Safety Pharmacology
Cardiovascular hERG Liability

INTRODUCTION & BACKGROUND
Evaluation of the drug development of a molecule with a <1uM hERG IC50

CHALLENGE
Many groups have arbitrary cutoffs of IC50 < 5uM resulting the potential loss of developable drugs. This molecule was a single candidate available from a program, no other candidates were available.
Single assays have low sensitivity and specificity risk assessment. Preponderance of evidence provides better guidance when molecule selections are limited.

APPROACH & EXECUTION
The approach was to use the preponderance of evidence to provide a more focused assessment of risk. This included assays of ex vivo tissue (Langendorff heart preparation) and in vivo large animal (telemeterized dogs) in addition to assessment of the free fraction of molecule in plasma and the EC50 for efficacy of the target action.

RESULTS
No other assays showed risk for the hERG interaction to produce arrhythmia. The molecule continued development to Phase I.

IMPACT
The impact of this approach was to continue a molecule to drug development and potential market rather than use a single assay and/or arbitrary acceptance criteria to determine the go-no-go selection of a molecule.