Application for a Marketing Authorisation:
Requirements and Criteria for the Assessment of
QT Prolonging Potential

Dr. med. Clemens Mittmann

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Bonn
Application for a Marketing Authorisation: Requirements and Criteria for the Assessment of QT Prolonging Potential

These are personal views that do not necessarily reflect a BfArM opinion
Prolongation of the QT interval by noncardiac drugs

Common cause of delays in development, non-approvals, and withdrawal from marketing.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic class</th>
<th>Year withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenylamine</td>
<td>Antianginal</td>
<td>1988</td>
</tr>
<tr>
<td>Terodilene</td>
<td>Originally antianginal. Re-developed for use in urinary incontinence</td>
<td>1991</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Histamine H&lt;sub&gt;1&lt;/sub&gt;-receptor antagonist</td>
<td>1998</td>
</tr>
<tr>
<td>Sertindole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Atypical antipsychotic</td>
<td>1998</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Histamine H&lt;sub&gt;1&lt;/sub&gt;-receptor antagonist</td>
<td>1999</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>Fluoroquinolone antibacterial</td>
<td>1999</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Gastric prokinetic</td>
<td>2000</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Antiemetic and antipsychotic</td>
<td>2001</td>
</tr>
<tr>
<td>Levacetylmethadon</td>
<td>Opioid analgesic</td>
<td>2001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Now recommended for re-introduction to the market.

QT-prolongation

- Pathophysiology
- Risk assessment
- Thorough QT study
- Decision based on thorough QT study
Aktionspotential

\[ I_{Kur} \]
\[ I_{kr} \quad \text{HERG-GEN} \]
\[ I_{KS} \]
Torsade de pointes tachycardia

1. Ionic currents

2. Action potential parameters in isolated cardiac preparations or specific electrophysiology parameters indicative of action potential duration in anesthetized animals.

3. ECG parameters: conscious or anesthetized animals

Additional investigations (in case of signal)
- Repolarisation assays, proarrhythmia models, transmural dispersion in repolarisation
Preclinical and clinical assessment

- No torsadogenic drugs with negative non-clinical profile have been identified
- S7B non-clinical studies prior to first administration in humans
Preclinical and clinical assessment (S7B)

Non-clinical Testing Strategy

- **In Vitro I\(_{Kr}\) Assay**
- **In Vivo QT Assay**
- **Chemical/Pharmacological Class**

Follow-up Studies → Integrated Risk Assessment → Evidence of Risk → Relevant Non-clinical and Clinical Information
Assessment of clinical risk

• Inhibition of HERG-channels? (IC50)

30 fold margin for plasma concentrations and IC50 values to block HERG channels, if other cardiac ion channels are not influenced
Assessment of clinical risk

- Inhibition of HERG-channels? (IC50)
- Mean maximal QT/QTc-prolongation

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Risk Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 ms</td>
<td>Little risk</td>
</tr>
<tr>
<td>5 - 10 ms</td>
<td>Depends on overall risk-benefit</td>
</tr>
<tr>
<td>10 – 20 ms</td>
<td>Uncertain</td>
</tr>
<tr>
<td>&gt; 20 ms</td>
<td>Probably high risk for TdP</td>
</tr>
</tbody>
</table>

5 ms threshold:
- Guidance for clinical program vs.
- Over-cautious reason for labelling
Assessment of clinical risk

- Inhibition of HERG-channels? (IC50)
- mean maximal QT/QTc-prolongation
- QT vs. QTc prolongation
QT-intervall correction

- Fridericia´s correction preferred > 80/min
  - \( QTc = QT/RR^{0.33} \)

- Bazett´s correction
  - \( QTc = QT/RR^{0.5} \)

- Population based correction for individual drugs
  - \( QTc = QT/RR^x \)

- Linear regression
  - \( QTc = a + b (1-RR) \)
  - \( QTc = QT + 0.154 (1-RR) \) (Framingham correction)

- Within subject correction
  - Regression analysis based on pre-therapy RR and QT
Assessment of clinical risk

- Inhibition of HERG-channels? (IC50)
- mean maximal QT/QTc-prolongation
- QT vs. QTc prolongation
- detection of „outliers“ ?

Thorough QT studies are usually not powered on outlier analysis
Assessment of clinical risk

• Inhibition of HERG-channels? (IC50)

• mean maximal QT/QTc-prolongation

• QT vs. QTc prolongation

• detection of „outliers“ ?

• clinical Torsade de Pointes tachycardias ?
Assessment of clinical risk

- Inhibition of HERG-channels? (IC50)
- mean maximal QT/QTc-prolongation
- QT vs. QTc prolongation
- detection of „outliers“?
- clinical Torsade de Pointes tachycardias?
- are there known class effects?

„Classes“ are usually heterogenous regarding TdP risk
Assessment of clinical risk

- Inhibition of HERG-channels? (IC50)
- mean maximal QT/QTc-prolongation
- QT vs. QTc prolongation
- detection of „outliers“?
- clinical Torsade de Pointes tachycardias?
- are there known class effects?
- are there better surrogates (e.g. transmural dispersion)?
Assessment of clinical risk
Assessment of clinical risk

- in the past relevant regulatory decisions have been based on e.g.:
  - QT/QTc prolongation + clinical TdP tachycardias
Thorough QT/QTc study

Necessary in case of:
- systemic bioavailability and
- non-clinical testing cannot exclude a clinical risk for QT/QTc prolongation and
- study is feasible (tolerability)

Possible exceptions (case by case decisions)
- hormones, blood or plasma products, i.v. amino acids or ion solutions, vaccines
- some orphan drugs like biotechnology products or enzyme replacement therapy
Thorough QT/QTc study

- **Aim**: Determine quality of data on QT/QTc to be collected in the target population.

- **Conduction early during the development (early phase II)**
Thorough QT/QTc study

Design
- **Healthy volunteers**
  - \( n \geq 40 \) per group (often 60 – 65), 50% females
  - ECG has to cover exposure to drug and metabolites over the whole period

- **Positive control if feasible**
  (placebo controlled QT/QTc prolongation ~ 5 ms, if appropriate of the same class)
Thorough QT/QTc study

Parallel group design

- Placebo
- Test (therapeutic dose)
- Test (supratherapeutic dose)
- Positive control
Thorough QT/QTc study

Parallel group design

- long t1/2 of substance or metabolites
- carry over effects
- multiple doses or treatment groups
- relevant drop out rate due to side effects
Thorough QT/QTc study

Cross over design

smaller numbers needed
individual heart rate correction
Thorough QT/QTc study

Dosing
Include the highest range of plasma concentrations

- higher doses (3x, 5x, or 10 x)
- concomitant inhibition of metabolizing enzymes
Thorough QT/QTc study

- Test (50 mg)
- Test (500 mg)
- Placebo
- Moxifloxacin
- Test (50 mg) + inhibitor
- Placebo
- Moxifloxacin
Thorough QT/QTc study

Drug → Metabolite

Drug → Metabolite

Drug → Metabolite, inhibitor
Thorough QT/QTc study

Dosing
Include the highest range of plasma concentrations

- higher doses (3x, 5x, or 10 x)
- concomitant inhibition of metabolizing enzymes

Consider effect of genetic polymorphisms in subgroups, renal or hepatic failure, drug-drug interactions

Discontinuations due to AEs at high doses may increase variability
Thorough QT/QTc study

Primary analysis: Mean peak change from baseline

„Threshold of regulatory concern“?

5 ms (placebo controlled)

~ 10 ms 95% one-sided CI for the largest mean effect

![Graph showing placebo corrected difference (ms) between Control and Test groups.](image-url)
Thorough QT/QTc study
Timing of ECG measurements

- QT/QTc changes do not necessarily parallel plasmalevels
- ECG throughout the dosing interval
- Single dose vs. multiple dose studies
Thorough QT/QTc study

Secondary analysis

Categorial analysis
- QTc > 450, > 480, > 500 ms
- change from baseline
  • > 30 ms
  • > 60 ms
Decision based on thorough QT/QTc results
Decision based on thorough QT/QTc study

negative

Baseline and periodic on-therapy ECGs

- Strong preclinical concerns
  - (class of concern?)
  - additional clinical evidence

positive

Expanded ECG safety evaluation
- full dose, concentration- and time relation
- TdP risk factors
- outliers and mean QT/QTc

Strong preclinical concerns (class of concern?)

Decision based on thorough QT/QTc study

Strong preclinical concerns

Baseline and periodic on-therapy ECGs

Expanded ECG safety evaluation
- full dose, concentration- and time relation
- TdP risk factors
- outliers and mean QT/QTc
Decision based on thorough QT/QTc study

negative

positive

Labelling?
(5 ms, 5-20 ms, >20 ms?)
Clinical studies

- Analysis of the largest time-matched mean difference of QT/QTc between drug and placebo
  - Possibly at individual cmax

- Categorial analysis
  - uncorrected and with different correction formulas
  - QTc > 450, > 480, > 500 ms
  - change from baseline > 30 ms, > 60 ms

- On therapy ECG abnormalities

- On therapy ECG changes as AEs
Clinicals studies

- Absence of TdP in clinical studies or post marketing databases does not prove absence of pro-arrhythmic risk

- Presence of only one documented TdP episode has a high probability to be drug related
Assessment of adverse events

Torsade de Pointes tachycardias

sudden death
ventricular tachycardia, flutter and fibrillation
syncope
seizures
dizziness

patient narratives for CV SAEs and discontinuations, analysis of patients with events and of dosage adjustments

subgroups of special interest
Drug induced QT prolongation: groups of special interest

- Electrolyte abnormalities, e.g., hypokalemia
- Congestive heart failure
- Impaired drug metabolizing capacity or clearance, e.g. due to liver or kidney impairment, or drug interactions
- Female gender
- Age <16 and >65 years
Parallel data on PK and QT

- possible: ADME studies (metabolites)
- thorough QT study
- target patient group
Pharmacogenetics and QT/QTc prolongation

In a patient with prolonged QT or suggestive adverse event

- screening for congenital long QT syndrome

- evaluation of relevant polymorphisms of metabolizing enzymes
Summary

• QT/QTc prolongation does not 1:1 translate to TdP

• No generally accepted criteria to reliably assess the potential of a drug to induce TdP tachycardias
Thank you for your attention

http://boldog.freeblog.hu/Files/complicated%20heart.jpg