V_{1/2}}{k}}}$ ($V_{1/2}$: reversal potential for species of ions which flows through channel^(*)) $E_{f,0}$: reversal potential of drug^(*) g_f: maximal conductance of channel^(*) $O(v) = \frac{1}{1 + e^{-\frac{v - V_{1/2}}{k}}}$ ($V_{1/2}$: half maximal drug-free maximal conductance of channel^(*)) D_f: drug concentration (SF TdP for example) 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, epi} - APD_{90, mid}$ where $APD_{90,P} = APD_{90}$ 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_{K1}.</p>
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
	Reverse use dependence on midmyocardial myocytes 		
Summary			
References	<ol style="list-style-type: none"> Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woooley RL (2015) www.crediblemeds.org GPA (2016) www.islextra.org/hes/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, 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, $APD_{40, 60 \text{ or } 90}$: 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNf : integration sum of $I_{CaL} I_{NaL} I_{K1} I_{K2} I_{K3} I_{K4}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{APD} : $APD_{90} - APD_{90}$ or $APD_{90} - APD_{90}$ ("triangulation"), TDR : torsade de pointes , V_{max} : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : volt per second</p>		

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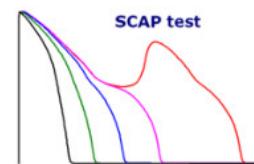
Drug	Nilotinib		
	Tyrosine kinase inhibitor used to treat chronic myeloid leukemia		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 17.5 μM (1.0) I_{to} : ---- μM (---) I_{Kr}: 1.0 μM (0.96) I_{NaL} : ---- μM (---) I_{Na}: 13.3 μM (2.11) I_{Kd} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.172 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : possible risk of TdP (class 2) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 3/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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} <p>$I_g = g_0(V - E_{on})^n$</p> <p>$B_f = \frac{g}{g_{control}} \left[1 + \left(\frac{g}{g_{control}} \right)^{\alpha} \right]^{-1}$</p> <p>g = maximal conductance of channel V = membrane voltage E_{on} = reversal potential for species of ions which flows through channel IC₅₀ = 50% of inhibition of a drug for a channel x = drug concentration (BP = EFTPC_{max} for example) CL = half-life</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{depi} (at CL of 1000 msec) RUD = AP_{mid} - AP_{depi} at CL₁₀₀₀ where AP_{depi} = AP_{mid} with - AP_{depi} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full scope</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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Kramer J et al. (2013) <i>Sci rep</i> 3 : 2100 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.Iseuxtra.org/hesi/science/cardiac/cipa/ Project 6. Winiarska 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 : AP duration at 40, 60 or 90 % of APA, APD ₉₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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 : mid-myocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{Kr} +I _{NaL} +I _{Kd} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₉₀ : APD ₉₀ -APD ₄₀ 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 _{mmin} : minimal rate of AP decrease at EAD take-off voltage, V _s /s : volt per second		

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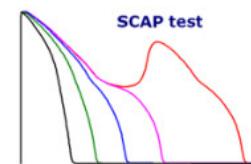
Drug	Nimodipine		
	Voltage-gated L-type Ca ⁺⁺ channel (Ca _v 1.2) blocker used to improve neurological outcomes in patients with subarachnoid hemorrhage		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 0.139 μM (0.63) I_{to} : ---- μM (---) I_{Kr}: 45.6 μM (1.0) I_{Na} : ---- μM (---) I_{Na} : ---- μM (---) I_{K1} : ---- μM (--) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.001 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>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 and IC_{50s} <p>$I_f = g_f(V - E_{1/2})$</p> <p>$\frac{g_f}{g} = \frac{1}{1 + \left(\frac{D}{IC_{50f}}\right)^n}$</p> <ul style="list-style-type: none"> g = maximal conductance of channel f = species of channel D = drug concentration (EFTPC for example) n = fold slope IC_{50f} = 50% of inhibition of a drug for channel f 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP₅₀ mid - AP₅₀ epi (at CL of 1000 msec) RUD = AP₅₀ Endo - AP₅₀ Mid where AP₅₀P_s = AP₅₀ with - AP₅₀ 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} in full slope</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>Human endocardial myocytes</p>		
	<p>Summary</p>		
References	<p>1. Passini E et al. (2017) <i>Front Physiol.</i> 8: 668 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. GPA (2016) www.Isiextra.org/hesi/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, 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_{50f} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dp, 40} : APD₄₀-APD₄₀ 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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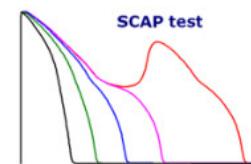
Drug	Nisoldipine Voltage-gated L-type Ca ⁺⁺ channel (Ca _v 1.2) blocker used to treat hypertension			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 0.079 μM (1.0) I_{to}: --- μM (---) I_{Kr}: 22.91 μM (1.0) I_{Na}: --- μM (---) I_{Na}: --- μM (---) I_{K1}: --- μM (---) I_{Ks}: 39.81 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</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>	
	<i>In silico</i> 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> <p>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 and IC_{50s}</p> $I_f = g_f(V - E_{1/2})$ <p>g_f= maximal conductance of channel E_{1/2}= half maximal activation voltage of channel V= voltage membrane V_{rev}= reversal potential for species of ions which flows through channel⁽⁹⁾</p> $\theta_f = \theta_{control} \left[1 + \left(\frac{\theta}{\theta_{IC50}} \right)^n \right]^{-1}$ <p>θ_f= open probability of channel at drug concentration θ θ_{IC50}= 50% of inhibition of a drug for channel⁽¹⁰⁾ θ_{IC50}= 50% of inhibition of a drug for channel⁽¹¹⁾ D= drug concentration (EFTPC for example) n= Hill slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{endo}-APD_{epi} where APD_{endo} = APD_{endo} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and ACFaL = active fraction (%) of the I_{Kr}, I_{CaL} and I_{CaL} in full scope</p>	
Results	<p>Human epicardial myocytes</p> <p>Nisoldipine x-fold EFTPC_{max} vs. IC_{50s} — no compound — x 100</p> <p>www.scapttest.com</p>	<p>Transmural dispersion of repolarisation</p> <p>No compound Nisoldipine 100-fold EFTPC_{max} vs. IC_{50s} — Epi — Mid — Endo — TDR</p> <p>www.scapttest.com www.scapttest.com</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>Nisoldipine 100-fold EFTPC_{max} vs. IC_{50s} — CL 1000 msec — CL 4000 msec</p> <p>www.scapttest.com</p>	
	<p>Human midmyocardial myocytes</p> <p>Nisoldipine x-fold EFTPC_{max} vs. IC_{50s} — no compound — x 100</p> <p>www.scapttest.com</p>			
	<p>Human endocardial myocytes</p> <p>Nisoldipine x-fold EFTPC_{max} vs. IC_{50s} — no compound — x 100</p> <p>www.scapttest.com</p>			
	<p>Summary</p> <p>Nisoldipine x-fold EFTPC_{max} vs. IC_{50s} Epi Mid Endo TDR — no drug — x 100</p> <p>Effect (%) APD90 msec - APD90t msec (msec)</p> <p>www.scapttest.com</p>		<p>Nisoldipine x-fold EFTPC_{max} vs. IC_{50s} Epi Mid Endo TDR — UD — RUD</p> <p>RUD Value (mV)</p> <p>www.scapttest.com</p>	
References	<p>1. Romero L et al. (2018) J.Chem.Inf.Model. 58: 867-878 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. G.PA (2016) www.IsiExtra.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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. Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26</p>			
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{40,60,90,99} : 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_{Kr}*I_{Na}*I_{Na}*I_{K1}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{EP,40} : APD₄₀-APD₄₀ 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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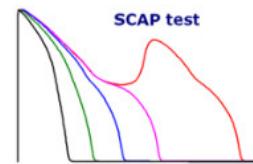
Drug	Nitrendipine		
	Voltage-gated L-type Ca ⁺⁺ channel (Ca _v 1.2) blocker used to treat hypertension		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 0.025 μM (0.78) I _{to} : ---- μM (---) I _{Kr} : 24.6 μM (0.82) I _{NaL} : ---- μM (---) I _{Na} : 21.6 μM (1.25) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.003 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not reported CiPA ⁽⁵⁾ : low risk or no risk of TdP (class 3) WP ⁽⁶⁾ : 0/7 (TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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 ⁺⁺] _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 and IC _{50s} $I_j = g_j(V - E_{j,0})^{(1 + (\frac{EFTPC_{j,max}}{IC_{50s}})^{-1})}$ g _j = maximal conductance of channel E _{j,0} = reversal potential for species of ions which flows through channel IC _{50s} = 50% of inhibition of a drug for a channel E= drug concentration (EFTPC for example) In full scope	TDR and RUD estimation: • TDR = AP _{mid} - AP _{depi} (at CL of 1000 msec) • RUD = AP _{Depeo} -AP _{Dmid} where AP _{Dmid} = AP _{D0} without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} .
	Human epicardial myocytes 		Transmural dispersion of repolarisation
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes
	Human endocardial myocytes 		
Summary			
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Isiextra.org/hesu/science/cardiac/cipa/ Project 6. Winiarska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16 7. O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 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 ₅₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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 _{NaL} +I _{K1} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₆₀ : APD ₄₀ -APD ₆₀ or AP ₀ -AP ₆₀ ("triangulation"), TdP : torsade de pointes , TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _{mmin} : minimal rate of AP decrease at EAD take-off voltage, V _s : volt per second		

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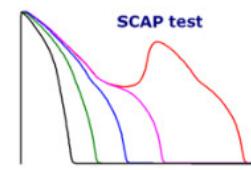
Drug	Ofloxacin			
	Quinolone/fluoroquinolone antibiotic used to treat various bacterial infections			
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk	
	I_{CaL} : --- μM (---) I_{Kr} : 1412.5 μM (1.0) I_{Na} : --- μM (---) I_K : --- μM (---)	I_{to} : --- μM (---) I_{NaL} : --- μM (---) I_{Ks} : --- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 8.656 μM	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-)
	<i>In silico</i> 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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 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_{50} $I_j = g_j(V - E_{jon})$ $E_{jon} = V_{max} + \frac{V_{max} - V_{min}}{e^{-\frac{V}{V_{inf}}}}$ V_{inf} = reversal potential for species of ions which flows through channel $e^{-\frac{V}{V_{inf}}} = \frac{g_{max} \cdot conductance \cdot (channel)}{g_{max} \cdot conductance \cdot (channel) + g_{min} \cdot conductance \cdot (channel)}$ $IC_{50} = 50\% \text{ inhibition of a drug for a channel}$ $D = \text{drug concentration (EFTPC for example)}$ $x = \text{full slope}$	TDR and RUD estimation: • $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) • $RUD = APD_{90, Endo} - APD_{90, Mid}$ where $APD_{90, P_i} = APD_{90}$ with - APD_{90} without compound at CL x	
Results	Human epicardial myocytes 		Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 			
	Human endocardial myocytes 			
	Reverse use dependence on midmyocardial myocytes 			
Summary	 			
References	1. Romero L et al. (2018) J.Chem.Inf.Model. 58 : 867-878 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.Isliefta.org/hesi/science/cardiac/cipa/ 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	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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL} , I_{Kr} , I_{NaL} , I_{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 60}$: $APD_{90, 60} - APD_{40}$ ("triangulation"), TdP : torsade de pointes , TDR : transmural dispersion of repolarization, V_m : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second			

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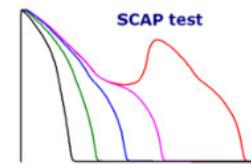
Drug	Olanzapine		
Raw data	IC_{50s} (slope) ⁽¹⁾ I_{CaL} : ---- μM (---) I_{Kr} : 9.99 μM (1.23) I_{Na} : 39.0 μM (1.0) I_K : ---- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 13.63 μM	TdP risk Redfern ⁽²⁾ : no published TdP report (class 5) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 1/5 (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): $[Na^+]$, 140 - $[Ca^{2+}]$, 1.8 - $[K^+]$, 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_{50} $I_j = g_j(V - E_{jon})$ $g_j = g_{j,control} \left[1 + \left(\frac{D}{IC_{50}} \right)^n \right]^{-1}$ where • $g_{j,control}$ = maximal conductance of channel j • $E_{j,control}$ = reversal potential for species of ions which flows through channel j • IC_{50} = 50% of inhibition of a drug for a channel j • D= drug concentration (EFTPC for example) n=half slope		TDR and RUD estimation: • TDR = $APD_{mid} - APD_{epi}$ (at CL of 1000 msec) • RUD = $APD_{endo} - APD_{epi}$ where $APD_{endo} = APD_{endo}$ without compound at CL x
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>		
Summary	<p>Olanzapine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Olanzapine V_{max} (mV) vs APD_{90} (msec)</p>		
References	<p>1. Abi-Gerges N et al. (2011) Br J Pharmacol. 164: 419-432 (+PMID: 21480866) 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. CIPA (2016) www.ihiextra.org/hesi/science/cardiac/cipa/ 6. Wirschniowska B et al. (2017) Drug discovery today 22: 10-16 7. O'Hara T et al. (2011) PLoS Comput. Biol. 7: e1002061 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</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: 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 $i_{CaL} + i_{Kr} + i_{Na} + i_{K1} + i_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, TEA : $APD_{90} - APD_{40}$ or APD_{90} (triangulation), TdP : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : membrane voltage, V_{min} : 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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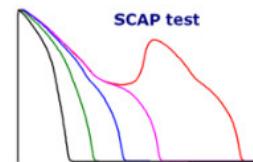
Drug	Omecamtiv mecarbil		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 581.8 \mu M (1.0)$ $I_{Kr} : 125.5 \mu M (1.1)$ $I_{Na} : 400.4 \mu M (1.0)$ $I_Ks : \text{---} \mu M (\text{---})$ $I_{Na} : \text{---} \mu M (\text{---})$ $I_{Kr} : \text{---} \mu M (\text{---})$ $I_{CaL} : \text{---} \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 <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 (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_j = g_j(V - E_{j,0})^{(1 + \left(\frac{g_j}{IC_{50j}}\right)^n)^{-1}}$ <p>where g_j = maximal conductance of channel $E_{j,0}$ = reversal potential of species of ions which flows through channel n = open probability of channel IC_{50j} = 50% of inhibition of a drug for channel x = drug concentration (EFTPC for example) \times full slope</p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, ep}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, ep}$ where $APD_{90, p} = APD_{90}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr/(AFNaL + AFCaL)/2)*100$ <p>where $AFKr$, $AFNaL$ and $AFCaL$ = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</p>	Human epicardial myocytes Transmural dispersion of repolarisation 	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	1. Qu Y et al. (2021) <i>Clin. Transl. Sci.</i> 14 : 1600-1610 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. GPA (2016) www.iisixtra.org/hesi/science/cardiac/cipa/project 6. Winiowska 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, $APD_{90, 40 \text{ or } 90}$: 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{dP, 40}$: $APD_{90} - APD_{40}$ 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		

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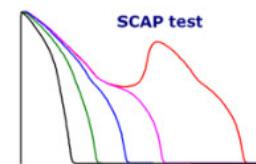
Drug	Ondansetron		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 22.551 \mu M (0.8)$ $I_{Kr} : 1.492 \mu M (1.0)$ $I_{Na} : \text{----} \mu M (---)$ $I_{Ks} : \text{----} \mu M (---)$ $I_{Na} : \text{----} \mu M (1.0)$ $I_K : \text{----} \mu M (---)$	$0.3585 \mu M$	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : intermediate risk of TdP (class 2) WP ⁽⁶⁾ : 4/1 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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): $[Na^+]_o = 140 - [Ca^{++}]_o = 1.8 - [K^+]_o = 5.4$ • 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} $I_j = g_j(V - E_{jon})$ $g_j = g_{max} \cdot \min\left(1 + \frac{V - V_{j,50}}{V_{j,50}}, 1\right)$ $V_{j,50} = \text{reversal potential for species of ions which flows through channel } j$ $E_{j,50} = \text{reverse potential for species of ions which flows through channel } j$ $g_{max} = \text{maximal conductance of channel } j$ $E_{j,50} = \text{reverse potential of channel } j$ $IC_{50s} = 50\% \text{ of inhibition of a drug for a channel } j$ $D = \text{drug concentration (EFTPC for example)}$ $\alpha = \text{half slope}$	TDR and RUD estimation: • $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) • $RUD = APD_{90, \text{endo}} - APD_{90, \text{epi}}$ where $APD_{90,P_i} = APD_{90} \text{ with } - APD_{90,i} \text{ without compound at CL } x$ IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ where $AFKr, AFNaL \text{ and } AFGaL = \text{active fraction (\%)} \text{ of the } I_{Ks}, I_{NaL} \text{ and } I_{CaL}$
Summary	<p>Human epicardial myocytes</p> <p>Human midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Transmural dispersion of repolarisation</p> <p>Reverse use dependence on midmyocardial myocytes</p>		
References	1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81 : 251-262 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.Isliefta.org/hesi/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 : e1002618 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, $APD_{40, 40-90}$: 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, ende : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $TE_{50, 40-APD_{40}}$: $TE_{50, 40-APD_{40}}$ ("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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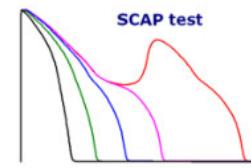
Drug	Oxybutynin			
	Muscarinic M ₁ , M ₂ and M ₃ receptor antagonist used to treat urinary incontinence			
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk	
	$I_{CaL} : 16.1 \mu M (0.95)$ $I_{Kr} : 11.4 \mu M (1.0)$ $I_{Na} : \text{---- } \mu M (-)$ $I_K : 28.7 \mu M (0.87)$	$I_0 : \text{---- } \mu M (-)$ $I_{NaL} : \text{---- } \mu M (-)$ $I_{K1} : 18.2 \mu M (1.0)$	$EFTPC_{max}$ ⁽¹⁾ 0.00005 μM	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
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	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_{50} $I_j = g_j(V - E_{jon})$ $g_j = g_{j,control} \left[1 + \left(\frac{\delta}{IC_{50}} \right)^n \right]^{-1}$ $E_{j,control} = E_{j,control} - \frac{g_{j,control}}{g_{j,control} + g_{j,control} \cdot (1 - IC_{50})} \cdot (50\% \text{ inhibition of a drug for channel } j)$ $\delta = \text{drug concentration (FEP for example)}$ $n = \text{half slope}$	TDR and RUD estimation: • TDR = $APD_{mid} - APD_{epi}$ (at CL of 1000 msec) • RUD = $APD_{endo} - APD_{epi}$ where $APD_{endo} = APD_{endo}$ with - APD _{endo} without compound at CL x	
Summary				
References	1. Llopis-Lorente J et al. (2020) <i>J Chem Inf Model</i> 60 : 5172-5187 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.Isliefta.org/hesi/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			
Abbreviations	AP : action potential, APA : AP amplitude, APD_{40-90} : AP duration at 40, 60 or 90 % of APA, APD ₉₀ : 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, IC_{50} : 50% inhibition concentration, m.u. : millisecond, mV : millivolt, qNet : integration sum of I_{CaL} , I_{Kr} , I_{NaL} , I_K , RMP : resting membrane potential, RUD : reverse use dependence, T_{AP-40} : $APD_{40} - APD_{40}$ or $APD_{90} - APD_{90}$ ("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			

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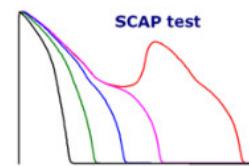
Drug	Paliperidone		
	Dopamine D ₂ and serotonin 5-HT ₂ receptor antagonist used to treat schizophrenia		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 193.9 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 0.78 μM (1.01) I_{NaL}: ---- μM (---) I_{Na}: 109.0 μM (1.33) I_{K1}: ---- μM (--) I_{Ks}: ---- μM (--)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.069 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾: not reported Kramer⁽³⁾: torsadogenic (class 2) CredibleMeds⁽⁴⁾: possible risk of TdP (class 2) CIPA⁽⁵⁾: not reported WP⁽⁶⁾: 3/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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} $I_g = g_o(V - E_{on})^{(1 + (\frac{g}{g_{control}})^{-1})^{-1}}$ where g = maximal conductance of channel ; g_o = open probability of channel ; E_{on} = reversal potential for species of ions which flows through channel ; $\frac{g}{g_{control}}$ = inhibition of inhibition of drug for channel ; IC₅₀ = 50% of inhibition of a drug for a channel ; x = drug concentration (EFTPC_{max} for example) on full scale 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀epi (at CL of 1000 msec) RUD = APD₉₀endo - APD₉₀mid where APD₉₀P_a = APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full scope</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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.islextra.org/hesi/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		
Abbreviations	AP : action potential , APA : AP amplitude , APD ₉₀ : AP duration at 40, 60 or 90 % of APA , APD ₉₀ : APD prolongation , a.u. : arbitrary unit , CL : cycle length , DA : degeneration abnormalities , EAD : early afterdepolarization , EFTPC _{max} : maximal effective free therapeutic plasma concentration , ende : 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 _{NaL} +I _{K1} +I _{Ks} , RMP : resting membrane potential , RUD : reverse use dependence , T ₄₀₋₆₀ : APD ₉₀ -APD ₄₀ 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		

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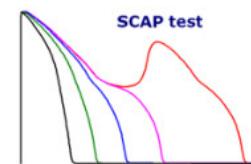
Drug	Palonosetron		
	Serotonin 5-HT ₃ receptor antagonist used to treat vomiting and nausea		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 398.107 \mu M (1.0)$ $I_{Kr} : 1.995 \mu M (1.0)$ $I_{Na} : 19.953 \mu M (1.0)$ $I_{Ks} : 50.119 \mu M (1.0)$ $I_{to} : \text{---- } \mu M (\text{---})$ $I_{NaL} : \text{---- } \mu M (\text{---})$ $I_{K1} : \text{---- } \mu M (\text{---})$	$EFTPC_{max}$ ⁽¹⁾ 0.004651 μM	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-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 <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 F (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_f = g_f(V - E_{f,0})$ $g_f = g_{max} \cdot f$ $f = \frac{1}{1 + \left(\frac{[Compound]}{IC_{50}}\right)^n}$ $g_{max} = \text{maximal conductance of channel}$ $V = \text{membrane potential}$ $E_{f,0} = \text{reverse potential for species of ions which flows through channel}$ $IC_{50} = 50\% \text{ of inhibition of a drug for channel}$ $n = \text{drug concentration (EF-TPC for example)}$ 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, TDR}$ where $APD_{90, P_s} = APD_{90}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL} in full range</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>Human endocardial myocytes</p> <p>Summary</p> <p>Effect (%)</p> <p>APD90ms - APD90ms (msec)</p>
References	1. Mirams GR et al. (2014) <i>J.Pharmacol.Tox.Methods</i> 70 : 246-254 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.Islieextra.org/hesi/science/cardiac/cipa/project 6. Wisiowska 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		
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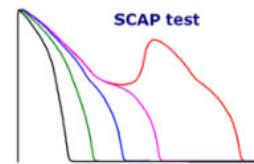
Drug	Paroxetine		
5-HT reuptake inhibitor used to treat depressive, anxiety, panic, obsessive compulsive or premenstrual dysphoric disorders and social phobia			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 3.9 μM (1.39) I_{to}: ---- μM (---) I_{Kr}: 1.9 μM (1.26) I_{NaL}: ---- μM (---) I_{Na}: 9.8 μM (1.34) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.014 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : conditional risk of TdP (class 3) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 4/0 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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> <p>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 and IC_{50s}</p> $I_j = g_j(V - E_{j,0}) \left[1 + \left(\frac{D}{IC_{50j}} \right)^n \right]^{-1}$ <p>g_j= maximal conductance of channel j E_{j,0}= reversal potential for species of ions which flows through channel j D= drug concentration (EF-TPC for example) n= half slope</p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{Depi} (at CL of 1000 msec) RUD = AP_{De0}-AP_{D0} where AP_{D0}=AP_{De0} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, 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>Human endocardial myocytes</p>	<p>Summary</p>
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Islieuxra.org/hesi/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		
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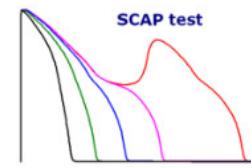
Drug	Pentamidine		
Raw data	IC _{50s} (slope) ⁽¹⁾ I _{CaL} : --- μM (---) I _{Kr} : 205.02 μM (1.0) I _{Na} : --- μM (---) I _{Ks} : --- μM (---)	EFTPC _{max} ⁽¹⁾ 0.010 μM	TdP risk Redfern ⁽²⁾ : numerous reports of TdP (class 3) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 8/1 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 100 (full inhibition) which is a function of a multiple of EFTPC and IC_{50s} $I_f = g_f(V - E_{f,0})$: maximum conductance of channel f $P_f = \frac{1}{1 + \left(\frac{V - V_{f,50}}{IC_{f,50}}\right)^n}$: open probability of channel f V_m = reversal potential for species of ions which flows through channel f $IC_{f,50}$ = 50% of inhibition of a drug for channel f D = drug concentration (F = F_{EP} for example) in nM 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{epi} (at CL of 1000 msec) RUD = AP_{mid} - AP_{endo} - AP_{epi} <p>where</p> <p>APD_{endo} = 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</p> <p>AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{Na} and I_{CaL} in full range</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> <p>Summary</p> <p>Pentamidine x-fold EFTPC_{max} vs. IC_{50s}</p> <p>References</p> <ol style="list-style-type: none"> McMillan et al. (2017) <i>Tox Rep</i> 6: 912-921 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 GPA (2016) www.IsiExtra.org/hesi/science/cardiac/cipa/ Włosińska 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 Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 <p>Abbreviations</p> <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 $i_{CaL} + i_{Kr} + i_{Na} + i_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{EP} : APD₄₀-APD₄₀ or APD₄₀ ("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



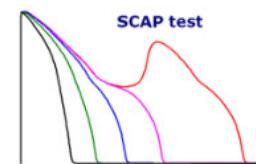
Drug	Pentobarbital		
GABA _A allosteric modulator used as barbiturate to treat seizure, cause sedation and induce sleep no longer marketed in Sweden (Onakpoya et al (2016) <i>BMC Med.</i> 14 : 10)			
Raw data	IC_{50s} (slope) ⁽¹⁾ $I_{CaL} : 299.0 \mu M (1.38)$ $I_{Kr} : 1433.9 \mu M (1.0)$ $I_{NaL} : 2686.0 \mu M (1.0)$ $I_{Ks} : --- \mu M (---)$	$EFTPC_{max}$ ⁽¹⁾ 5.171 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/3 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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_{50}. $I_j = g_j O(V - E_{j,0})$ $g_j = g_{j,0} P_{open}^{(j)}$ $\theta_j = g_{j,0} P_{open}^{(j)} \left[1 + \left(\frac{D}{IC_{50j}} \right)^n \right]^{-1}$ <p>where: $P_{open}^{(j)}$ = open probability of channel j $E_{j,0}$ = reversal potential for species of ions which flows through channel j $g_{j,0}$ = maximal conductance of channel j D = drug free maximal conductance of channel j n = Hill slope IC_{50j} = half-inhibition concentration (e.g. for channel j) D = drug concentration (0% to 100% for example)</p>	TDR and RUD estimation: <ul style="list-style-type: none"> TDR = $APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) RUD = $APD_{90, Endo} - APD_{90, Mid}$ when $APD_{90, Endo} > APD_{90, Mid}$ IC index calculation⁽⁹⁾: $IC\ index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100$ where: $AFKr$ = AFKr/((AFNaL+AFCaL)/2) $AFNaL$ and $AFCaL$ = active fraction (%) of the I_{Kr} , I_{NaL} and I_{CaL} .
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	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>
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary	<p>Pentobarbital x-fold EFTPC_{max} vs. IC_{50s}</p> <p>www.scapttest.com</p>	<p>www.scapttest.com</p>	<p>www.scapttest.com</p>
References	1. Kramer J et al. (2013) <i>Sci. Rep.</i> 3 : 2100 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. Worsley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.ilectra.org/hes/science/cardiac/cipa/Project 6. Wirsniowska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16	7. O'Hearn T et al. (2014) <i>PLoS Comput. Biol.</i> 10 : e1003861 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 9. Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96 : 15-26
Abbreviations	AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APP : AP 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Ks}$, RMP : resting membrane potential, 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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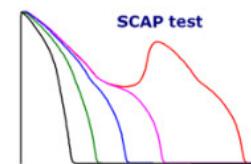
Drug	Phenytoin		
	Non-specific voltage-gated Na ⁺ channel blocker used as anticonvulsant to treat seizure		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 21.9 μM (0.99) I _{to} : ---- μM (---) I _{Kr} : 147.0 μM (1.0) I _{Na} : ---- μM (---) I _{Na} : 72.4 μM (1.06) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 4.36 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/5 (TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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} $I_j = g_j(V - E_{jon})$ $\frac{g_j}{g_{j,control}} = \left[1 + \left(\frac{\delta}{(IC_{50})^n}\right)^{-1}\right]$ g _j = maximal conductance of channel δ= drug concentration IC ₅₀ = 50% of inhibition of a drug for channel n= drug concentration (EF _{TPC} for example) no full slope	TDR and RUD estimation: • TDR = APD _{mid} - APD _{epti} (at CL of 1000 msec) • RUD = APD _{90epti} -APD _{90mid} where APD ₉₀ P _a = APD ₉₀ without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{CaL} and I _{CaL}
	Human epicardial myocytes Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes 		
	Human endocardial myocytes Summary 		
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Isiextra.org/hesi/science/cardiac/cipa/ 6. Winiarska 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 : e1002618 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 ₉₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, ende : 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 _{Na} +I _{K1} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₆₀ : APD ₉₀ -APD ₄₀ 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		

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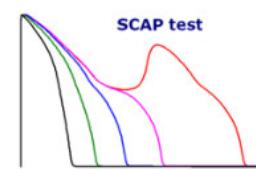
Drug	Pimozide				
	Dopamine D ₂ receptor antagonist used to treat debilitating motor and phonic tics in Tourette's disorder				
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk		
	$I_{CaL} : 0.24 \mu M (1.49)$ $I_{Kr} : 0.04 \mu M (1.16)$ $I_{Na} : 1.1 \mu M (1.05)$ $I_K : \text{---} \mu M (\text{---})$ $I_{Ks} : \text{---} \mu M (\text{---})$	$EFTPC_{max}^{(1)}$ 0.0005 μM	Redfern ⁽²⁾ : numerous reports of TdP (class 3) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : intermediate risk of TdP (class 2) WP ⁽⁶⁾ : 12/0 (TdP+/TdP-)		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾				
Results	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): $[Na^+]_o = 140 - [Ca^{2+}]_o = 1.8 - [K^+]_o = 5.4$ 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} $I_j = g_j(V - E_{j,0})$ $\frac{g_j}{g_{j,0}} = \frac{1 + \left(\frac{\delta}{EFTPC_{max}}\right)^{-1}}{1 + \left(\frac{\delta}{IC_{50s}}\right)^{-1}}$ <p>g_j = maximal conductance of channel V = voltage membrane E_{j,0} = reversal potential for species of ions which flows through channel IC_{50s} = 50% of inhibition of a drug for a channel δ = drug concentration (EF_j for example) in full range</p>	TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{endo}-APD_{endo} where APD _{endo} = APD _{endo} without compound at CL x		
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr/(AFNaL + AFCaL)/2) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Ks} , I_{CaL} and I_{CaL} in full range		
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ul 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	1. Kramer J et al. (2013) <i>Sci rep</i> 3 : 2100 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.Iseuxtra.org/hesi/science/cardiac/cipa/ 6. Winiarska 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 ₄₀₋₅₀ : AP duration at 40, 50 or 90 % of APA, APD _{mid} : APD _{mid} - APD _{epi} : AP prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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 $I_{CaL} + I_K + I_{Na} + I_{Kr}$, RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₅₀ : APD ₄₀ -APD ₅₀ or APD ₅₀ ("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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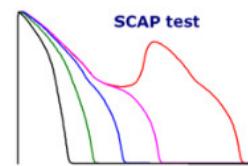
Drug	Piperacillin		
	Penicillin antibiotic used to treat various bacterial infections		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 1226.0 μM (1.0) I_{to} : ---- μM (---) I_{Kr} : 3405.1 μM (1.0) I_{NaL} : ---- μM (---) I_{Na} : 2433.8 μM (1.0) I_K1 : ---- μM (--) I_Ks : ---- μM (---)</p>	<p>$EFTPC_{max}$⁽¹⁾</p> <p>1378.0 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : conditional risk of TdP (class 3) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/4 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ $\delta_f = \frac{g_f}{g_{f,0}} \left[1 + \left(\frac{\delta}{IC_{50f}} \right)^n \right]^{-1}$ g_f = maximal conductance of channel f $E_{f,0}$ = reversal potential for species of ions which flows through channel f IC_{50f} = 50% of inhibition of a drug for channel f D= drug concentration (F=PC for example) in full range 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, cpi}$ (at CL of 1000 msec) $RUD = APD_{90,endo} - APD_{90, mid}$ where $APD_{90, x} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFK + (AFNaL + AFCaL)/2) * 100$ <p>where AFK, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full range</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>Legend: 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. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Ilextra.org/heis/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, $APD_{90, 40 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, au. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPCmax : 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 $i_{Ca,L} + i_{Na,L} + i_{K1,L} + i_{Kr,L}$, RMP : resting membrane potential, RUD : reverse use dependence, $TdP_{+/-}$: $APD_{90, mid} - APD_{90, endo}$ ("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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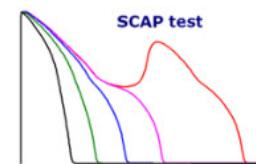
Drug	Prenylamine		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 1.24 \mu M (1.0) \quad I_{to} : 0.0 \mu M (---)$ $I_{Kr} : 0.065 \mu M (1.0) \quad I_{NaL} : 0.0 \mu M (---)$ $I_{NaL} : 2.52 \mu M (1.0) \quad I_{K1} : 0.0 \mu M (---)$ $I_K : 0.0 \mu M (---)$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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} $I_j = g_j O(V - E_{j,0})$ (g_j: maximal conductance of channel^(*), O: open probability of channel^(*), $E_{j,0}$: reversal potential for species of ions which flows through channel^(*)) $\theta_j = g_{control,j} \left[1 + \left(\frac{D}{IC_{50s,j}} \right)^{n_j} \right]^{-1}$ ($g_{control,j}$: maximal conductance of channel^(*), D: drug concentration (ET₅₀ for example) in nM, n_j: Hill slope) 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{50, mid} - APD_{50, epi}$ (at CL of 1000 msec) $RUD = APD_{50,endo} - APD_{50,endo}$ 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_{Kr} , I_{NaL} and I_{CaL} .
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary			
References	1. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 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.isleextra.org/hes/science/cardiac/cipa/Project 6. Wiatrowska 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	AP : action potential , APA : AP amplitude, $APD_{50,60,90}$: 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 $q_{NaL}, q_{Kr}, q_{NaL}, q_{CaL}, q_{K1}, q_{NaL}$, RMP : resting membrane potential, RUD : reverse use dependence, TdP_{50} : $APD_{50} - APD_{50,endo}$ (triangulation), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : membrane voltage, V_{mem} : maximal rate of AP rise, V_{min} : volt per second		

Safe Cardiac Action Potential Test



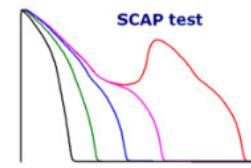
Drug	Primidone		
	Transmembrane Na^+ and Ca^{++} channel transport (TRPM3) blocker used to treat grand mal, psychomotor and focal epileptic seizures		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	I_{CaL} : --- μM (---) I_{Kr} : 3360 μM (1.0) I_{Na} : 640 μM (1.0) I_{Ks} : --- μM (---)	I_{to} : --- μM (---) I_{NaL} : --- μM (---) I_{K1} : --- μM (---)	$20.6 \mu\text{M}$ Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/2(TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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): $[\text{Na}^+]$, 140 - $[\text{Ca}^{++}]$, 1.8 - $[\text{K}^+]$, 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 and IC_{50s} $I_j = g_j(V - E_{j,0})$ (j: maximal conductance of channel ; V: membrane potential ; $E_{j,0}$: reversal potential for species of ions which flows through channel ; g_j: maximal conductance of channel ; $E_{j,0}$: reversal potential of channel ; $g_j \cdot 0.5$: 50% of inhibition of a drug for channel ; IC_{50s}: 50% of inhibition of a drug for channel ; D: drug concentration (EFTPC for example) in full scale) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $\text{TDR} = \text{APD}_{\text{mid}} - \text{APD}_{\text{epi}}$ (at CL of 1000 msec) $\text{RUD} = \text{APD}_{\text{endo}} - \text{APD}_{\text{epi}}$ where $\text{APD}_{\text{endo}} = \text{APD}_{\text{endo}}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr}((\text{AFNaL} + \text{AFCaL})/2)) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Ks}, I_{CaL} 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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Passini E et al. (2017) <i>Front Physiol.</i> 8 : 668 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.Isiextra.org/hesi/science/ciapa/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	AP : action potential, APA : AP amplitude, $APD_{40,60,90}$: 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, EFTPCmax : 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 $i_{Na} \cdot t_{Na} + i_{K1} \cdot t_{K1} + i_{CaL} \cdot t_{CaL}$, RMP : resting membrane potential, RUD : reverse use dependence, TdP_{40} : $APD_{40} - APD_{90}$ ("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		

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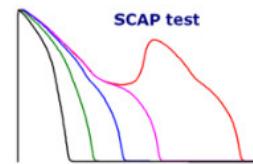
Drug	Procainamide		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	<p>Voltage-gated Na^+ channel blocker used as class IA antiarrhythmic to treat ventricular arrhythmias</p> <p>I_{CaL}: 389.5 μM (0.83) I_{to} : --- μM (---) I_{Kr}: 272.4 μM (1.0) I_{NaL} : --- μM (---) I_{Na}: 746.6 μM (1.0) I_{K1} : --- μM (---) I_{Ks} : --- μM (---)</p>		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[\text{Na}^+]_o$: 140 - $[\text{Ca}^{++}]_o$: 1.8 - $[\text{K}^+]_o$: 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} $I_j = g_j(V - E_{j,0})$ g_j= maximal conductance of channel $E_{j,0}$= reversal potential for species of ions which flows through channel $B_j = \frac{g_j}{g_{j,control}} = [1 + (\frac{\delta}{IC_{50s}})^n]^{-1}$ δ= inhibition constant n=open probability of channel IC_{50s}= 50% of inhibition of a drug for a channel IC_{50s} = 50% of inhibition of a drug for channel δ= drug concentration (BP for example) n= full slope 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> \bullet TDR = $APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) \bullet RUD = $APD_{90, \text{endo}} - APD_{90, \text{mid}}$ where $APD_{90, \text{P}_x} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr/(AFNaL+AFCaL)/2) * 100$ <p>where $AFKr$, $AFNaL$ and $AFCaL$ = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL} in full slope</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> <p>Summary</p> <p>Procainamide</p> <p>x-fold $EFTPC_{max}$ vs. IC_{50s}</p> <p>Procainamide</p> <p>$EFTPC_{max}$ (msec) vs. IC_{50s}</p>
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Iseuxtra.org/hesi/science/cardiac/cipa/ Project 6. Winiarska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, $APD_{90, \text{endo}}$: AP duration at 40, 60 or 90 % of APA, APD_{90} : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : dissociation abnormalities, EAD : early afterdepolarization, $EFTPC_{max}$: maximal effective free therapeutic plasma concentration, ende : 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 $I_{\text{CaL}} + I_{\text{Kr}} + I_{\text{NaL}} + I_{\text{Ks}}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{40, \text{AP}}$: $APD_{90, \text{AP}} - APD_{40}$ 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</p>		

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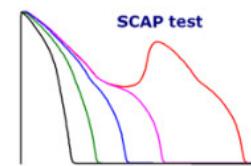
Drug	Propafenone		
Voltage-gated Na^+ channel blocker and β -adrenoreceptor antagonist used as class IC antiarrhythmic to treat ventricular arrhythmia and paroxysmal atrial fibrillation			
Raw data	<p>IC_{50} (slope)⁽¹⁾</p> <p>$I_{\text{Cal}} : 1.55 \mu\text{M} (0.9)$ $I_{\text{to}} : \text{---- } \mu\text{M} (\text{---})$ $I_{\text{Kr}} : 0.481 \mu\text{M} (0.8)$ $I_{\text{NaL}} : 4.036 \mu\text{M} (0.9)$ $I_{\text{Na}} : 3.886 \mu\text{M} (0.9)$ $I_{\text{K1}} : \text{---- } \mu\text{M} (\text{---})$ $I_{\text{Ks}} : \text{---- } \mu\text{M} (\text{---})$</p>	<p>$\text{EFTPC}_{\text{max}}$⁽¹⁾</p> <p>0.131 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : isolated reports of TdP (class 4) Kramer⁽³⁾ : not reported CredibleMeds⁽⁴⁾ : conditional risk of TdP (class 3) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 5/4 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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): $[\text{Na}^+]_0 : 140$ - $[\text{Ca}^{++}]_0 : 1.8$ - $[\text{K}^+]_0 : 5.4$ Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <ul style="list-style-type: none"> Cell conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of a multiple of $\text{EFTPC}_{\text{max}}$ and IC_{50} $I_j = g_j(V - E_{j,\text{on}})$ $E_{j,\text{on}} = \text{reverse potential for species of ions which flows through channel } j$ $g_j = \text{maximal conductance of channel } j$ $V = \text{voltage membrane}$ $E_{\text{rev}} = \text{reverse potential for species of ions which flows through channel } j$ $\text{IC}_{50} = 50\% \text{ of inhibition of rate of depolarization}$ $D = \text{drug concentration (EFTPC for example)}$ $\times = \text{half slope}$ 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $\text{TDR} = \text{APD}_{50, \text{mid}} - \text{APD}_{50, \text{cp1}}$ (at CL of 1000 msec) $\text{RUD} = \text{APD}_{50, \text{P}_{\text{endo}}} - \text{APD}_{50, \text{P}_{\text{mid}}}$ where $\text{APD}_{50, \text{P}_x} = \text{APD}_{50}$ with - APD_{50} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = $(\text{AFKr} / ((\text{AFNaL} + \text{AFCaL})/2)) * 100$</p> <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, 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>Human endocardial myocytes</p> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woolesley RL (2015) www.CredibleMeds.org GPA (2016) www.lisixtra.org/hsis/science/cardiac/cipa/Project Wieniowska 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 (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $\text{APD}_{50, \text{mid}}$: AP duration at 50, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, $\text{EFTPC}_{\text{max}}$: 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 $I_{\text{CaL}} + I_{\text{NaL}} + I_{\text{K1}} + I_{\text{Ks}}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{40-60} : $\text{APD}_{40} - \text{APD}_{60}$ or $\text{APD}_0 - \text{APD}_{40}$ ("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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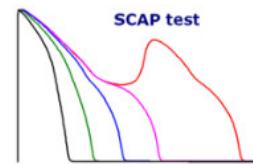
Drug	Propranolol		
β -adrenoceptor antagonist used to treat hypertension, angina, atrial fibrillation, myocardial infarction, migraine or essential tremor			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 19.498 μM (1.0) I_{to}: ---- μM (---) I_{Kr}: 8.128 μM (1.0) I_{Na}: ---- μM (---) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: 1000.0 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0101 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⁾: 0/4 (TdP+/TdP-)</p>
In silico cardiac action potential study (ORd model)⁽⁷⁾			
Results	<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): $[\text{Na}^+]$, 140 - $[\text{Ca}^{++}]$, 1.8 - $[\text{K}^+]$, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <p>Cell 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}</p> $I_j = g_j(V - E_{j,0})$ <p>g_j: maximal conductance of channel j $E_{j,0}$: reversal potential of species of ions which flows through channel j τ_{on}: reversal potential for species of ions which flows through channel j</p> $\beta_j = \frac{\partial}{\partial (IC_{50s})} \left[1 + \left(\frac{\partial}{\partial (EFTPC_{\text{max}})} \right)^{-1} \right]$ <p>IC₅₀ = 50% of inhibition of a drug for a channel j D_j: drug concentration (EF_jPC for example) n: half slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{50, mid} - APD_{50, cpi} (at CL of 1000 msec) RUD = APD_{50, P_{extra}} - APD_{50, P_{too}} where APD_{50, P_x} = 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_{Na} and I_{CaL}.</p>	<p>Human epicardial myocytes</p> <p>Transmural dispersion of repolarisation</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 midmyocardial myocytes</p> <p>Human endocardial myocytes</p>
Summary	<p>Propranolol x-fold EFTPC_{max} vs. IC_{50s}</p> <p>Propranolol x-4fold EFTPC_{max} vs. IC_{50s}</p>		
References	<p>1. Romero L et al. (2018) J.Chem.Inf.Model. 58: 867-878 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Isliefta.org/hes/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD_{50, 40-90} : AP duration at 40, 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 $i_{CaL} + i_{Kr} + i_{Na} + i_{NaL} + i_{K1}$, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₆₀ : 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, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>		

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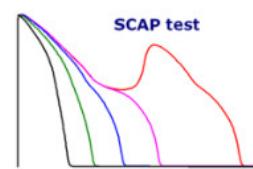
Drug	Quetiapine		
	Dopamine D ₂ and serotonin 5-HT ₂ receptor antagonist used to treat major depressive and bipolar disorders or schizophrenia		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 10.471 μM (1.0) I _{to} : ---- μM (---) I _{Kr} : 3.802 μM (1.0) I _{NaL} : ---- μM (---) I _{Na} : ---- μM (---) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 0.4619 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 3/3 (TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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} $I_j = g_j(V - E_{jon})^{n_j}$ $\delta_j = \frac{g_j}{g_{j,control}} \left[1 + \left(\frac{\delta_j}{IC_{50s}} \right)^{n_j} \right]^{-1}$ g _j = maximal conductance of channel j E _{jon} = reversal potential for species of ions which flows through channel j n _j = reverse probability of channel j IC _{50s} = 50% of inhibition of a drug for channel j δ _j = drug concentration (BP/IC _{50s} for example) on full scale	TDR and RUD estimation: • TDR = AP _{mid} - AP _{depi} (at CL of 1000 msec) • RUD = AP _{Depeo} -AP _{Deptd} where AP _{Deo} =AP _{Deo} with - AP _{Deo} without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} in full scope
	Human epicardial myocytes Human midmyocardial myocytes Human endocardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes
Summary	 		
References	1. Romero L et al. (2018) J.Chem.Inf.Model. 58 : 867-878 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. Wootton RL (2015) www.CredibleMeds.org 5. CiPA (2016) www.Ilextra.org/hesi/science/cardiac/cipa/ Project 6. Wirschniowska 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 : e1002063,8 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 ₉₀₋₅₀ : AP duration at 40, 60 or 90 % of APA, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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 _{NaL} +I _{K1} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₆₀ : APD ₉₀₋₅₀ -APD ₄₀ 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



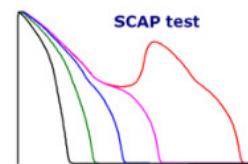
Drug	Quinidine		
Non selective cardiac ionic channel blocker used as Class IC antiarrhythmic to treat atrial fibrillation or flutter, ventricular arrhythmia or restore normal sinus rhythm			
Raw data	IC_{50s} (slope) ⁽¹⁾ I _{CaL} : 6.4 μM (0.68) I _{to} : ---- μM (---) I _{Kr} : 0.72 μM (1.06) I _{Na} : ---- μM (---) I _{Na} : 14.6 μM (1.22) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC _{max} ⁽¹⁾ 3.237 μM	TdP risk Redfern ⁽²⁾ : class IA or III antiarrhythmics (class 1) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : high risk of TdP (class 1) WP ⁽⁶⁾ : 16/0 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <p>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}</p> $I_j = g_j \cdot O(V - E_{j,0}) \cdot \left[1 + \left(\frac{g_j}{g_{j,0} IC_{50s}} \right)^n \right]^{-1}$ <p>g_j = maximal conductance of channel O = open probability of channel V = voltage membrane E_{j,0} = reversal potential for species of ions which flows through channel⁽⁹⁾ IC_{50s} = 50% of inhibition of a drug for a channel⁽¹⁰⁾ D = drug concentration (F = FPC for example) x = fold increase</p>	TDR and RUD estimation: <ul style="list-style-type: none"> TDR = APD_{90, mid} - APD_{90, epi} (at CL of 1000 msec) RUD = APD_{90, mid} - APD_{90, endo} where APD_{90, x} = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾: $IC\ index = (AFKr / (AFNaL + AFCaL)) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full scope</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>		
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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. GIPA (2016) www.Ilexxtra.org/hesi/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		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{90, 40 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, T _{EP} : $APD_{90, 40} - APD_{90, 60}$ ("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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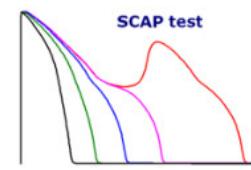
Drug	Quinine					
	Gametocytocidal activity against malaria parasite used to treat malaria					
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}^{(1)}$	TdP risk			
	$I_{CaL} : 27.178 \mu M (1.0)$ $I_{Kr} : 5.17 \mu M (1.0)$ $I_{Na} : 24.151 \mu M (1.1)$ $I_Ks : 37.453 \mu M (1.1)$ $I_{to} : 79.254 \mu M (1.0)$ $I_{NaL} : 11.053 \mu M (0.4)$ $I_{KL} : \text{---- } \mu M (\text{---})$	3.9567 μM	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 4/0 (TdP+/TdP-)			
	<i>In silico</i> 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): $[Na^+]_o = 140$ - $[Ca^{2+}]_o = 1.8$ - $[K^+]_o = 5.4$ Cycle length : 1000 msec Beat number: 100 	Effect of drugs on AP⁽⁸⁾: A 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} $I_f = g_f O(V - E_{ION})$ $O = \text{maximal conductance of channel}$ $E_{ION} = \text{resting membrane potential}$ $g_f = \text{conductance for species of ion which flows through channel}$ $g_f^* = \text{maximal conductance of channel}$ $IC_{50s} = \text{50% of inhibition of drug for channel}$ $EFTPC_{max} = \text{maximal effect of drug}$ $\theta_f = \text{inhibition}$	TDR and RUD estimation: <ul style="list-style-type: none"> TDR = $APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) RUD = $APD_{90, \text{endo}} - APD_{90, \text{epi}}$ where: $APD_{90,i} = APD_{90}$ with - i APD₉₀ without compound at CL x 			
Results	Human epicardial myocytes 		Transmural dispersion of repolarisation 			
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes <ul 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	1. Crumb WI et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81 : 251-262 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.ictsa.org/ictsa/science/cardiac/cipa/ 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22 : 10-16					
Abbreviations	AP : action potential, APA : action potential area, APD _{90,endo,epi} : AP duration at 90, 50 or 0% of AP, APDP : APD prolongation, DA : depolarization abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, Epi : endo-epicardial myocyte, Epi : epicardial myocyte, EAD index : ion channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{Na}, I_K, I_{Kr}, I_{CaL}, I_{NaL}, I_{NaK}, I_{KL}$, RMP : resting membrane potential, RUD : reverse use dependence, T ₉₀ : time to 90% of AP de polarization, TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V _m : membrane potential, M_r : maximal rate of AP de polarization, θ_f : drug effect, θ_f^* : intrinsic rate of AP de polarization, θ_f^{max} : maximum rate of AP de polarization at Epi/Endo, UD : uniform dispersion of AP de polarization, Ud : uniform dispersion of AP de polarization					

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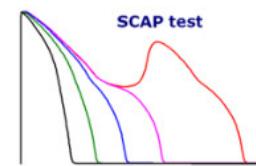
Drug	Raltegravir				
	HIV integrase inhibitor used to treat HIV infections				
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: 246.7 μM (1.0) I_{to} : --- μM (---) I_{Kr}: 782.8 μM (1.0) I_{Na} : --- μM (---) I_{Na}: 824.2 μM (1.0) I_{K1} : --- μM (---) I_{Ks} : --- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.7 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/2 (TdP+/TdP-)</p>		
	In silico cardiac action potential study (ORD model) ⁽⁷⁾				
Results	<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 and IC_{50s} $I_j = g_j(V - E_{j,0}) \left[1 + \left(\frac{g}{g_{max}} \right)^n \right]^{-1}$ <p>g_j= maximal conductance of channel j E_{j,0}= reversal potential for species of ions which flows through channel j n= open probability of channel j g= reversal potential for species of ions which flows through channel j IC₅₀= 50% of inhibition of a drug for a channel j IC_{50s}= 50% of inhibition of a drug for all channels</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀epi (at CL of 1000 msec) RUD = APD₉₀endo - APD₉₀mid where APD₉₀s = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation ⁽⁹⁾:</p> $\text{IC index} = (\text{AFKr}/(\text{AFNaL}+\text{AFCaL}/2)) * 100$ <p>where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{Kr}, I_{CaL} and I_{CaL} in full range</p>		
	<p>Human epicardial myocytes</p> <p>www.scapttest.com</p>	<p>Transmural dispersion of repolarisation</p> <p>www.scapttest.com</p>			
	<p>Human midmyocardial myocytes</p> <p>www.scapttest.com</p>	<p>Reverse use dependence on midmyocardial myocytes</p> <p>www.scapttest.com</p>			
	<p>Human endocardial myocytes</p> <p>www.scapttest.com</p>				
Summary	<p>Raltegravir x-fold EFTPC_{max} vs. IC_{50s}</p> <p>www.scapttest.com</p>	<p>Raltegravir</p> <p>www.scapttest.com</p>			
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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. GIPA (2016) www.IsiExtra.org/hesi/science/cardiac/gipa/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_{90,40,60,90} : 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_{Kr}*I_{Na}*I_{Na}*I_{K1}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{EP,90} : 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, V_{min} : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>				

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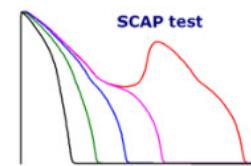
Drug	Ranolazine		
	Voltage-gated K ⁺ and Na ⁺ channels blocker used to treat chronic angina		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : ---- μM (---) I_{to} : ---- μM (---) I_{Kr} : 6.49 μM (0.8) I_{Na} : 7.884 μM (0.9) I_{Na} : ---- μM (---) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>1.9482 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⁾ : low or no risk of TdP (class 3) WP⁽⁶⁾ : 2/5 (TdP+/TdP-)</p>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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 and IC_{50s} $I_f = g_f(V - E_{f,rest})$ (g_f: maximal conductance of channel ; $E_{f,rest}$: reversal potential of species of ions which flows through channel ; f: drug concentration) $B_f = \frac{g_f}{g_f,control} \left[1 + \left(\frac{B_f}{IC_{50f}} \right)^n \right]^{-1}$ ($g_f,control$: control conductance of channel ; IC_{50f}: 50% of inhibition of a drug for channel ; n: drug concentration (EFTPC for example) ex: 5/2 <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP₉₀ mid - AP₉₀epi (at CL of 1000 msec) RUD = AP₉₀mid-AP₉₀endo where AP₉₀P_a = AP₉₀without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, 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>Human endocardial myocytes</p> <p>Summary</p>	
References	<p>1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Illsieux.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, 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_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dP,90} : APD₉₀-APD₄₀ 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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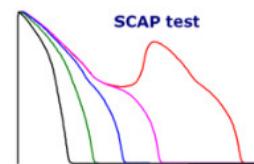
Drug	Ribavirin		
	Viral RNA and protein synthesis inhibitor used to treat Hepatitis C		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 622.5 μM (1.0) I_{to} : ---- μM (---) I_{Kr}: 967.0 μM (1.0) I_{NaL} : ---- μM (---) I_{Na}: 2997.5 μM (1.0) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>27.88 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not classified with TdP risk (class 4) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/2 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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} <p>$I_j = g_j(V - E_{j,0})$</p> <p>$\delta_j = \frac{g_j(V - E_{j,0})}{g_j(V - E_{j,0}) + 1 + \left(\frac{\delta_j}{IC_{50s}}\right)^n}$</p> <p>g_j = maximal conductance of channel V = voltage membrane E_{j,0} = reversal potential for species of ions which flows through channel IC_{50s} = 50% of inhibition of a drug for a channel δ = drug concentration (EFTPC_{max} for example) n = Hill slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{mid} - APD_{endo} where APD_{endo} = APD_{endo} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p> <p>Summary</p>
References	<p>1. Kramer J et al. (2013) <i>Sci rep</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Iseuxtra.org/hesi/science/cardiac/cipa/ Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, APD₅₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₆₀ : APD₄₀-APD₆₀ 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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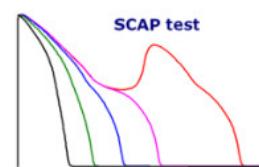
Drug	Risperidone		
	Dopamine D ₂ and serotonin 5-HT _{2A} receptor antagonist used to treat schizophrenia, bipolar mania, psychosis or depression		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 34.2 μM (0.79) I _{to} : --- μM (---) I _{Kr} : 0.26 μM (0.99) I _{Na} : --- μM (---) I _{Na} : 43.4 μM (0.98) I _{K1} : --- μM (---) I _{Ks} : --- μM (---)	EFTPC_{max}⁽¹⁾ 0.002 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CiPA ⁽⁵⁾ : intermediate risk of TdP (class 2) WP ⁽⁶⁾ : 5/5 (TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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 and IC _{50s} $I_j = g_j(V - E_{j,0})^{1 - \frac{1}{1 + (\frac{g_j}{IC_{50j}})^n}}$ g _j = maximal conductance of channel j E _{j,0} = reversal potential for species of ions which flows through channel j n= exponent of inhibition (0.5 for half inhibition) IC _{50j} = 50% of inhibition of a drug for channel j D= drug concentration (BP/EC ₅₀ for example) BP= basal value	TDR and RUD estimation: • TDR = AP _{mid} - AP _{Depi} (at CL of 1000 msec) • RUD = AP _{Decc} -AP _{Decc} where AP _{Decc} = AP _{Decc} without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes
	Human endocardial myocytes 		
Summary			
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Isicextra.org/hesi/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. Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96 : 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{40,60,90} : 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 _{K1} +I _{Kr} +I _{Ks} +I _{Na} +I _{Na} ⁻ , RMP : resting membrane potential, RUD : reverse use dependence, T _{Decc} : APD ₉₀ -APD ₄₀ 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		

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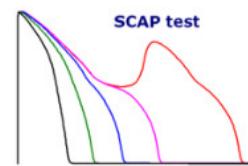


Drug	Ritonavir		
	HIV protease inhibitor used to treat HIV infections		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL}: 8.228 μM (1.0) I_{Kr}: 5.157 μM (1.0) I_{Na}: ---- μM (---) I_{K1}: ---- μM (---) I_{Ks}: ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.4369 μM</p>	<p>TdP risk</p> <p>Redfern ⁽²⁾: not reported Kramer ⁽³⁾: not reported CredibleMeds ⁽⁴⁾: not reported CIPA ⁽⁵⁾: not reported WP ⁽⁶⁾: 1/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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} <p>$I_f = g_o(V - E_{f,0}) \left[1 + \left(\frac{g}{g_o} \right)^{\alpha} \right]^{-1}$</p> <p>g = maximal conductance of channel V = open membrane E_f = reversal potential for species of ions which flows through channel α = sigmoidal coefficient of inhibition IC₅₀ = 50% of inhibition of a drug for a channel gF = drug concentration (F/P for example) x = fold slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{Depi} (at CL of 1000 msec) RUD = AP_{D00}-AP_{D00} where AP_{D00}=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 AFGaL = active fraction (%) of the I_{Kr}, I_{CaL} 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>Human endocardial myocytes</p> <p>Summary</p>
References	<p>1. Crumb WJ et al. (2016) <i>J Pharmacol Toxicol Methods</i> 81: 251-262 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.Iseuxtra.org/hesi/science/cardiac/cipa/Project 6. Winiarska 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 : AP duration at 40, 60 or 90 % of APA, APD₅₀ : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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_{Na}+I_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₅₀ : APD₅₀-APD₄₀ or AP₅₀-AP₄₀, 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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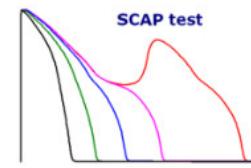


Safe Cardiac Action Potential Test



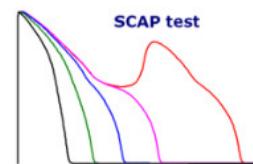
Drug	Saquinavir		
HIV protease inhibitor used to treat HIV infections			
Raw data	IC_{50s} (slope) ⁽¹⁾ I _{CaL} : 1.9 μM (1.15) I _{to} : ---- μM (---) I _{Kr} : 16.9 μM (1.72) I _{Na} : ---- μM (---) I _{Na} : 12.1 μM (2.34) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	$EFTPC_{max}$ ⁽¹⁾ 0.13 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : possible risk of TdP (class 2) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 1/4 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	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 - $[Ca^{++}]$ _o : 1.8 - $[K^+]$ _o : 5.4 • Cycle length : 1000 msec • Beat number: 100	Effect of drugs on AP⁽⁸⁾: • Cell 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_{50} $I_j = g_j(V - E_{jon})$ $E_{jon} = g_j \cdot V_{max} / (g_{max} \cdot V_{max})$ $E_{max} = V_{max} + (V_{max} - V_{min}) / e^{-k \cdot D}$ $D = \ln(g/g_{control}) / \ln(1 + (\frac{D}{IC_{50}})^n)$ $n = 5$ $g_{max} = \text{maximal conductance of channel}$ $V_{max} = \text{maximum membrane potential}$ $V_{min} = \text{minimum membrane potential}$ $g_{control} = \text{control conductance of channel}$ $IC_{50} = 50\% \text{ of inhibition of a drug for a channel}$ $D = \text{drug concentration (BP/PC for example)}$ $e = \text{base of natural logarithm}$	TDR and RUD estimation: • TDR = $APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) • RUD = $APD_{90, \text{endo}} - APD_{90, \text{mid}}$ where $APD_{90, P_i} = APD_{90, \text{no comp}} \text{ with } - APD_{90, i}$ without compound at CL x
	Human epicardial myocytes 		
	Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes 		
Summary	Reverse use dependence on midmyocardial myocytes 		
References	1. Kramer J et al. (2013) Sci. Rep. 3 : 2100 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.pharmaexptech.org/scientific/cardiac/cipa/ 6. Widenowska B et al. (2017) Drug discovery today 22 : 10-16 7. O'Hearn T et al. (2011) PLoS Comput. Biol. 7 : e1003061-8 8. Mirams GR et al. (2011) Cardiovasc. Res. 91 : 53-61 9. Christophe B & Crumb WJ Jr (2019) <i>Pharmacol Toxicol Methods</i> 96 : 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{90, no comp} : 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, EFTPCmax : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC index : half channel inhibition index, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{Kr} + I_{Na} + I_{NaL} + I_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $IC_{50, 10}$: APD _{90, 10} / 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		

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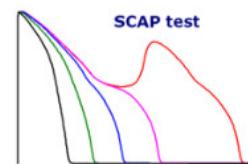
Drug	Sertindole				
Dopamine D ₂ , serotonin 5-HT _{2A} and 5-HT _{2C} and G ₁ -adrenergic receptors antagonist used to treat schizophrenia no longer marketed in UK, Bulgaria and Spain (Onakpoya et al (2016) <i>BMC Med.</i> 14 : 10)					
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 6.3 μM (1.29) I _{to} : ---- μM (--) I _{Kr} : 0.033 μM (1.25) I _{NaL} : ---- μM (--) I _{Na} : 6.9 μM (1.19) I _{K1} : ---- μM (--) I _{Ks} : ---- μM (--)	EFTPC_{max}⁽¹⁾ 0.002 μM	TdP risk Redfern ⁽²⁾ : unacceptable risk of TdP (class 2) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 11/1 (TdP+/TdP-)		
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾					
Results	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} $I_j = g_j O(V - E_{j,0})$ $O(x) = \frac{1}{1 + \left(\frac{x}{IC_{50s}}\right)^n}$ where: g _j = maximal conductance of channel j O(x) = open probability of channel j E _{j,0} = reversal potential for species of ions which flows through channel j IC _{50s} = drug-free minimal concentration of ions that inhibits channel j by 50% n = drug concentration (0-100, for example) x = fold slope	TDR and RUD estimation: • TDR = APD ₉₀ mid - APD ₉₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ endo/APD ₉₀ epi where: APD ₉₀ x = APD ₉₀ with - APD ₉₀ without compound at CL x		
Human epicardial myocytes Transmural dispersion of repolarisation Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes Human endocardial myocytes 					
Summary	 				
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.lisieux.org/hes/science/cardiac/cipa/ 6. Włoszniowska 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 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 _{50s} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNQ : integration sum of I _{CaL} +I _{to} +I _{NaL} +I _{Na} +I _{K1} , RMP : resting membrane potential, RUD : reverse use dependence, T _{dp} : APD ₉₀ -APD ₉₀ or APD ₉₀ (triangulation), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{m,0} : maximal rate of AP rise, V _{m,1} : volt per second				

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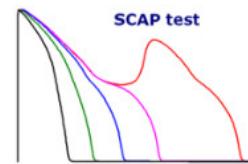
Drug	Sertraline		
	Serotonin reuptake inhibitor used to treat major depressive or social anxiety disorders		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 2.6 μM (1.9) I_{to} : ---- μM (---) I_{Kr}: 0.7 μM (1.3) I_{NaL} : ---- μM (---) I_{Na}: 6.1 μM (0.7) I_{K1}: 10.5 μM (2.1) I_{Ks}: 12.3 μM (2.5)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.6 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⁾ : 0/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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} $I_j = g_j(V - E_{j,0})^{n_j}$ $\frac{g_j}{g_{j,0}} = \frac{1 + \left(\frac{D}{IC_{50j}}\right)^{n_j}}{1 + \left(\frac{D}{IC_{50j}}\right)^{n_j}}$ <p>g_j = maximal conductance of channel j E_{j,0} = reversal potential for species of ions which flows through channel j D = drug concentration (EF-TPC for example) n_j = Hill slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{mid} - APD_{endo} <p>where APD_n = APD₀ with - APD₀ without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr/(AFNaL+AFCaL)/2) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL}.</p>
	<p>Human epicardial myocytes</p>	<p>Transmural dispersion of repolarisation</p>	
	<p>Human midmyocardial myocytes</p>		
	<p>Human endocardial 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>		
Summary	<p>Effect (%)</p> <p>APD90 / APD50 (msec)</p>		
References	<p>1. Lee H-A et al. (2012) <i>Korean J Physiol Pharmacol</i> 16: 327-332 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Ilextra.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, 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_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{dp,40} : APD₄₀-APD₄₀ 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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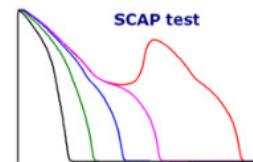
Drug	Sildenafil		
	Phosphodiesterase PDE-5 inhibitor used to treat erectile dysfunction		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 100.0 μM (1.0) I _{to} : 501.187 μM (1.0) I _{Kr} : 31.623 μM (1.0) I _{Na} : ---- μM (---) I _{Na} : 501.187 μM (1.0) I _{K1} : ---- μM (---) I _{Ks} : 398.107 μM (1.0)	EFTPC_{max}⁽¹⁾ 0.071513 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
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 and IC _{50s} $I_j = g_j(V - E_{j,0}) \left[1 + \left(\frac{g_j}{IC_{50j}} \right)^n \right]^{-1}$ g _j = maximal conductance of channel j E _{j,0} = reversal potential for species of ions which flows through channel j n= reversal probability of channel j IC _{50j} = 50% of inhibition of a drug for channel j D= drug concentration (EF-TPC for example) in full range	TDR and RUD estimation: • TDR = APD ₉₀ mid - APD ₉₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ mid-APD ₉₀ endo where APD ₉₀ P _a = APD ₉₀ with - APD ₉₀ without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} in full range
	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. Mirams GR et al. (2014) <i>J Pharmacol. Toxicol. Methods</i> 70 : 246-254 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.IsiExtra.org/hesi/science/cardioc/cipa/Project 6. Winiowska 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 : e1002618 8. Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91 : 53-61 9. Christope B & Crumb WJ Jr (2019) <i>J Pharmacol Toxicol Methods</i> 96 : 15-26		
Abbreviations	AP : action potential, APA : AP amplitude, APD _{40, 60 or 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 _{Kr} *I _{NaL} *I _{CaL} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{40, 50} : APD ₄₀ -APD ₄₀ or APD ₅₀ ("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



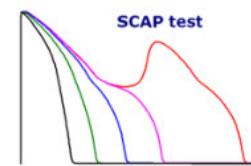
Drug	Silodosin		
	α_{1A} -adrenoceptor antagonist used to treat benign prostatic hyperplasia		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 794.3 μM (1.0) I_{to}: 316.228 μM (1.0) I_{Kr}: 7.943 μM (1.0) I_{NaL}: ---- μM (---) I_{Na}: 63.096 μM (1.0) I_{K1}: ---- μM (---) I_{Ks}: 251.189 μM (1.0)</p>	<p>$EFTPC_{max}$⁽¹⁾</p> <p>0.009409 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>
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 5.4 Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> <p>◆ 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}</p> $I_j = g_j(V - E_{jon})$ <p>g_j= maximal conductance of channel j E_{jon}= reversal potential for species of ions which flows through channel j \bar{g}_j= minimal conductance of channel j \bar{E}_{jon}= reversal potential for species of ions which flows through channel j $IC_{50} = 50\% \text{ of inhibition of a drug for channel } j$ D= drug concentration (FEP^C for example) x= half slope</p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = $APD_{mid} - APD_{epi}$ (at CL of 1000 msec) RUD = $APD_0 - APD_{mid} - APD_{epi}$ where $APD_{0,i} = APD_{mid}$ with - APD_{mid} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr/(AFNaL + AFCaL)/2)*100$ <p>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 repolarisation</p>	
Summary	<p>Silodosin x-fold $EFTPC_{max}$ vs. IC_{50s}</p> <p>Reverse use dependence on midmyocardial myocytes</p> <p>Legend: 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 midmyocardial myocytes</p> <p>Human endocardial myocytes</p>	
References	<p>1. Mirams GR et al. (2014) <i>J Pharmacol. Toxicol. Methods</i> 70: 246-254 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Islextra.org/hes/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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> 95: 15-26</p>	<p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $APD_{40-90-90}$: 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{CaL}, I_{Kr}, I_{NaL}, I_{K1}, I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, TE_{40-60} : $APD_{40}-APD_{60}$ ("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</p>	

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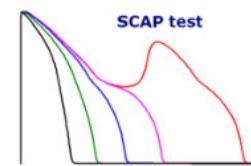
Drug	Sitagliptin		
	Dipeptidyl peptidase-4 inhibitor used to treat type 2 diabetes mellitus		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 147.1 μM (1.0) I_{to} : ---- μM (---) I_{Kr}: 174.7 μM (1.0) I_{Nal} : ---- μM (---) I_{Na}: 1220.8 μM (1.0) I_{K1} : ---- μM (---) I_{Ks} : ---- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.442 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : non-torsadogenic (class 1) CredibleMeds⁽⁴⁾ : not reported CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 0/2(TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 and IC_{50s} $I_j = g_j(V - E_{j,rest})$ (g_j= maximal conductance of channel ; $E_{j,rest}$= reversal potential for species of ions which flows through channel) $B_j = \frac{g_j}{g_j,control} \left[1 + \left(\frac{D_j}{IC_{50j}} \right)^n \right]^{-1}$ (D_j= drug concentration (BP) for channel ; IC_{50j}= 50% of inhibition of a drug for channel ; n= drug concentration (BP) for example) no tailage 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD_{mid} - APD_{epi} (at CL of 1000 msec) RUD = APD_{mid} - APD_{endo} where APD_{endo} = APD_{endo} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, 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>Human endocardial myocytes</p>		
Summary	<p>Sitagliptin x-fold EFTPC_{max} vs. IC_{50s}</p>	<p>Sitagliptin</p>	
References	<p>1. Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. GIPA (2016) www.Isiextra.org/hesi/science/cardiac/cipa/Project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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, 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_{Kr}*I_{NaL}*I_{CaL}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₅₀ : APD₄₀-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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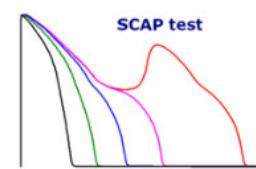
Drug	Solifenacin		
	Muscarinic M ₂ and M ₃ receptor antagonist used to treat urinary incontinence		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 4.3 μM (1.47) I _{Kr} : 0.28 μM (0.90) I _{Na} : 1.5 μM (1.32) I _{Ks} : --- μM (---)	EFTPC_{max}⁽¹⁾ 0.003 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : conditional risk of TdP (class 3) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 3/1(TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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} $I_j = g_j(V - E_{j,0}) \cdot \frac{g_{j,0}}{g_{j,0} + (\frac{D}{IC_{50s}})^n}$ g _j = maximal conductance of channel E _{j,0} = reversal potential for species of ions which flows through channel n= reversal potential for species of ions which flows through channel IC _{50s} = 50% of inhibition of a drug for a channel D= drug concentration (BP/IC _{50s} for example) BP= half-slope	TDR and RUD estimation: • TDR = AP _{mid} - AP _{Depi} (at CL of 1000 msec) • RUD = AP _{De00} -AP _{Dp100} where AP _{Dp100} = AP _{De00} without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} in full slope
	Human epicardial myocytes Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary	 		
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Isiextra.org/hesi/science/cardiac/cipa/ 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	AP : action potential, APA : AP amplitude, APD _{40,60,90} : AP duration at 40, 60 or 90 % of APA, APD _p : AP 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 _{Kr} *I _{NaL} *I _{CaL} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₉₀ : APD ₄₀ -APD ₉₀ or APD ₄₀ ("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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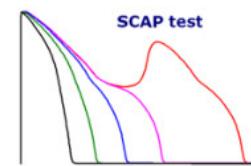
Drug	Sotalol		
 β1-adrenoceptor antagonist used to treat ventricular arrhythmia or maintain sinus rhythm in atrial fibrillation			
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 193.3 μM (1.0) I _{to} : ---- μM (---) I _{Kr} : 111.4 μM (0.73) I _{NaL} : ---- μM (---) I _{Na} : 7013.9 μM (1.0) I _{K1} : ---- μM (---) I _{Ks} : ---- μM (---)	EFTPC_{max}⁽¹⁾ 14.69 μM	TdP risk Redfern ⁽²⁾ : class IA or III antiarrhythmics (class 1) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CiPA ⁽⁵⁾ : high risk of TdP (class 1) WP ⁽⁶⁾ : 14/0 (TdP+/TdP-)
In silico cardiac action potential study (ORD model)⁽⁷⁾			
Results	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} $I_j = g_j(V - E_{j,0})$ $\frac{g_j}{g_{j,0}} = \text{Control} \cdot \left[1 + \left(\frac{D}{IC_{50j}} \right)^n \right]^{-1}$ g _j = maximal conductance of channel j g _{j,0} = maximal conductance of channel j at control level IC _{50j} = 50% of inhibition of conductance of channel j D = drug concentration (EFTPC _{max} for example) n = half slope	TDR and RUD estimation: • TDR = APD ₅₀ mid - APD ₅₀ cpi (at CL of 1000 msec) • RUD = APD ₅₀ P _{extra} -APD ₅₀ P _{too} where APD ₅₀ P ₀ = APD ₅₀ without compound at CL x APD ₅₀ P _x = APD ₅₀ with - APD ₅₀ without compound at CL x
Human epicardial myocytes Transmural dispersion of repolarisation Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes Human endocardial myocytes 			
Summary	 		
References	1. Kramer J et al. (2013) Sci Rep. 3: 2100 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. CiPA (2016) www.pharmcentral.org/scientific/cardiac/cipa/Project 6. Wéniowka B et al. (2017) Drug discovery today 22: 10-16 7. O'Hearn T et al. (2011) PLoS Comput. Biol. 7: e1003061.8 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	AP : action potential , APA : AP amplitude , APD ₅₀₋₉₀ : AP duration at 50, 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 ₅₀ : 50% inhibition concentration , mid : midmyocardial myocyte , msec : millisecond , mV : millivolt , qNet : integration sum of I _{CaL} +I _{Kr} +I _{K1} +I _{NaL} +I _{Na} , RMP : resting membrane potential , RUD : reverse use dependence , T ₄₀₋₆₀ : APD ₅₀ -APD ₄₀ or APD ₅₀ ("triangulation") , TdP : torsade de pointes , TDR : transmural dispersion of repolarization , V _m : membrane voltage , V _{max} : maximal rate of AP rise , V _s : volt per second		

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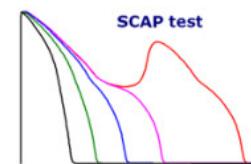
Drug	Sparfloxacin			
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk	
	$I_{CaL} : 88.8 \mu M (1.0)$ $I_{Kr} : 22.1 \mu M (0.93)$ $I_{NaL} : 2555.0 \mu M (1.0)$ $I_K : \text{---} \mu M (\text{---})$ $I_Ks : \text{---} \mu M (\text{---})$	$I_{CaL} : 88.8 \mu M (1.0)$ $I_{Kr} : 22.1 \mu M (0.93)$ $I_{NaL} : 2555.0 \mu M (1.0)$ $I_K : \text{---} \mu M (\text{---})$ $I_Ks : \text{---} \mu M (\text{---})$	$EFTPC_{max}$ ⁽¹⁾ 1.766 μM	Redfern ⁽²⁾ : isolated reports of TdP (class 4) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 8/2 (TdP+/TdP-)
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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 100 (full inhibition) which is a function of a multiple of $EFTPC_{max}$ and IC_{50s} $I_f = g_f O(V - E_{f,0})$ (open probability of channel f) $E_{f,0}$ = reversal potential for species of ions which flows through channel f g_f = maximal conductance of channel f $O(V) = \frac{1}{1 + \left(\frac{V - V_{1/2}}{K_f}\right)^n}$ (sigmoidal drug-free maximal conductance of channel f) K_f = half maximal inhibition concentration of channel f Drip concentration (87% for example) in Hill slope 	TDR and RUD estimation: <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, 100}$ where $APD_{90,P_x} = APD_{90}$ with - P_x without compound at CL x 	
	Human epicardial myocytes 			
	Transmural dispersion of repolarisation 			
	Human midmyocardial myocytes 			
	Reverse use dependence on midmyocardial myocytes 			
	Human endocardial myocytes 			
Summary				
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Abbreviations	AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: 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 $i_{CaL} + i_{Kr} + i_{NaL} + i_K + i_{Ks}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{40,60}$: $APD_{40} - APD_{60}$ or $APD_{40} - APD_{90}$ (triangulation), TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V_{max} : membrane voltage, V_{max} : maximal rate of AP rise, V_{min} : volt per second			

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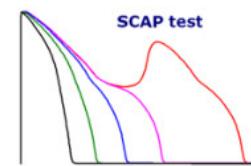
Drug	Sunitinib		
	Tyrrosine kinase inhibitor used to treat renal cell carcinoma and gastrointestinal stromal tumor		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL}: 33.4 μM (1.09) I_{to} : --- μM (---) I_{Kr}: 1.2 μM (1.0) I_{NaL} : --- μM (---) I_{Na}: 16.5 μM (1.22) I_{K1} : --- μM (---) I_{Ks} : --- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.013 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : not reported Kramer⁽³⁾ : torsadogenic (class 2) CredibleMeds⁽⁴⁾ : possible risk of TdP (class 2) CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 4/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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> <p>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}</p> $I_j = g_j(V - E_{j,0}) \cdot \left[1 + \left(\frac{g_j}{IC_{50s}} \right)^n \right]^{-1}$ <p>g_j= maximal conductance of channel V= voltage membrane E_{j,0}= reversal potential for species of ions which flows through channel IC_{50s}= 50% of inhibition of a drug for a channel n= drug concentration (EF-TPC_{max} for example) no full slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = APD₉₀ mid - APD₉₀ epi (at CL of 1000 msec) RUD = APD₉₀endo-APD₉₀mid where APD₉₀P_s = APD₉₀ with - APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC\ index = (AFKr/(AFNaL+AFCaL)/2) * 100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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> <p>Summary</p>
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Iseuxtra.org/hesi/science/cardiac/cipa/ 6. Winiarska 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 ₉₀ : AP duration at 40, 60 or 90 % of APA, APD ₅₀ : APD prolongation, apu : arbitrary unit, CL : cycle length, DA : degeneration 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 _{NaL} +I _{K1} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₆₀ : APD ₉₀ -APD ₄₀ 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		

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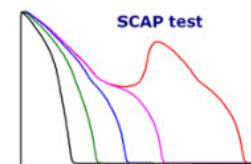
Drug	Tadalafil		
	Phosphodiesterase PDE-5 inhibitor used to treat erectile dysfunction, benign prostatic hyperplasia and pulmonary arterial hypertension		
Raw data	IC _{50s} (slope) ⁽¹⁾ I _{CaL} : ----- μM (---) I _{Kr} : 100.0 μM (1.0) I _{Na} : 125.9 μM (1.0) I _{Ks} : 158.49 μM (1.0)	EFTPC _{max} ⁽¹⁾ 0.13605 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 (full inhibition) which is a function of a multiple of EFTPC and IC _{50s} $I_j = g_j(V - E_{j,0})^n \left[1 + \left(\frac{g_j}{IC_{50j}} \right)^m \right]^{-1}$ where n=1 (open probability of channel), m=2 (open probability of channel ²) IC _{50j} =50% of inhibition of a drug for channel j x-fold drug concentration (30-fold EFTPC for example) on top scale	TDR and RUD estimation: • TDR = APD ₉₀ mid - APD ₉₀ epi (at CL of 1000 msec) • RUD = APD ₉₀ endo - APD ₉₀ mid where APD ₉₀ P _a = APD ₉₀ without compound at CL x	IC index calculation ⁽⁹⁾ : IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{CaL} and I _{Ks}
Results	Human epicardial myocytes	Transmural dispersion of repolarisation	Reverse use dependence on midmyocardial myocytes
	Human midmyocardial myocytes		
	Human endocardial myocytes		
Summary			
References	1. Mirams GR et al. (2014) <i>J Pharmacol. Toxicol. Methods</i> 70 : 246-254 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. GPA (2016) www.Isiextra.org/hesi/science/cardiac/cipa/Project 6. Wisiowska 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 _{90,40,60,90} : 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, ende : 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 _{Kr} *I _{Na} *I _{CaL} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{dp,40} : APD ₉₀ -APD ₄₀ 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		

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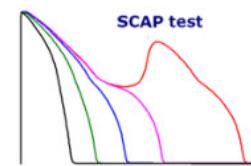
Drug	Tamoxifen		
	Estrogen receptor modulator used to treat breast cancer		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : --- μM (---) I _{to} : --- μM (---) I _{Kr} : 0.777 μM (1.0) I _{NaL} : --- μM (---) I _{Na} : --- μM (---) I _{K1} : --- μM (---) I _{Ks} : --- μM (---)	EFTPC_{max}⁽¹⁾ 0.018 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : possible risk of TdP (class 2) CiPA ⁽⁵⁾ : low or no risk of TdP (class 3) WP ⁽⁶⁾ : 1/5 (TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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} $I_j = g_j(V - E_{j,0})^{1 - \frac{1}{1 + (\frac{g_j}{IC_{50s}})^n}}$ $n = \text{inverse probability of channel}$ $g_j = \text{maximal conductance of channel}$ $E_{j,0} = \text{reverse potential for species of ions which flows through channel}$ $IC_{50s} = 50\% \text{ inhibition of inhibition of drug for channel}$ IC _{50s} = 50% of inhibition of a drug for a channel x-fold drug concentration (EF ¹⁰ for example) on full scale	TDR and RUD estimation: • TDR = AP _{mid} - AP _{depi} (at CL of 1000 msec) • RUD = AP _{mid} - AP _{depi} at CL ₁₀₀₀ where AP _{depi} = AP _{mid} with - AP _{mid} without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{CaL} and I _{CaL}
	Human epicardial myocytes 		
	Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes 		
Summary	Reverse use dependence on midmyocardial myocytes 		
	Human endocardial myocytes 		
References	1. Ando H et al. (2017) J Pharmacol Tox Meth 58:111-127 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. CiPA (2016) www.lseictra.org/hesi/science/cardiac/cipa/Project 6. Winiarska 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	AP : action potential, APA : AP amplitude, APD _{mid} : AP duration at 40, 60 or 90 % of APA, APD _{max} : AP duration at 40, 60 or 90 % of APA, APD _{min} : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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 _{NaL} +I _{K1} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₆₀ : APD ₆₀ -APD ₄₀ or AP 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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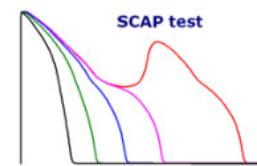
Drug	Tedisamil		
	Voltage-gated K ⁺ channel blocker to treat atrial fibrillation		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : ---- μM (---) I_{Kr} : 0.219 μM (1.0) I_{Na} : ---- μM (---) I_{K1} : ---- μM (---) I_{Ks} : 6.457 μM (1.0)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.085 μM</p>	<p>TdP risk</p> <p>Redfern⁽²⁾ : class IA or III antiarrhythmics (class 1) Kramer⁽³⁾ : not reported CredibleMeds⁽⁴⁾ : not reported CIPA⁽⁵⁾ : not reported WP⁽⁶⁾ : 4/0 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ $g_f = g_{max} \cdot f$ $f = \frac{1}{1 + \left(\frac{D}{IC_{50f}}\right)^n}$ <ul style="list-style-type: none"> g_{max}= maximal conductance of channel f = open probability of channel D = drug concentration (e.g. EFTPC for example) IC_{50f} = 50% of inhibition of a drug for a channel n = drug exponent (e.g. 10 for EFTPC for example) 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{depi} (at CL of 1000 msec) RUD = AP₉₀ - AP₉₀ without compound at CL x <p>where AP₉₀ = AP₉₀ with - AP₉₀ without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr/(AFNaL+AFCaL)/2)*100$ <p>where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{CaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p>		
Summary	<p>Tedisamil</p> <p>x-fold EFTPC_{max} vs. IC_{50s}</p>		
References	<p>1. Romero L et al. (2018) J.Chem.Inf.Model. 58: 867-878 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. G.PA (2016) www.Ilexxtra.org/hesic/science/cardiac/cipa/project 6. Wiśniewska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>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_{40,60,90,99} : 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, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I_{Kr}*I_{Na}*I_{CaL}*I_{K1}*I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T_{AP,90} : APD₉₀-APD₄₀ 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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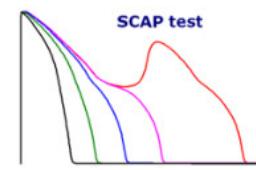
Drug	Telbivudine		
	Thymidine nucleoside analog used to treat chronic hepatitis B		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 713.9 μM (1.0) I _{to} : --- μM (---) I _{Kr} : 422.7 μM (1.0) I _{Nal} : --- μM (---) I _{Na} : 1095.2 μM (1.0) I _{K1} : --- μM (---) I _{Ks} : --- μM (---)	EFTPC_{max}⁽¹⁾ 19.72 μM	TdP risk Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not reported CiPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 0/2 (TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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} $I_j = g_j(V - E_{j,0}) \cdot \left[1 + \left(\frac{g_j}{IC_{50s}} \right)^n \right]^{-1}$ g _j = maximal conductance of channel V=membrane potential E _{j,0} = reversal potential for species of ions which flows through channel IC _{50s} = 50% of inhibition of a drug for a channel n= drug concentration (EF-TCP _{max} for example) no full slope	TDR and RUD estimation: • TDR = AP _{mid} - AP _{Depi} (at CL of 1000 msec) • RUD = AP _{De00} -AP _{DeTDR} where AP _{De00} = AP _{De} without compound at CL x IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{CaL} and I _{CaL}
	Human epicardial myocytes Transmural dispersion of repolarisation 		
	Human midmyocardial myocytes Reverse use dependence on midmyocardial myocytes 		
	Human endocardial myocytes 		
Summary	 		
References	1. Kramer J et al. (2013) Sci rep. 3: 2100 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. CiPA (2016) www.lisextra.org/hesl/science/cardiac/cipa/Project 6. Winiarska 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	AP : action potential, APA : AP amplitude, APD ₄₀₋₅₀ : AP duration at 40, 50 or 90 % of APA, APD ₅₀₋₉₀ : AP prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration abnormalities, EAD : early afterdepolarization, EFTPC _{max} : maximal effective free therapeutic plasma concentration, endo : endocardial myocyte, epi : epicardial myocyte, IC ₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of I _{CaL} +I _{Kr} +I _{Na} +I _{K1} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₅₀ : APD ₄₀ -APD ₅₀ or APD ₅₀ ("triangulation"), TDR : 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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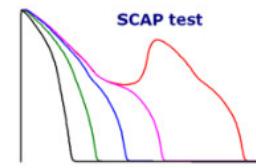
Drug	Terfenadine		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 0.93 \mu M (1.8)$ $I_{Ko} : \text{---} \mu M (\text{---})$ $I_{Kr} : 0.05 \mu M (1.15)$ $I_{NaL} : \text{---} \mu M (\text{---})$ $I_{Na} : 2.0 \mu M (1.81)$ $I_{K1} : \text{---} \mu M (\text{---})$ $I_K : \text{---} \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾		
Results	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 <p>Effect of drugs on AP⁽⁸⁾:</p> $I_j = g_j O(V - E_{j,0})$ $\theta_j = g_{control,j} \left[1 + \left(\frac{D}{IC_{50,j}} \right)^n \right]^{-1}$ <p>where g_j: maximal conductance of channel^j O: oxygen probability of channel^j $E_{j,0}$: reversal potential for series of ions which flows through channel^j $g_{control,j}$: minimal conductance of channel^j D: drug-free maximal conductance of channel^j $IC_{50,j}$: half-maximal inhibition concentration of channel^j n: Hill slope</p>	<p>TDR and RUD estimation:</p> $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ $RUD = APD_{90, \text{apo}} - APD_{90, \text{apo}}$ <p>where $APD_{90,P_i} = APD_{90}$ with - P_i without compound at CL x</p> <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ <p>where $AFKr$, $AFNaL$ and $AFCaL$: active fraction (%) of the I_{Ko}, 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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Kramer J et al. (2013) Sci. rep. 3 : 2100 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. CIPA (2016) www.IcIndex.org/en/science/cardioc/cipa/ 6. Widrowska B et al. (2017) Drug discovery today 22 : 10-16 7. O'Hearn T et al. (2011) PLoS Comput. Biol. 7 : e1003061 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	AP : action potential, APA : AP amplitude, $APD_{40, 60, 90}$: AP duration at 40, 60 or 90 % of APA, APPD : 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{K1} + I_K$, RMP : resting membrane potential, RUD : reverse use dependence, TE_{90} : $APD_{90, Epi}/APD_{90, Mid}$ or $APD_{90, Endo}/APD_{90, Mid}$ (triangulation), TDR : torsade de pointes, TDR : transmural dispersion of repolarization, V_{max} : 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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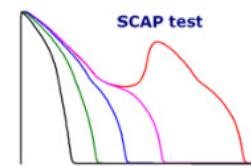
Drug	Terodiline		
Voltage-gated Ca^{++} channel ($\text{Ca}_{v1.2}$) blocker and cholinergic receptor antagonist used to treat urinary incontinence no longer marketed worldwide (Onalpoylu et al (2016) <i>BMC Med.</i> 14 : 10)			
Raw data	IC_{50s} (slope) ⁽¹⁾ $I_{\text{CaL}} : 4.8 \mu\text{M} (1.01)$ $I_{\text{to}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Kr}} : 0.65 \mu\text{M} (1.02)$ $I_{\text{NaL}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Na}} : 7.4 \mu\text{M} (1.23)$ $I_{\text{K1}} : \text{--- } \mu\text{M} (\text{---})$ $I_{\text{Ks}} : \text{--- } \mu\text{M} (\text{---})$	$EFTPC_{\text{max}}$ ⁽¹⁾ 0.145 μM	TdP risk Redfern ⁽²⁾ : unacceptable risk of TdP (class 2) Kramer ⁽³⁾ : torsadogenic (class 2) CredibleMeds ⁽⁴⁾ : known risk of TdP (class 1) CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : 7/0 (TdP+/TdP-)
<i>In silico</i> cardiac action potential study (ORd model) ⁽⁷⁾			
Results	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): $[\text{Na}^+]_{\text{o}} : 140 - [\text{Ca}^{++}]_{\text{o}} : 1.8 - [\text{K}^+]_{\text{o}} : 5.4$ Cycle length : 1000 msec Beat number: 100 <p>Effect of drugs on AP⁽⁸⁾:</p> $I_j = g_j O(V - E_{j,\text{rest}})$ $\theta_j = g_{\text{control}} j \left[1 + \left(\frac{D}{IC_{50j}} \right)^n \right]^{-1}$ <p>where: g_j: maximal conductance of channel^j O: open probability of channel^j V: membrane potential $E_{j,\text{rest}}$: reversal potential of ions which flows through channel^j g_{control}: minimal conductance of channel^j D: drug-free maximal conductance of channel^j IC_{50j}: 50% inhibition concentration of channel^j n: Hill slope</p> <p>TDR and RUD estimation:</p> $TDR = APD_{90,\text{mid}} - APD_{90,\text{epi}}$ $RUD = APD_{90,\text{Epi}}/APD_{90,\text{Mid}}$ <p>where: APD_{90,P_x} = APD_{90} with - P_x without compound at CL x</p> <p>IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / (AFNaL + AFCaL)/2) * 100$</p> <p>where: $AFKr$, $AFNaL$ and $AFCaL$: active fraction (%) of the I_{Ks}, 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> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Redfern WS et al. (2003) <i>Cardiolog. Res.</i> 58, 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woolesley RL (2015) www.CredibleMeds.org CIPA (2016) www.IcIndex.org/scientific/cardiac/cipa/ Widmowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hearn 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 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $APD_{40, 60 \text{ or } 90}$: AP duration at 40, 60 or 90 % of APA, APP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : depolarization abnormalities, EAD : early afterdepolarization, $EFTPC_{\text{max}}$: 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 $I_{\text{CaL}} + I_{\text{NaL}} + I_{\text{K1}} + I_{\text{Ks}}$, RMP : resting membrane potential, RUD : reverse use dependence, T_{EAD} : $APD_{90,\text{EAD}}/APD_{90}$ or $APD_{90,\text{tri}}$, TdP : torsade de pointes, TDR : transmural dispersion of repolarization, V_{max} : 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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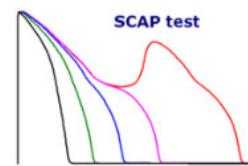
Drug	Thioridazine		
Raw data	IC _{50s} (slope) ⁽¹⁾	EFTPC _{max} ⁽¹⁾	TdP risk
In silico cardiac action potential study (ORd model) ⁽⁷⁾			
Simulation conditions: <ul style="list-style-type: none"> Cell geometry, channel conductance, state variables and scaling factors for endo-, mid- and epicardial myocytes as described in ORd model External ionic concentrations (mM): $[Na^+]$: 140 - $[Ca^{++}]$: 1.8 - $[K^+]$: 4.5 Cycle length : 1000 msec Beat number: 100 		Effect of drugs on AP⁽⁸⁾: <p>channel conductance modified by a scaling factor ranked from 1 (no inhibition) to 0 (full inhibition) which is a function of multiple of EFTPC_{max} and IC_{50s}</p> $I_j = g_j O(V - E_{j,0})$ $\theta_j = g_{j,0} \left[1 + \left(\frac{D}{IC_{50s}} \right)^{\alpha_j} \right]^{-1}$ <p>g_j: minimal conductance of channel^j O: open probability of channel^j E_{j,0}: reversal potential for species of ions which flows through channel^j D: drug concentration (M) IC_{50s}: half maximal drug-induced minimal conductance of channel^j α_j: Hill coefficient g_j: minimal conductance of channel^j g_{j,0}: drug-free minimal conductance of channel^j IC_{50s}: half maximal drug-induced minimal conductance of channel^j D: drug concentration (M) For example: in Hill slope</p>	TDR and RUD estimation: <ul style="list-style-type: none"> 1 - CL = APD_{90, mid} - APD_{90, epi} (at CL of 1000 msec) 2 - RUD = APD_{90, Epi}/APD_{90, mid} where APD_{90, P} = APD₉₀ with - APD₉₀ without compound at CL x IC index calculation⁽⁹⁾: $IC\ index = (AFKr / ((AFNaL + AFCaL) / 2)) * 100$ <p>where AFKr : known risk of TdP (class 1) AFNaL and AFCaL : active fraction (%) of the I_{Kr}, I_{Na} and I_{CaL}.</p>
Results	Human epicardial myocytes 	Transmural dispersion of repolarisation 	Reverse use dependence on midmyocardial myocytes
	Human midmyocardial myocytes 		
	Human endocardial myocytes 		
References	1. Kramer J et al. (2013) Sci. rep. 3 : 2100 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. CIPA (2016) www.heart-rhythm.org/science/cardiac/cipa/Project 6. Wideröwska B et al. (2017) Drug discovery today 22 : 10-16 7. O'Hearn T et al. (2011) PLoS Comput. Biol. 7 : e1002061 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	AP : action potential, APA : AP amplitude, APD _{90, 60 or 90} : AP duration at 40, 60 or 90 % of APA, APP : 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 $I_{Na,K} + I_{K1} + I_{K2} + I_{Ca,L}$, RMP : resting membrane potential, RUD : reverse use dependence, T _{90, 60} : APD ₉₀ -APD ₆₀ or APD ₉₀ -triangulation, TDR : torsade de pointes , TDR : transmural dispersion of repolarization, V _m : membrane voltage, V _{max} : maximal rate of AP rise, V _s : volt per second		

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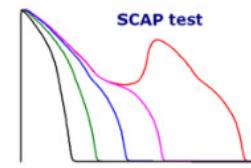
Drug	Tolterodine		
	Non selective muscarinic receptor antagonist used to treat urinary incontinence		
Raw data	<p>IC_{50s} (slope) ⁽¹⁾</p> <p>I_{CaL} : ---- μM (---) I_{Kr} : 0.0126 μM (1.0) I_{Na} : 6.310 μM (1.0) I_{Ks} : 79.43 μM (1.0)</p> <p>I_{to} : 12.59 μM (1.0) I_{NaL} : ---- μM (---) I_{K1} : ---- μM (---)</p>	<p>EFTPC_{max} ⁽¹⁾</p> <p>0.000993 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⁾		
Results	<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 and IC_{50s} $I_f = g_f(V - E_{on})$ $\frac{g_f}{g} = \frac{1}{1 + \left(\frac{D}{IC_{50f}}\right)^n}$ $n = 1$ (minimal conductance of channel) $n = 2$ (open probability of channel) $n = 3$ (inhibition of channel) $n = 4$ (50% of inhibition of a drug for channel) IC₅₀ = 50% of inhibition of a drug for channel D = drug concentration (F/TDPC for example) in nM 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{depi} (at CL of 1000 msec) RUD = AP_{Endo}-AP_{Mid}-AP_{Endo} <p>where AP_{Depi} = AP_{Depi} with - AP_{Depi} 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 AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full range</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>Human endocardial myocytes</p> <p>Summary</p>
References	<p>1. Mirams GR et al. (2014) <i>J Pharmacol Toxicol Methods</i> 20: 246-254 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</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Iseuxtra.org/hesi/science/cardiac/cipa/Project 6. Wirsniowska B et al. (2017) <i>Drug discovery today</i> 22: 10-16</p> <p>7. O'Hara T et al. (2011) <i>PLoS Comput Biol</i> 7: e1002618 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 : degeneration 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_{K1}, RMP : resting membrane potential, V_{max} : maximal rate of AP rise, V_m : minimal rate of AP decrease at EAD take-off voltage, V_s : volt per second</p>		

Safe Cardiac Action Potential Test



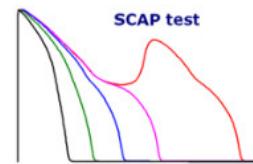
Drug	Vandetanib		
Vascular endothelial (VEGFR) or epidermal (EGFR) growth factor receptor antagonist and RET tyrosine kinase inhibitor used to treat medullary thyroid cancer			
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{to} : --- μM (---) I_{Kr} : 0.4 μM (1.0) I_{NaL} : --- μM (---) I_{Na} : --- μM (---) I_{K1} : --- μM (---) I_{Ks} : --- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.11 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⁾ : high risk of TdP (class 1) WP⁽⁶⁾ : 2/0 (TdP+/TdP-)</p>
<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾			
Results	<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 and IC_{50s} $I = g(V - E_{\text{rest}})$ (g= maximal conductance of channel) $P_{\text{open}} = \frac{1}{1 + (\frac{V - V_{\text{rest}}}{IC_{50}})^n}$ (open probability of channel) $V_{\text{rest}} = \text{reverse potential for species of ions which flows through channel}$ $IC_{50} = 50\% \text{ of inhibition of a drug for a channel}$ $\text{EFTPC} = \text{drug concentration (FPC for example)}$ 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP₉₀ mid - AP₉₀ epi (at CL of 1000 msec) RUD = APD_{90,endo}-APD_{90,epi} where APD_{90,x} = APD₉₀ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> <p>IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I_{Kr}, I_{NaL} and I_{CaL} in full slope</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>Human endocardial myocytes</p> <p>Summary</p>
References	1. Ando H et al. (2017) J Pharmacol Toxicol Meth 84:111-127 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. CIPA (2016) www.Ilextra.org/hsip/science/cardiac/cipa/Project 6. Wiśniewska 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	AP : action potential, APA : AP amplitude, APD _{90,60 or 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 _{Kr} *I _{NaL} *I _{CaL} *I _{K1} *I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T _{dp} : APD ₉₀ -APD ₄₀ 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		

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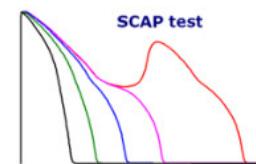
Drug	Vanoxerine Dopamine transporter antagonist used to treat cocaine addiction		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 0.0162 \mu M (0.63)$ $I_{Kr} : 0.0093 \mu M (1.11)$ $I_{Na} : 0.0346 \mu M (0.97)$ $I_K : 2.9 \mu M (1.0)$	$I_{to} : 2.0 \mu M (1.0)$ $I_{NaL} : 0.0852 \mu M (1.62)$ $I_{K1} : 98.124 \mu M (1.0)$ $0.00831 \mu M$	Redfern ⁽²⁾ : not reported Kramer ⁽³⁾ : not reported CredibleMeds ⁽⁴⁾ : not reported CIPA ⁽⁵⁾ : not reported WP ⁽⁶⁾ : not reported
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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 <p>Effect of drugs on AP⁽⁸⁾:</p> $I_j = g_j O(V - E_{j,rest})$ $\theta_j = \theta_{control} \left[1 + \left(\frac{\theta}{IC_{50j}} \right)^n \right]^{-1}$ <p>where: O = maximum open probability of channel V = voltage membrane $E_{j,rest}$ = reversal potential for species of ions which flows through channel g_j = maximum drug-free maximum conductance of channel IC_{50j} = 50% of inhibition of a drug for channel θ = drug concentration (SF TPC for example) n = Hill slope</p>	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, EAD} - APD_{90, UD}$ where $APD_{90, P} = APD_{90, P}$ with - $APD_{90, P}$ without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFKr / ((AFNal + AFCal) / 2)) * 100$ <p>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 repolarisation</p> <p>Human midmyocardial myocytes</p> <p>Reverse use dependence on midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Obejero-Paz C et al. (2016) <i>Nature Sci. Rep.</i> 5: 17623 Redfern W et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Woooley RL (2015) www.CredibleMeds.org CIPA (2016) www.Ilextra.org/hest/science/cardiac/cipa/ Mirams GR et al. (2011) <i>Cardiovasc. Res.</i> 91: 53-61 Winiarska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hara T et al. (2011) <i>PLoS Comput. Biol.</i> 7: e10020618 Christophe B & Crumb WJ (2019) <i>J Pharmacol Toxicol Methods</i> 96: 15-26 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $APD_{90, 40\% to 90\%}$: 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, IC_{50} : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $i_{CaL} + i_{Kr} + i_{NaL} + i_{Na} + i_K$, RMP : resting membrane potential, RUD : reverse use dependence, T_{dP} : $APD_{90} - APD_{40}$ or APD_{90} ("triangulation"), TDR : torsade de pointes, TDR : transmural dispersion of repolarization, V_{max} : 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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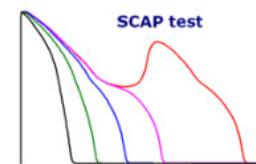
Drug	Vardenafil		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 15.849 \mu M (1.0)$ $I_{to} : 79.433 \mu M (1.0)$ $I_{Kr} : 31.623 \mu M (1.0)$ $I_{NaL} : ---- \mu M (---)$ $I_{Na} : 2511.9 \mu M (1.0)$ $I_{K1} : ---- \mu M (---)$ $I_{Ks} : 630.96 \mu M (1.0)$		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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 and IC_{50s} $I_f = g_f(V - E_{f,0})$ $\frac{g_f}{g_m} = \frac{1}{1 + \left(\frac{[D]}{IC_{50f}}\right)^n}$ <p>where g_m = maximal conductance of channel $E_f,0$ = reversal potential for species of ions which flows through channel V_m = membrane potential n = reversal probability of channel D = drug concentration (e.g. 100-fold EFTPC for example) IC_{50f} = 50% of inhibition of a drug for channel f</p> <p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, mid} - APD_{90, epi}$ (at CL of 1000 msec) $RUD = APD_{90, mid} - APD_{90, endo}$ where $APD_{90,P_i} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $IC \text{ index} = (AFK_r / (AFK_r + AFNaL + AFCaL)) * 100$ <p>where AFK_r, $AFNaL$ and $AFCaL$ = active fraction (%) of the I_{Ks}, I_{NaL} and I_{CaL} in full scope</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> <p>Summary</p> <p>Vardenafil x-fold EFTPC_{max} vs. IC_{50s}</p> <p>References</p> <ol style="list-style-type: none"> Mirams GR et al. (2014) <i>J Pharmacol. Toxicol. Methods</i> 70: 246-254 Redfern WS et al. (2003) <i>Cardiovasc. Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. Rep.</i> 3: 2100 Woolesley RL (2015) www.CredibleMeds.org GPA (2016) www.Isiextra.org/hesi/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: e1002061.8 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 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, $APD_{90, 40, 60, 90}$: 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, IC₅₀ : 50% inhibition concentration, mid : midmyocardial myocyte, msec : millisecond, mV : millivolt, qNet : integration sum of $I_{CaL} + I_{NaL} + I_{Ks} + I_{K1} + I_{Kr}$, RMP : resting membrane potential, RUD : reverse use dependence, $T_{AP, 90}$: $APD_{90} - APD_{40}$ 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</p>	

Safe Cardiac Action Potential Test



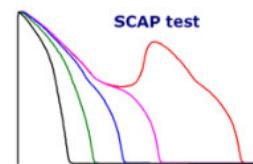
Drug	Verapamil		
	Voltage-gated L-type Ca ⁺⁺ channel (Ca _v 1.2) blocker used to treat angina, arrhythmia and hypertension		
Raw data	IC_{50s} (slope)⁽¹⁾ I _{CaL} : 0.20 μM (0.80) I _{Kr} : 0.25 μM (0.89) I _{Na} : 32.5 μM (1.33) I _{Ks} : --- μM (---)	EFTPC_{max}⁽¹⁾ 0.088 μM	TdP risk Redfern ⁽²⁾ : no published report of TdP (class 5) Kramer ⁽³⁾ : non-torsadogenic (class 1) CredibleMeds ⁽⁴⁾ : not classified with TdP risk (class 4) CiPA ⁽⁵⁾ : low or no risk of TdP (class 3) WP ⁽⁶⁾ : 0/13 (TdP+/TdP-)
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	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 ⁺⁺] _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} $I_j = g_j(V - E_{j,0})^n \left[1 + \left(\frac{g_j}{IC_{50s}} \right)^n \right]^{-1}$ g _j = maximal conductance of channel V = open probability of channel E _{j,0} = reversal potential for species of ions which flows through channel IC _{50s} = 50% of inhibition of a drug for channel x = drug concentration (EFTPC _{max} for example) in full scale	TDR and RUD estimation: • TDR = APD _{mid} - APD _{epi} (at CL of 1000 msec) • RUD = APD _{endo} -APD _{epi} where APD _{endo} = APD _{endo} without compound at CL x
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	IC index calculation⁽⁹⁾: IC index = (AFKr/(AFNaL+AFCaL)/2)*100 where AFKr, AFNaL and AFGaL = active fraction (%) of the I _{Kr} , I _{NaL} and I _{CaL} in full scale
	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. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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.Isiextra.org/hesi/science/cardiac/cipa/ Project 6. Wirsniowska 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, APDP : APD prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneracy 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 _{NaL} +I _{Ks} , RMP : resting membrane potential, RUD : reverse use dependence, T ₄₀₋₉₀ : APD ₄₀ -APD ₉₀ or APD ₀ ("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



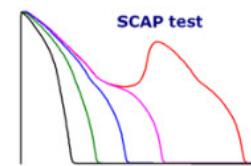
Drug	Vernakalant		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 84.0 \mu M (1.0)$ $I_{Kr} : 20.0 \mu M (1.0)$ $I_{Na} : 90.0 \mu M (1.0)$ $I_K : \text{--- } \mu M (\text{---})$ $I_{Na} : \text{--- } \mu M (\text{---})$ $I_K : \text{--- } \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	<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} $I_f = g_f(V - E_{f,0})$ $E_{f,0}$: reversal potential for species of ions which flows through channel g_f: maximal conductance of channel E_m: membrane potential at time t IC_{50s}: 50% of inhibition of a drug for a channel D: drug concentration (FPC for example) η: half slope 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> $TDR = APD_{90, \text{mid}} - APD_{90, \text{epi}}$ (at CL of 1000 msec) $RUD = APD_{90, \text{endo}} - APD_{90, \text{mid}}$ where $APD_{90, P_i} = APD_{90}$ with - APD_{90} without compound at CL x <p>IC index calculation⁽⁹⁾:</p> $\text{IC index} = (AFKr / ((AFNaL + AFCaL)/2)) * 100$ <p>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 repolarisation</p> <p>Human midmyocardial myocytes</p> <p>Reverse use dependence on midmyocardial myocytes</p> <p>Human endocardial myocytes</p> <p>Summary</p> <p>References</p> <ol style="list-style-type: none"> Eutarte H et al. (2019) <i>Pharmacol Res.</i> 148: 104444 Redfern WS et al. (2003) <i>Cardiovasc Res.</i> 58: 32-45 Kramer J et al. (2013) <i>Sci. rep.</i> 3: 2100 Weesley BL (2015) www.Scapttest.com GPA (2016) www.Ilextra.org/hsiv/science/cardiac/cipa/Project Widoniwska B et al. (2017) <i>Drug discovery today</i> 22: 10-16 O'Hearn T et al. (2011) <i>PLoS Comput Biol.</i> 7: e1003618 Mirams GR et al. (2011) <i>Cardiovasc Res.</i> 91: 53-61 Christophe B & Crumb WJ Jr (2019) <i>Pharmacol Toxicol Methods</i> 96: 15-26 <p>Abbreviations</p> <p>AP : action potential, APA : AP amplitude, APD_{90,xx-xx} : AP duration at 40, 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 $I_{CaL} + I_{Kr} + I_{NaL} + I_{Na} + I_K$, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₅₀ : APD₉₀-APD₉₀ or APD₉₀ : membrane voltage, V_{max} : maximal rate of AP rise, V_m : minimal rate of AP decrease at EAD take-off voltage, V/s : volt per second</p>

Safe Cardiac Action Potential Test



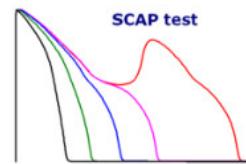
Drug	Voriconazole		
Raw data	IC_{50s} (slope) ⁽¹⁾	$EFTPC_{max}$ ⁽¹⁾	TdP risk
	$I_{CaL} : 414.2 \mu M (1.0)$ $I_{to} : \text{--- } \mu M (\text{---})$ $I_{Kr} : 490.9 \mu M (1.0)$ $I_{NaL} : \text{--- } \mu M (\text{---})$ $I_{Na} : 1550.5 \mu M (1.0)$ $I_{K1} : \text{--- } \mu M (\text{---})$ $I_K : \text{--- } \mu M (\text{---})$		
	<i>In silico</i> cardiac action potential study (ORD model) ⁽⁷⁾		
Results	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): $[Na^+]$, 140 - $[Ca^{++}]$, 1.8 - $[K^+]$, 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} $I_j = g_j O(V - E_{j0})$ $O = \frac{g_{max}}{g_{min}} \cdot \frac{1}{1 + \left(\frac{V - V_{1/2}}{IC_{50}} \right)^n}$ $V_{1/2} = \text{reversal potential for species of ions which flows through channel}$ $g_{max} = \text{maximal conductance of channel}$ $g_{min} = \text{minimal conductance of channel}$ $IC_{50} = 50\% \text{ of inhibition of a drug or channel}$ $n = \text{drug concentration (EFTPC for example)}$ $\text{--- } \text{inhalation}$	TDR and RUD estimation: • TDR = $APD_{50, \text{mid}} - APD_{50, \text{epi}}$ (at CL of 1000 msec) • RUD = $APD_{50, \text{endo}} - APD_{50, \text{mid}}$ where $APD_{50,P_i} = APD_{50, \text{endo}} \text{ with } - APD_{50, \text{endo}} \text{ without compound at CL } x$ IC index calculation⁽⁹⁾: $IC \text{ index} = (AFKr / (AFNaL + AFCaL)) * 100$ where AFKr, AFNaL and AFCaL = active fraction (%) of the I_{CaL} , I_{NaL} and I_{Kr} .
	Human epicardial myocytes 	Transmural dispersion of repolarisation 	
	Human midmyocardial myocytes 		Reverse use dependence on midmyocardial myocytes
	Human endocardial myocytes 		
Summary			
References	1. Kramer J et al. (2013) <i>Sci. rep.</i> 3 : 2100 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. GIPA (2016) www.ilsexta.org/hesi/science/cardiac/gipa/Project 6. Winiowska 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	AP : action potential, APA : AP amplitude, $APD_{50, \text{endo}}$: 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_{NaL} , I_{Kr} , I_{K1} , I_K , RMP : resting membrane potential, RUD : reverse use dependence, TdP_{40} : $APD_{50, \text{endo}} - APD_{40}$ or APD_{50} ("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	Ziprasidone		
	Dopamine D ₂ and serotonin 5-HT _{2A} receptor antagonist used to treat schizophrenia or bipolar mania		
Raw data	<p>IC_{50s} (slope)⁽¹⁾</p> <p>I_{CaL} : --- μM (---) I_{Kr} : 0.24 μM (1.0) I_{Na} : 170.0 μM (1.0) I_{Ks} : --- μM (---)</p> <p>I_{to} : --- μM (---) I_{Naf} : --- μM (---) I_{K1} : --- μM (---)</p>	<p>EFTPC_{max}⁽¹⁾</p> <p>0.0073 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⁾ : 3/1 (TdP+/TdP-)</p>
	In silico cardiac action potential study (ORD model)⁽⁷⁾		
Results	<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} $I_j = g_j(V - E_{on})^{n_j}$ (n_j = minimal conductance if channel is open probability of channel) V_m= reversal potential for species of ions which flows through channel $\delta_j = \frac{g_j}{g_{j,control}} \left[1 + \left(\frac{\delta_j}{IC_{50s}} \right)^{n_j} \right]^{-1}$ ($g_{j,control}$ = maximal conductance of channel) IC₅₀ = 50% of inhibition of a drug for a channel D = drug concentration (EF_{TPC} for example) in full range 	<p>TDR and RUD estimation:</p> <ul style="list-style-type: none"> TDR = AP_{mid} - AP_{depi} (at CL of 1000 msec) RUD = AP_{mid} - AP_{depi} at CL₀ where AP_{depi} = AP_{mid} with - AP_{mid} 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 AFGaL = active fraction (%) of the I_{Kr}, I_{CaL} 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>Ziprasidone x-fold EFTPC_{max} vs. IC_{50s}</p> <p>APD₅₀ - APD₉₀ (msec)</p>		
References	<p>1. Ando H et al. (2017) J Pharmacol Toxicol Meth 84:111-127 2. Redfern WS et al. (2003) Cardiovasc Res 58: 32-45 3. Kramer J et al. (2013) Sci. rep. 3: 2100</p> <p>4. Woosley RL (2015) www.CredibleMeds.org 5. CIPA (2016) www.Iseuxtra.org/hesi/science/cardiac/cipa/Project 6. Winiarska B et al. (2017) Drug discovery today 22: 10-16</p> <p>7. O'Hara T et al. (2011) PLoS Comput Biol. 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</p>		
Abbreviations	<p>AP : action potential, APA : AP amplitude, APD₅₀₋₉₀ : AP duration at 50 or 90 % of APA, APDP : AP prolongation, a.u. : arbitrary unit, CL : cycle length, DA : degeneration 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_{Na}+I_{K1}+I_{Ks}, RMP : resting membrane potential, RUD : reverse use dependence, T₄₀₋₆₀ : APD₅₀-APD₄₀ or APD₅₀ ("triangulation"), TDR : 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



Class 1 (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	
Bephratelide	****	****	***			○○○○				1	•••	10.6	
Chloroquine	***					○○○				1	•••	33.9	x 85
Chlorpromazine	***	***	***			○○○				1	•••	29.5	
Cilostazol	**	*	*			○○○				1	•••	55.1	
Ciprofloxacin	***					○○○				1	•••	31.6	x 61
Cisapride	***	*	*			○○○				1	•••	31.7	x 15
Citalopram	***	*	*			○○○				1	•••	33.2	
Clarithromycin	***					○○○				1	•••	31.6	x 48
Disopyramide	***	*	*			○○○				1	•••	31.4	x 48
Dofetilide	***	*	*			○○○				1	•••	32.1	x 29
Domperidone	***					○○○				1	•••	33.1	x 13
Donepezil	**	*	*			○○○				1	•••	70.3	
Dronedarone	***	**	**			○○○				1	•••	29.2	
Dropoperidol	***	*	*			○○○				1	•••	33.6	x 8
Erythromycin	***					○○○				1	•••	33.7	x 10
Flecainide	***	*	**			○○○				1	•••	29.7	x 7
Gatifloxacine	***					○○○				1	•••	32.0	x 7
Halofantrine	****	**	*			○○○				1	•••	25.8	
Haloperidol	***	*	*			○○○				1	•••	32.2	x 20
Hydrochloroquine	****	**				○○○				1	•••	35.4	x 12
Ibutilide	****	*		*		○○○				1	•••	33.7	x 0.3
Levofloxacin	***			*		○○○				1	•••	32.2	x 30
Methadone	***	*		*		○○○				1	•••	31.3	x 17
Moxifloxacin	****	****	**			○○○				1	•••	14.8	
Ondansetron	***	**				○○○				1	•••	30.6	x 14
Pentamidine	*					○○○				○	=	99.9	
Pimozide	***	*	*			○○○				○	=	45.6	
Procainamide	****	****	****		2	2	2	2	2	2	2	8.7	
Quinidine	****	**	*			○○○				1	•••	27.4	x 0.8
Sertindole	***	*	*			○○○				○	=	32.2	x 31
Sotalol	****	****	*			○○○				○	=	23.7	
Sparfloxacin	****	***	*			○○○				1	•••	18.9	
Terfenadine	***	*	*			○○○				1	•••	31.6	x 12
Terodiline	***	**	*			○○○				1	•••	26.7	x 16
Thioridazine	***	**	***			○○○				1	•••	36.9	x 2
Vandetanib	***					○○○				1	•••	34.2	x 8

§ : Crediblemeds classification of compound TdP risk

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

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{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 % (●●●)

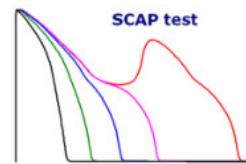
€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

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

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

² Depolarisation abnormality

Safe Cardiac Action Potential Test



Class 2 (Possible TdP risk) [§]	I _{Kr} [#]	I _{CaL} [#]	I _{Na} [#]	I _{NaL} [#]	APA ^{##}	V _{max} ^{##}	APD ₉₀ ^{##}	T ₆₀ ^{##}	TDR ^{##}	RUD ^{##}	V _{min} ^{##}	IC index ϵ	EAD ϵ	
Alfuzosin	*	*	*									99.8		
Clozapine	***	***	**			○○	●	●	●	●	●	37.6		
Dasatinib	*	*	*			2	2	2	2	2	●	91.0		
Desipramine	****	****	****			○○	●●●●	●●●●	●●●●	1	2	20.2	x 35	
Dolasetron	***	***	**			○○○○	●●●●	●●●●	●●●●	1	●●●●	32.7		
Imipramine	***	***	***			○○○○	●●●●	●●●●	●●●●	1	●●●●	33.9		
Ketanserin	***					●●●●	●●●●	●●●●	●●●●	1	●●●●	31.8	x 78	
Lapatinib	***	*	*			○○○○	●●●●	●●●●	●●●●	1	●●●●	31.9	x 55	
Lopinavir	****	****				●●●●	●●●●	●●●●	●●●●	1	●●●●	7.1		
Nicardipine	****	****	***			○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	30.4		
Nilotinib	***	*	*			●●●●	●●●●	●●●●	●●●●	1	●●●●	29.5	x 17	
Oflloxacin	**					●●●●	●●●●	●●●●	●●●●	●●●●	●●●●	62.0		
Paliperidone	***	*	*			●●●●	●●●●	●●●●	●●●●	1	●●●●	32.9	x 25	
Palonosetron	*	*	*			●●●●	●●●●	●●●●	●●●●	●●●●	●●●●	81.1		
Saquinavir	**	****	***			○○○○	●●●●	●●●●	●●●●	○	●●●●	111		
Sunitinib	***	*	*			●●●●	●●●●	●●●●	●●●●	●●●●	●●●●	48.7		
Tamoxifen	***					●●●●	●●●●	●●●●	●●●●	1	●●●●	31.7	x 94	
Tolterodine	***		*			●●●●	●●●●	●●●●	●●●●	1	●●●●	32.0	x 28	
Vardenafil	*	*	*			●●●●	●●●●	●●●●	●●●●	●●●●	●●●●	100		

§ : Crediblemeds classification of compound TdP risk

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

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{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 % (•••)

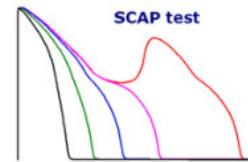
€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

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

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

² Depolarisation abnormality

Safe Cardiac Action Potential Test



Class 3 (Conditional TdP risk) [§]	I _{Kr} [#]	I _{CaL} [#]	I _{Na} [#]	I _{NaL} [#]	APA ^{##}	V _{max} [#]	APD ₉₀ ^{##}	T ₆₀ ^{##}	TDR ^{##}	RUD ^{##}	V _{min} [#]	IC index ε	EAD £
Amitriptyline	**	***	**	**	○	○○	●●	●●	●	○	●●●	128	
Diltiazem	**	****	**	*	○	○○	●●	●●	●	●	●●●	101	
Diphenhydramine	**	*	*		○	○	●●	●●	●	●	●●●	60.9	
Famotidine	*				○	○○	●●	●●	●	●	●●●	98.6	
Fluoxetine	**	**	*		○	○○	●●●	●●●	●	●	●●●	67.1	
Fluvoxamine	****	****	**	*	○	○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	21.8	
Hydroxyzine	***	*	***	*	○	○○○○	●●●●	●●●●	1	●●●●	●●●●	34.4	x 90
Ivabradine	**	*	*		○	●●	●●●●	●●●●	●	●●●●	●●●●	73.3	
Ketoconazole	***		*		○	●●●●	●●●●	●●●●	1	●●●●	●●●●	32.2	x 43
Metronidazole	****	****	****		2	2	2	2	2	2	2	12.8	
Nelfinavir	*		*		○	●●	●●●●	●●●●	●●●●	●●●●	●●●●	63.9	
Olanzapine	***		**		○○	●●●●	●●●●	●●●●	1	●●●●	●●●●	33.1	x 1.4
Paroxetine	*	*	*		○	●●●●	●●●●	●●●●	●●●●	●●●●	●●●●	65.9	
Piperacillin	****	****	****		2	2	2	2	2	2	2	4.8	
Propafenone	****	****	***	***	○	○○○○	●●●●	●●●●	○○	●●●●	●●●●	34.5	
Quetiapine	****	****			○	●●●●	●●●●	●●●●	●●●●	1	●●●●	12.8	
Quinine	***	**	**	***	○○	●●●●	●●●●	●●●●	●●●●	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	***	*	*		○	●●●●	●●●●	●●●●	●●●●	●●●●	●●●●	48.9	
Voriconazole	***	***	**		○○	●●●●	●●●●	●●●●	●●●●	●●●●	●●●●	58.1	
Ziprasidone	***		*		○○	●●●●	●●●●	●●●●	1	●●●●	●●●●	31.6	x 72

§ : Crediblemeds classification of compound TdP risk

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

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{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 % (●●●)

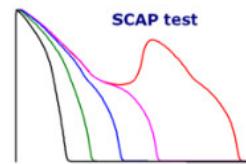
€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

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

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

² Depolarisation abnormality

Safe Cardiac Action Potential Test



Class 4 (No TdP risk) [§]	I _{Kr} [#]	I _{CaL} [#]	I _{Na} [#]	I _{NaL} [#]	APA ^{##}	V _{max} ^{##}	APD ₉₀ ^{##}	T ₆₀ ^{##}	TDR ^{##}	RUD ^{##}	V _{min} ^{##}	IC index [€]	EAD [£]
Ambrisentan	*	*	*									97.7	
Amlodipine	****	****	***									26.3	
Aspirin	*											99.2	
Atenolol	*											91.4	
Ceftriaxone	****	****	****									30.4	
Cetirizine	*											97.7	
Chlorpheniramine	*											91.5	
Darifenacin	***	*	*									36.9	
Darunavir	**		***									77.4	
Desvenfalexine	***		***									49.4	
Diazepam	*	*	*									101	
Doxorubicin	**		*									68.3	
Duloxetine	**	**	*									91.1	
Eltrombopag	***		*									33.3	x 12
Everolimus	*		*									98.7	
Fexofenadine	*											93.6	
Gefitinib	***											32.5	x 26
Lacosamide	*	****	****		2	2	2	2	2	2	2	177	
Lamivudine	**	****	***									98.8	
Lamotrigine	***	**	****									41.4	x 14
Levocetirizine	*											94.1	
Lidocaine												197	
Linezolid	****	****	***									31.8	
Loratadine	*	*	*									99.9	
Mefloquine	**											59.7	
Metoprolol	**	*	****	**								116	
Mexiletine												198	
Milrinone	*											96.4	
Mitoxantrone	*	**	*									128	
Nebivolol	**		*									77.1	
Nifedipine	*	****	*									190	
Oxybutynin	*	*										100	
Phenytoin	***	****	****		2	2	2	2	2	2	2	48.1	
Propranolol	*	*										91.2	
Raltegravir	*	**	*									103	
Ribavirin	***	****	**									43.6	
Sildenafil	*	*	*									84.4	
Silodosin	*	*	*									89.5	
Tadalafil	*											88.0	
Verapamil	****	****	*									7.7	

§ : Crediblemeds classification of compound TdP risk

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

: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{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 % (••••)

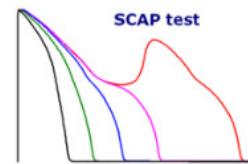
€ : IC index: Ion Channel inhibition index calculated at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{50s} ratio (x-fold-1) before the presence of an EAD (see page 4 for calculation)

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

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

² Depolarisation abnormality

Safe Cardiac Action Potential Test



Class 5 (not reported) [§]	I _{Kr} [#]	I _{CaL} [#]	I _{Na} [#]	I _{NaL} [#]	APA ^{##}	V _{max}	APD ₉₀ ^{##}	T ₆₀ ^{##}	TDR ^{##}	RUD ^{##}	V _{min} ^{##}	IC index [€]	EAD [£]
Ajmaline	***	*	**			○○	****	****	-	1	****	31.6	x 93
Almokalant	***	*	*			○○	****	****	•	1	****	31.9	x 48
Alvimopan	*					○○○	****	****	1	1	****	109	
Azimilide	***					○○○	****	****	1	1	****	31.6	x 13
Cibenzoline	***					○○○	****	****	1	1	****	36.2	x 8
Deferasirox	*	*	***			○○○	●	●	●	●	●	102	
Dobutamine ^{§§}	*	*	*			○○○	●	●	●	●	●	86.0	
Doripenem	***	****	****			○○○	●	●	●	●	●	82.6	
E-4031	***	*	*			○○○	●●●	●●●	1	1	●●●	37.6	x 7
Ebastine	*					○○○	●●●	●●●	●●●	●●●	●●●	98.1	
Encaïnide	***		**			○○○	●●●	●●●	●●●	●●●	●●●	47.0	
Etravirine	*		*			○○○	●●●	●●●	●●●	●●●	●●●	99.8	
Levosimendan	*	*	*			○○○	●●●	●●●	●●●	●●●	●●●	95.6	
Maraviroc	**		*			○○○	●●●	●●●	●●●	●●●	●●●	78.4	
Mibepradil	**	***	*			○○○	●●●	●●●	●●●	●●●	●●●	101	
Nimodipine	*	**				○○○	●●●	●●●	●●●	●●●	●●●	129	
Nisoldipine	*	*				○○○	●●●	●●●	●●●	●●●	●●●	106	
Nitrendipine	*	****	*			○○○	●●●	●●●	●●●	●●●	●●●	173	
Omecamtiv mecarb	*	*	*			○○○	●●●	●●●	●●●	●●●	●●●	84.9	
Pentobarbital	**	***	*			○○○	●●●	●●●	●●●	●●●	●●●	111	
Prenylamine	***	*	*			○○○	●●●	●●●	●●●	●●●	●●●	28.9	x 51
Primidone	**		***			○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	62.0	
Ritonavir	****	****		***		○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	65.4	
Rufinamide		****				○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	192	
Sitagliptin	**	**	*			○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	90.2	
Tedisamil	***					○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	34.0	x 5.5
Telbivudine	****	***	***	****	2	○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	27.9	
Vanoxerine	****	****	****	****	2	○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	13.3	
Vernakalant	****	****	****	****	2	○○○○	●●●●	●●●●	●●●●	●●●●	●●●●	44.8	

§ : Crediblemeds classification of compound TdP risk

§§ : Drug not reported in classes 1, 2, 3 or 4 but drug to avoid in congenital long QT

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

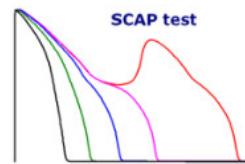
: Effect measured on the midmyocardial myocyte at an EFTPC_{max}/EC_{50s} ratio of 100-fold in absence of EAD or at the last EFTPC_{max}/EC_{50s} ratio (x-fold-1) before the presence of an EAD: -5 to 5 % (=), -5 to -20 % (-), -20 to -40 % (○○), -40 to -60 % (○○○), > -60 % (○○○○), 5 to 20 % (+), 20 to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

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

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

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

² Depolarisation abnormality



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

Drugs:

Ajmaline	6	Dolasetron	44	Lidocaine	82	Propafenone	120
Alfuzosin	7	Domperidone	45	Linezolid	83	Propranolol	121
Almokalant	8	Donepezil	46	Lopinavir	84	Quetiapine	122
Alvimopan	9	Doripenem	47	Loratadine	85	Quinidine	123
Ambrisentan	10	Doxorubicin	48	Maraviroc	86	Quinine	124
Amiodarone	11	Dronedarone	49	Mefloquine	87	Raltegravir	125
Amitriptyline	12	Droperidol	50	Methadone	88	Ranolazine	126
Amlodipine	13	Duloxetine	51	Metoprolol	89	Ribavirin	127
Aspirin	14	E-4031	52	Metronidazole	90	Risperidone	128
Astemizole	15	Ebastine	53	Mexiletine	91	Ritonavir	129
Atenolol	16	Eltrombopag	54	Mibepradil	92	Rufinamide	130
Azimilide	17	Encainide	55	Milrinone	93	Saquinavir	131
Azithromycin	18	Erythromycin	56	Mitoxantrone	94	Sertindole	132
Bepridil	19	Etravirine	57	Moxifloxacin	95	Sertraline	133
Ceftriaxone	20	Everolimus	58	Nebivolol	96	Sildenafil	134
Cetirizine	21	Famotidine	59	Nelfinavir	97	Silodosin	135
Chloroquine	22	Fexofenadine	60	Nicardipine	98	Sitagliptin	136
Chlorpheniramine	23	Flecainide	61	Nifedipine	99	Solifenacin	137
Chlorpromazine	24	Fluoxetine	62	Nilotinib	100	Sotalol	138
Cibenzoline	25	Fluvoxamine	63	Nimodipine	101	Sparfloxacin	139
Cilostazol	26	Gatifloxacin	64	Nisoldipine	102	Sunitinib	140
Ciprofloxacin	27	Geftinib	65	Nitrendipine	103	Tadalafil	141
Cisapride	28	Halofantrine	66	Ofloxacin	104	Tamoxifen	142
Citalopram	29	Haloperidol	67	Olanzapine	105	Tedisamil	143
Clarithromycin	30	Hydroxychloroquine	68	Omecamtiv mecarbil	106	Telbuvidine	144
Clozapine	31	Hydroxyzine	69	Ondansetron	107	Terfenadine	145
Darifenacin	32	Ibutilide	70	Oxybutynin	108	Terodiline	146
Darunavir	33	Imipramine	71	Paliperidone	109	Thioridazine	147
Dasatinib	34	Ivabradine	72	Palonosetron	110	Tolterodine	148
Deferasirox	35	Ketanserin	73	Paroxetine	111	Vandetanib	149
Desipramine	36	Ketoconazole	74	Pentamidine	112	Vanoxerine	150
Desvenlafaxine	37	Lacosamide	75	Pentobarbital	113	Vardenafil	151
Diazepam	38	Lamivudine	76	Phenytoin	114	Verapamil	152
Diltiazem	39	Lamotrigine	77	Pimozone	115	Vernakalant	153
Diphenylhydramine	40	Lapatinib	78	Piperacillin	116	Voriconazole	154
Disopyramide	41	Levocetirizine	79	Prenylamine	117	Ziprasidone	155
Dobutamine	42	Levofloxacin	80	Primidone	118		
Dofetilide	43	Levosimendan	81	Procainamide	119		

Summary tables:

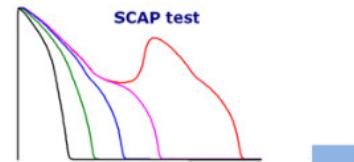
Compounds with known TdP risk (Crediblemeds classification: Class 1), page 156

Compounds with possible TdP risk (Crediblemeds classification: Class 2), page 157

Compounds with conditional TdP risk (Crediblemeds classification: Class 3), page 158

Compounds reviewed by Crediblemeds but no classified in class 1, 2 or 3 (Crediblemeds classification: Class 4), page 159

Compounds not reported by Crediblemeds classification, page 160



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.

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The implementation of this database is still in progress. 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. (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