A PK/PD meta-analysis to assess inter-study variability and translational value of preclinical exposure-QTc relationships

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Background

- Drug-induced QTc-interval prolongation (ΔQTc) is systematically assessed in preclinical cardiovascular (CV) safety studies as a surrogate for pro-arrhythmic risk in human.
- Such studies in conscious telemetered dogs (4-8 animals) can be based on varying designs (e.g. dose range, number of doses, route of administration, study duration, PK/PD sampling in same animals or a satellite group, no PK assessment).

Methods & Results

- The work-flow of this meta-analysis is shown below, followed by an illustration of main results.
- For moxifloxacin, inter-study variability (ISV) was additionally assessed in a hierarchical random-effects model1.

![Flowchart of meta-analysis](Image)

**Consistency of ΔQTc-predictions at upper therapeutic exposure (Fig.1):**

- The 95%CI of 13/14 (93%) study-predictions comprised the meta-prediction, despite varying structural models.
- Inter-study variability (ISV) of ΔQTc-predictions was 30% (range: 1-69%).

**Model-based assessment of ISV (moxifloxacin):**

- Including an ISV-level in the meta-model decreased between-subject variability (BSV) in PD by 10-26%, most on the hill coefficient.
- Estimated ISV (24-39%, RSE=100%) did not exceed BSV (28-37%).

**Pharmacodynamic characterization (Fig.2):**

The preclinical PDs of all 3 drugs was best characterized by Emax-meta-models (ΔQTcmax = 50-55ms or 20-22% from baseline).

**Preclinical ΔQTc meta-predictions (therapeutic range):**

- Moxifloxacin: 4–12 ms (2.9–5.6 μM, EC50: 11.6 μM)
- Dofetilide: 4–18 ms (0.4–2 nM, EC50: 4.2 nM)
- Sotalol: 14-19 ms (3.7-11 μM, EC50: 10.1 μM)

**Translation: clinical ΔQTc predictions**

- Expressed as %change from baseline, clinical & pre-clinical ΔQTc effects we overlapping

**Summary & Conclusions**

This first quantitative assessment suggests that consistent ΔQTc predictions can be obtained from highly varying preclinical studies by systematic PK/PD analysis → suitable for translational purpose

A 10% ΔQTc in the dog seems to correspond to an almost half-maximal effect (and ≥35ms ΔQTc in human) → 10% effect2 is an unsatisfying study sensitivity target → PK/PD analysis can improve the detection of small preclinical ΔQTc3