Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments




What will it take to convince a regulator?

Colette Strnadova, Ph.D.
Senior Scientific Advisor
TPD, HPFB, Health Canada

Canada

Disclaimer

- **The views expressed in the presentation are those of the speaker and not necessarily those of Health Canada.**

ICH S7B Core Battery

- ***in vitro*** **I_{Kr} assay (usually hERG assay)**
- ***in vivo*** **QT assay**

hERG Assay

- **Useful for hazard identification with many drugs <u>but</u>**
  - ***in vitro* potency estimates are difficult to interpret (target vs. actual concentrations, comparison with free or total plasma concentrations?, IC20/IC50?)**
  - **potential effects of metabolites will not be detected unless these are tested separately**
  - **hERG is NOT the only possible mechanism underlying QTc prolongation**
  - **the QTc interval is NOT the only ECG parameter of regulatory interest**

In Vivo ECG Assay

- **Persisting concerns regarding false negative results in *in vivo* ECG assays:**
  - **small sample size**
  - **usually single dose only**
  - **low/undefined sensitivity**
  - **high variability**
  - **lack of concurrent positive control**
  - **non-standardised assay conditions**
  - **pharmacokinetic data often lacking**
  - **inter-species differences**

SAD/MAD Clinical Studies

- **Regulatory experience with ECG data from SAD/MAD studies is limited and the following concerns exist:**
  - **small cohort size/low statistical power/high variability**
  - **# subjects on drug & placebo usually not balanced**
  - **doses tested are sometimes lower than eventual therapeutic dose**
  - **inconsistent ECG assessment methodology**
  - **collection of serial ECGs over dosing interval is not routine**
  - **baseline ECG data not routinely time-matched to on treatment ECGs**
  - **lack of concurrent positive control**

Propoxyphene MAD Study

- sequential MAD
- randomised, double-blind, parallel
- N=18 healthy subjects
- 3 treatments: placebo, propoxyphene 600 mg, propoxyphene 900 mg
- N=6 on propoxyphene & N=2 on placebo/cohort
- 11 days of treatment
- continuous 12 lead ECG recordings on days -1, 1, 4, 11
- triplicate ECGs at each nominal time point
- cardiologist over-read

http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234330.pdf

Propoxyphene MAD Study

PK and ECG Sampling Schedule on Days -1, 1, 4, and 11.

Study Day	-1	1	4	11
12-Lead ECGs	Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12	Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12	Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12	Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12
PK Samples for propoxyphene and norpropoxyphene	None collected	Days 1, 4, and 11 at Hour 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12.	Days 1, 4, and 11 at Hour 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12.	Days 1, 4, and 11 at Hour 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 9, 12, 24, 36, 48, 60.

Propoxyphene: QTcF

The Point Estimates and 90% Confidence Interval Corresponding to the Largest Mean ΔΔQTcF Interval for Propoxyphene (600 mg, 600 mg repeated, and 900 mg)

Treatment	Outcome	Time (hour)	Mean and 90% CI (ms)
Dose Level 1: 600 mg	ΔΔQTcF	7	29.8 (11.7, 47.9)
Dose Level 1R: 600 mg	ΔΔQTcF	2	18.8 (-0.2, 37.9)
Dose Level 2: 900 mg	ΔΔQTcF	2	38.2 (19.0, 57.4)

Propoxyphene: PR/QRS

The Point Estimates and 90% Confidence Interval Corresponding to the largest ΔΔPR, and ΔΔQRS Interval for Propoxyphene (600 mg, 600 mg repeated, and 900 mg)

Treatment	Outcome	Time (hour)	Mean and 90% CI (ms)
Dose Level 1: 600 mg	ΔΔPR	4	28.3(4.3, 52.3)
Dose Level 1R: 600 mg	ΔΔPR	2	17.7 (-4.2, 39.6)
Dose Level 2: 900 mg	ΔΔPR	2	25.1 (4.4, 45.7)
Dose Level 1: 600 mg	ΔΔQRS	7	15.4 (5.7, 25.0)
Dose Level 1R: 600 mg	ΔΔQRS	2	7.2 (-1.0, 15.3)
Dose Level 2: 900 mg	ΔΔQRS	2	17.9 (8.9, 27.0)

Norpropoxyphene: PK/PD

Exposure-response Analysis of Norpropoxyphene Associated ΔΔQTcF Prolongation

Parameter	Estimate	P-value	IIV
Model 1: ΔΔQTcF = Intercept + Slope * Norpropoxyphene Concentration			
Intercept (ms)	-5.02 (-6.82; -3.22)	0.0001	2.38
Slope (ms per ng/mL)	0.0255 (0.0194;	<.0001	13.39
Residual Variability (ms)	10.62		

PK/PD Analyses

- **Useful for follow-up analysis of QTc data for many drugs, but**
  - **positive PK/PD relationships have not been demonstrated for all QTc-prolonging drugs**
    - **e.g., fingolimod, telaprevir, voriconazole, eribulin, degarelix, sorafenib**
  - **usefulness depends on underlying mechanism and broad range of concentrations**
  - **PK/PD modelling methodology is not standardised**
  - **alternative models can yield different or discordant results**
  - **most regulatory experience with PK/QTc analyses is based on TES or Phase 2/3, not SAD/MAD**

Future Directions: Safety Pharmacology

- **Supplement hERG assay with additional assays for other cardiac ion channels?**
- **CSRC-ILSI HESI-ICH S7B collaboration to address strategies to optimise the *in vivo* ECG assay?**

Future Directions: SAD/MAD

- **Submission of SAD/MAD ECG data with central tendency and PK/PD analysis in NDS/NDA as supplement to thorough ECG study to determine concordance?**
- **Publication of ECG results from SAD/MAD studies in journal articles or reports on regulatory internet sites?**
- **Contribution of SAD/MAD ECG data to a shared database (CSRC, ILSI-HESI)?**
- **CSRC White Paper to encourage best practices for ECG assessment in SAD/MAD studies?**