Cardiac safety evaluation – early phase studies- A regulator's view

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AHHPI Meeting; Oct 2015, London.

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Current paradigm

E-14 and Thorough QT study; Achievements;

- E-14 (& S7B)
  - provided a framework for evaluation of QT liability
  - Defined expectations (for sponsors)
  - reduced accidental discovery of QT liability of drugs

- Thorough QT study
  - Defined a set of parameters for identifying a risk
  - A decision making tool for --regulators and sponsors
  - Perhaps, they standardized the interpretation and methods of testing

ICH E14/S7B have resulted in no drugs with unrecognized risk being approved or removed from the market

However, (CP-2)

>400 TQT studies
~ 10 years of data
Millions of $$$ / £££/ €€€s

- at a significant cost
- Negative impact on drug development

  Premature discontinuation due to hERG or QT "signal"

  (Inaccurate) perception of risk leading to drug discontinuation

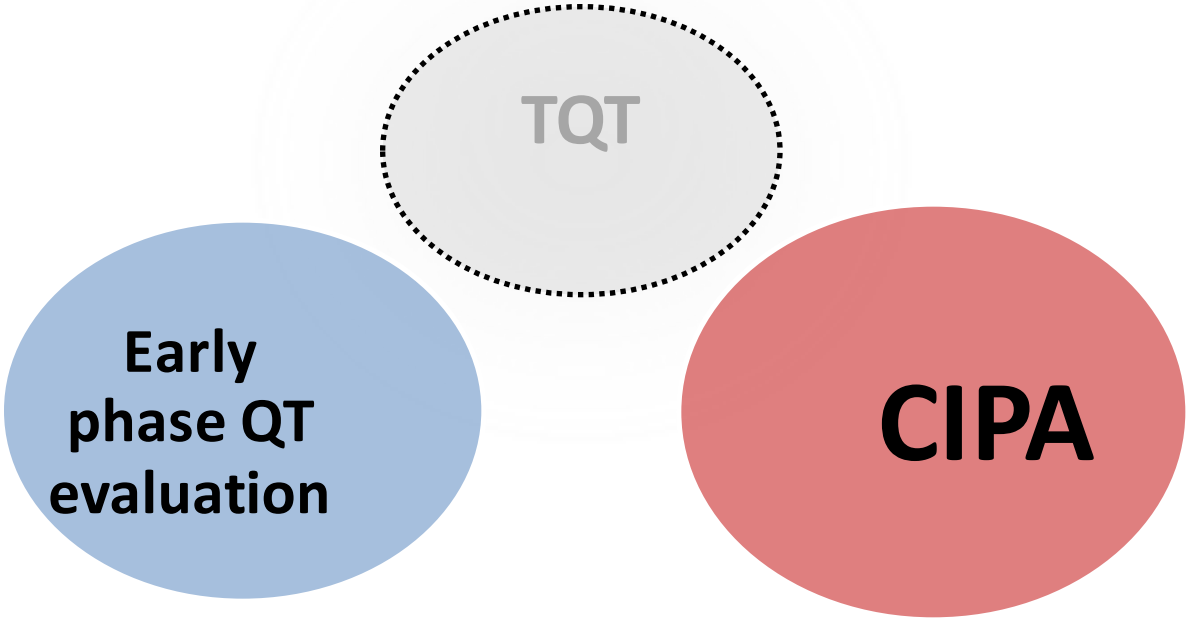
  Estimates of up to 60%

  Burdensome- TQT cost ($ x10^5) and time in development

- Many potentially good compounds not evaluated in humans due to a hERG effect.

Is the Current paradigm sustainable??

Two possible alternatives !!



Any new paradigm is expected to

- Be standardized and validated.
- Tackle the limits (and pitfalls) and inconsistency
- Address accuracy & predict torsade (TdP) risk

Early QT assessment; components

Am Heart J, 2014;168:262-72.

Opportunity exists, ...

- Based on C-R relationship evaluation
- Need a range of doses and DDI data
- Modelling and simulation
- Need defined sampling and statistical methods
  - assay sensitivity
- Needs a pre-clinical background
  - Standardisation of techniques

How effective is an early study? Can it be done?

Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase

B Darpo[1,2*], C Benson[3†], C Dota[4*], G Ferber[5], C Garnett[6*], CL Green[7], V Jarugula[8†], L Johannesen[9],

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 97 NUMBER 4 | APRIL 2015

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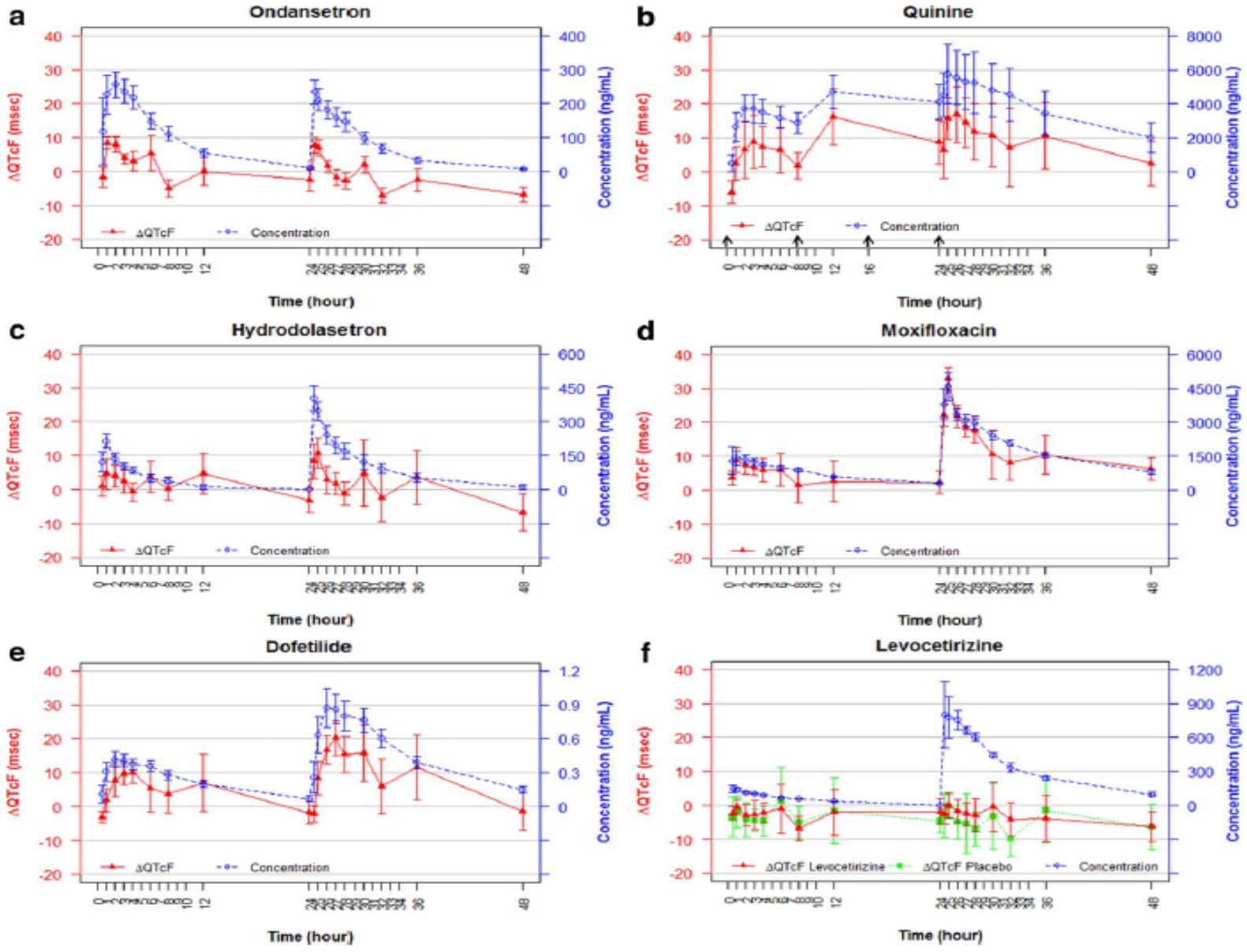
Ondansetron Quinine Dolasetron Moxifloxacin Dofetilide	Levocetirizine


a
Ondansetron
ΔQTcF (msec)
Concentration (ng/mL)
ΔQTcF
Concentration
Time (hour)
b
Quinine
ΔQTcF (msec)
Concentration (ng/mL)
ΔQTcF
Concentration
Time (hour)
c
Hydrodolasetron
ΔQTcF (msec)
Concentration (ng/mL)
ΔQTcF
Concentration
Time (hour)
d
Moxifloxacin
ΔQTcF (msec)
Concentration (ng/mL)
ΔQTcF
Concentration
Time (hour)
e
Dofetilide
ΔQTcF (msec)
Concentration (ng/mL)
ΔQTcF
Concentration
Time (hour)
f
Levocetirizine
ΔQTcF (msec)
Concentration (ng/mL)
ΔQTcF Levocetirizine
ΔQTcF Placebo
Concentration
Time (hour)

How Acceptable is it! ??

Depends---

On What!
Has anyone else done it?
What type of Molecules
How do I go about it..

Address Potential limitations

- Sample size is often small
- Consistent experimental & clinical conditions needed.
- Limitations of CEM
  - Modelling- may become complex
  - Linearity and underprediction of effect size
- Assay sensitivity- use of active control?
- information on metabolites/ hysteresis

Examples...

PII063

Concentration-QTc Modeling in First-in-Human Study to Assess the Effect of the Investigational Drug GS-4997 on Cardiac Repolarization

Cara H Nelson, Liang Fang, FuChih Cheng, Lu Wang, Mischa Hepner, Joseph Lin, and Srini Ramanathan

Gilead Sciences Inc., Foster City CA, USA

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Tel: (650) 574-3000

Introduction

- **Proarrhythmic Risk Assessment**
  - QT interval prolongation may lead to development of torsade de pointes
  - ICH E14 Guidance' established recommended guidelines for assessing QT prolongation risk that are generally applicable to almost all new drugs
  - Current ICH E14 Guidance recommends a thorough QT (TQT study) to asses the effect of the drug on QT interval
  - Concentration-QT analysis of ECG data collected in early phase studies is an alternative approach to assess proarrhythmic risk in lieu of a TQT study
- **GS-4997**
  - Selective and potent, small-molecule, ASK1 inhibitor
  - Metabolite A is an inactive metabolite of GS-4997
  - Currently being evaluated in two dose-ranging Phase 2 studies in subjects with diabetic kidney disease and pulmonary arterial hypertension

Objective

- To evaluate the proarrhythmic risk of the investigational drug GS-4997 and its metabolite (Metabolite A) using concentration-QT analysis using intensive ECG collected in the first-in-human study to obtain a waiver from a dedicated TQT study

Study Design

- Phase 1, single center, double-blinded, single- and multiple-ascending dose (SAD and MAD) study in healthy subjects
- GS-4997 Doses: 1, 3, 10, 30, and 100 mg
- SAD cohorts: 6 active, 2 placebo per dose level
- MAD cohorts: 8 active, 2 placebo per dose level
- Subjects in MAD cohorts dosed once daily for 14 days

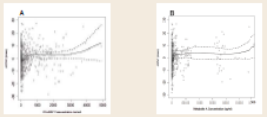
Acquisition and Analysis of ECG Data

- **ECG Collection:**
  - Triplicate ECGs digitally collected at the following time points:
    - Days -1, 1, and 7 (MAD portion only); approximately 1, 3, 6, and 12 hours post dose
    - Plasma PK samples collected at time points corresponding to ECG collection; concentrations of GS-4997 and Metabolite A determined by validated LC/MS/MS assay
  - ECG data extracted from a single lead were read centrally and manually by licensed cardiologists blinded as to time point and treatment to derive heart rate corrected QT intervals corrected using Fridericia's method (QTcF)
- **ECG data quality:**
  - Variability of triplicate reads of QTcF interval estimated with a mixed model; triplicate QTcF values as dependent variables

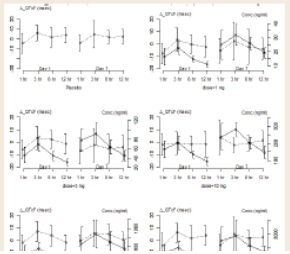
Model Development

- Linearity and hysteresis effect assessed to determine appropriateness of linear mixed effects model
- No indication of a nonlinear relationship between ΔQTcF and GS-4997 or Metabolite A plasma concentrations
- No evidence of a hysteresis effect between ΔQTcF and GS-4997 and Metabolite A plasma concentrations
- Linear mixed effects model was deemed appropriate for both GS-4997 and Metabolite A

Observed ΔQTcF versus GS-4997 concentrations (A) and Metabolite A concentrations (B) with LOESS trend line (solid line) and 95% confidence interval (dashed lines)



Observed ΔQTcF and GS-4997 plasma concentrations by time point for each GS-4997 dose level on Day 1 and Day 7



- Six models explored; final models selected based on lowest AIC
- GS-4997 and Metabolite A modeled separately
- Final model used compound symmetry covariance structure with covariates: treatment group, postdose timepoint, sex, baseline QTcF time-matched to ΔQTcF, GS-4997 or Metabolite A concentration
- Predicted time-matched, baseline-adjusted, placebo-corrected QTcF (ΔΔQTcF) estimated by the linear function:

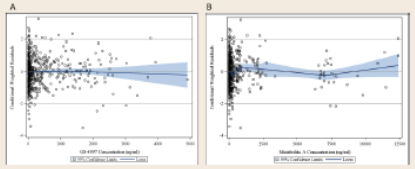
$$\hat{\delta}1^{*}\text{concentration} + \hat{\delta}2^{*}\text{TRTC}$$

- $\hat{\delta}1$ and $\hat{\delta}2$ are coefficient estimates from final models; TRTC (1=active, 0=placebo) is treatment group factor used to correct for placebo
- Two-sided 90% CIs of predicted ΔΔQTcF at the observed geometric mean $C_{ss,g}$ at each dose level were obtained using bootstrap procedure

Model Evaluation

- **Model Evaluation**
  - GS-4997 and Metabolite A concentration versus weighted residuals (WRES) and conditional weighted residuals (CWRES) plotted with LOESS trend line
  - QQ-plots, histograms of residuals, plots of residuals versus covariates, and plots of predicted versus observed ΔQTcF in the C-QTc models were generated

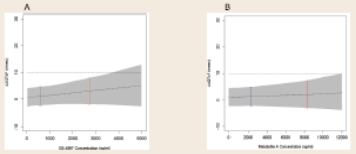
CWRES plots for the C-QTc models of GS-4997 (A) and Metabolite A (B)



- Majority of CWRES were within 2 standard deviations of mean CWRES (ie, zero) for both GS-4997 and Metabolite A
  - Similar findings for WRES plots

Model Results

Model predicted ΔΔQTcF versus GS-4997 concentrations (A) and Metabolite A concentrations (B). Blue and red lines represent 90% CIs of predicted ΔΔQTcF at therapeutic and supratherapeutic concentrations, respectively



- Slope estimates (90% CIs) for GS-4997 and Metabolite A plasma concentrations versus predicted baseline-adjusted, placebo corrected QTcF were 0.0009 (-0.0007, 0.0024) msec per ng/mL and 0.0002 (-0.0004, 0.0007) msec per ng/mL, respectively.

Predicted Values of ΔΔQTcF and 2-Sided 90% CIs at the Projected or Observed $C_{ss,g}$ of GS-4997 and Metabolite A Following Once Daily Dosing of Therapeutic (18 mg) and Supratherapeutic (100 mg) Doses of GS-4997

Analyte	Dose of GS-4997	Concentration (ng/ml)	Predicted ΔΔQTcF (msec)	90% Confidence Interval (msec)
GS-4997	18 mg, once daily (Therapeutic)	575[a]	1.14	(-2.22, 4.63)
	100 mg, once daily (Supratherapeutic)	2717[b]	3.05	(-1.85, 7.92)
Metabolite A	18 mg, once daily (Therapeutic)	2300[a]	1.36	(-2.14, 4.94)
	100 mg, once daily (Supratherapeutic)	8308[b]	2.37	(-3.01, 7.36)

a Projected mean steady-state $C_{ss,g}$ following once daily oral dosing of 18 mg GS-4997
b Observed geometric mean $C_{ss,g}$ following once daily oral dosing of 100 mg GS-4997 for 7 days

- Upper limits of 90% CIs of ΔΔQTcF at therapeutic and supratherapeutic concentrations were below 10 msec for GS-4997 and Metabolite A
- Both GS-4997 and Metabolite A met the pre-specified 'QT-negative' criteria

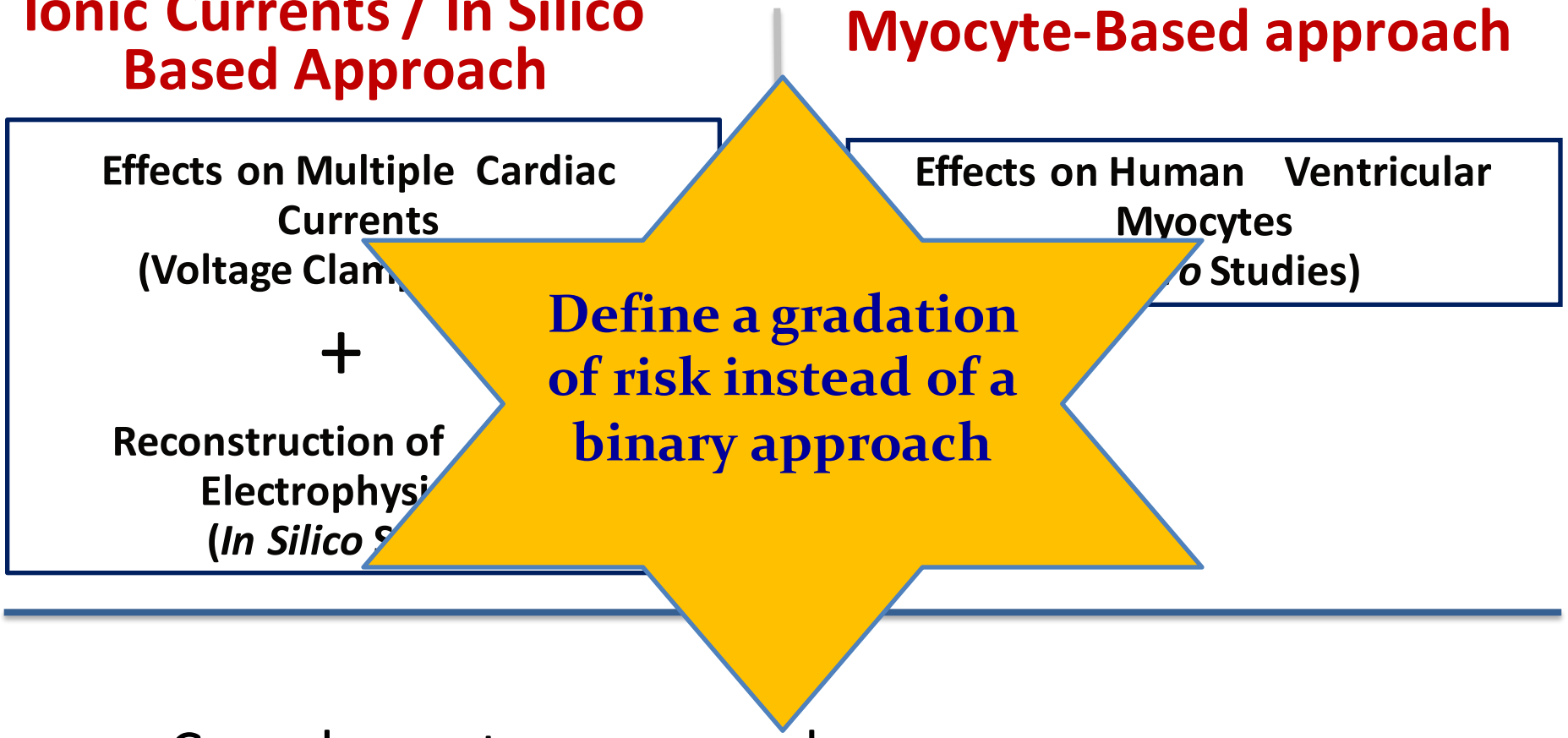
Abstract :

The effects of GS-4997 (ASK1 inhibitor) ….This ……was deemed adequate to assess the proarrhythmic risk of GS-4997/metabolite by the FDA and EMA ……..

Some relevant questions

- Are sufficient exposures achieved in SAD/MAD studies
- Period and sequence effects in ascending dose studies
- Clear exposition of PK of parent + metabolites..
- Modelling– could be crucial(operator dependency needs to be addressed.
- Study designs- XO, parallel or partial XO
- Would CE analysis in Early phase
  - Provide confidence in Risk evaluation?
  - Appropriately guide B:R evaluation? and labelling.

CiPA: Integrated, Mechanism-based Proarrhythmia Assessment



- Complementary approaches
- Not designed to reproduce arrhythmia

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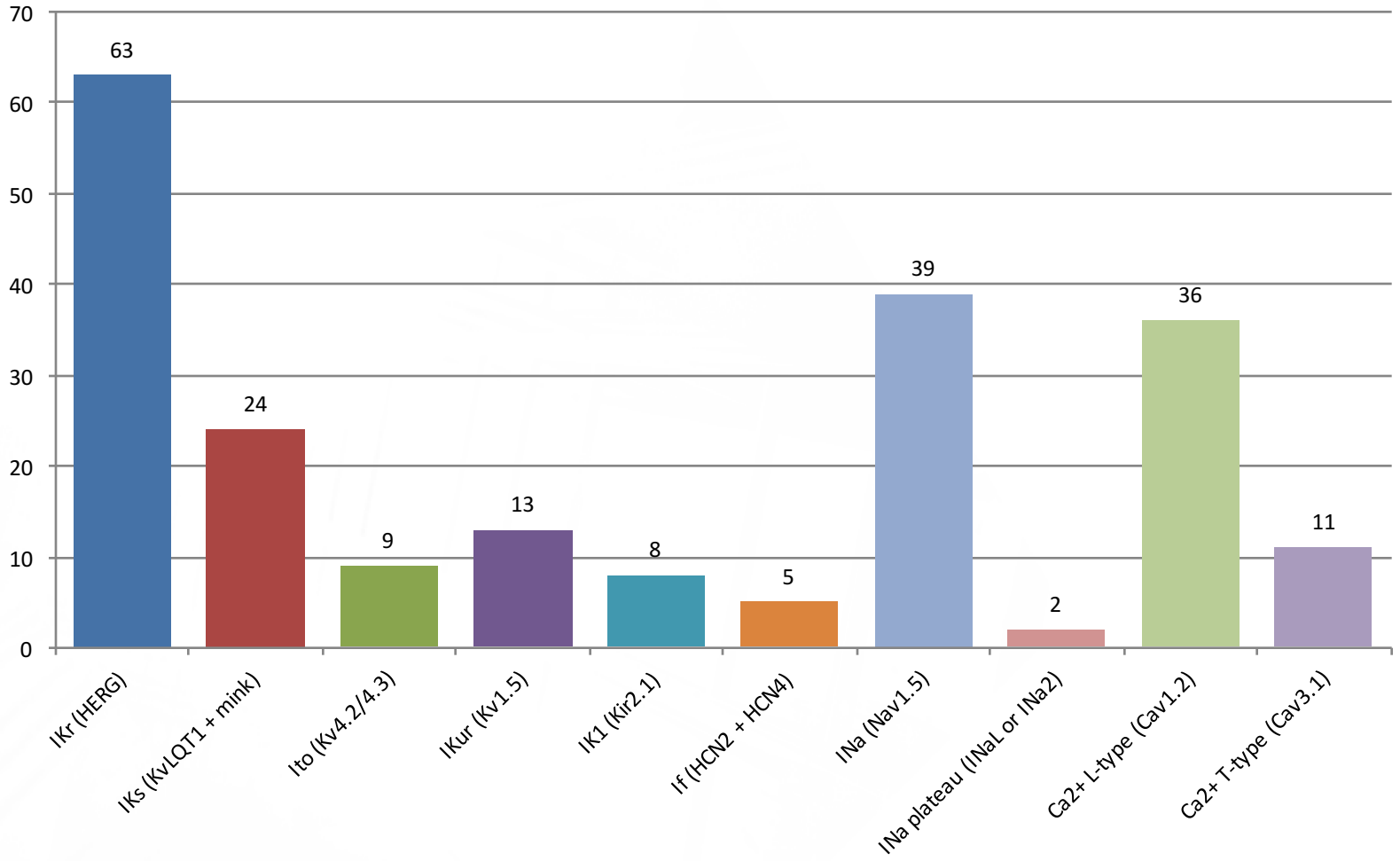
Pre-CiPA State of Ion Channel Testing
Cardiac Ion Channels Screened for Safety (65)



Data from HESI / CiPA project

Comprehensive *In Vitro* ProArrhythmia Assay (*CiPA*)

What It Is:

Proposal to evaluate proarrhythmic risk based on mechanistic electrophysiologic understanding of proarrhythmia with two primary components

I. *In vitro* drug effects, multiple cardiac channels
   + *In silico* reconstruction of electrical effects

II. Confirmation using human stem-cell derived cardiomyocytes

It is Not: *an a*pproach that negates well-controlled *in vivo* ECG assessment in preclinical studies

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Slide From CiPA Group

CiPA: Expectations

What It Will Do:

- Standardize *in vitro* & *in silico* assays; establish best practices
- Prevent early attrition due to hERG liabilities
- Provide a more complete assessment of proarrhythmic risk
- May improve efficiency
- Potential to re-label drugs with risk warnings

What It Will Not Do:

Replace phase 1 ECG safety studies or in-vivo studies with fully integrated systems

Slide From CiPA group- modified

How do we go forward?

Discussions at ICH

1. Early phase studies/ CRR

1. Q and A on Concentration Response analysis
2. Setting up parameters as applicable to CCR in early phase studies

2. CiPA initiatives and outcomes
    1. Setting parameters
    2. Agreeing to standards.

Once established, we expect the discussion to focus on revision/ update of S7B and E-14.

Summary;

- At this point in time, for some cases, TQT study might still be the most cost effective option!
- CiPA in not replacement for Early QT evaluation
- Early phase studies are still binary (yes or no) but need non-clinical background to be most useful.
- In either case the approaches would be complementary.
- The success is dependent on what each of the sponsors will incorporate.

Thank you for Listening.