PK-QT analysis of bedaquiline:

*Bedaquiline appears to antagonize its main metabolite’s QTcF interval prolonging effect*

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Bedaquiline

Accelerated FDA approval in Dec 2012

- **BENEFIT**
  - Shortening of the time to sputum culture conversion
  - Increase of the cure rate

- **RISK**
  - Prolongation of the heart’s QT interval
  - Torsade de pointes: a potentially fatal ventricular arrhythmia

*FDA: Food and Drug Administration*
Background

Main findings

In vitro¹
- Clear inhibition of IKr in hERG transfected kidney cells by M2 and BDQ
  - No conclusion about the magnitude of the effect

In vivo¹
- No effect after single high dose administration in dogs and guinea pigs
- Positive signal with longer treatment (1 week to 6 months) in dogs

Clinical²
- TQT trial (single 800mg BDQ dose)
  - No significant QTc prolongation effect of BDQ
  - Too low concentrations of M2
- C208 trial
  - Positive M2 concentration-QTc relationship
  - “… M2 concentrations are responsible for the QTc prolongation observed in Trial C208”³

¹. FDA Pharmacology review; 2. FDA Clinical Pharmacology and Biopharmaceutics review; 3. FDA Summary review

BDQ: bedaquiline; M2: bedaquiline’s main metabolite; TQT: Thorough QT
To investigate potential relationships between:

**bedaquiline (BDQ) / main metabolite (M2) concentrations** & **QTcF interval** (QT interval corrected with Fridericia’s coefficient)

in multi-drug resistant tuberculosis patients using the approved BDQ dose regimen
2 Phase IIb studies

**C208**
TMC207-C208, ClinicalTrials.gov number NCT00449644
- Placebo-controlled study
- 24 weeks of BDQ (400mg QD for 14 days, then 200mg TIW) on top of a defined background regimen of 5 drugs
- PK: Rich sampling
- QT:
  - Single ECGs performed at each patient’s visit
  - Triplicate ECGs at pre-dose and 5 hour post-dose at week 2, 8 and 24

**C209**
TMC207-C209, ClinicalTrials.gov number NCT00910871
- Interventional open-label study
- 24 weeks of BDQ (400mg QD for 14 days, then 200mg TIW) on top of an individualized background regimen
- PK: Sparse sampling
- QT:
  - Single ECGs performed at each patient’s visit
  - Triplicate ECGs at pre-dose and 5 hour post-dose at week 2, 8, 12 and 24

**ECG**: ElectroCardioGram; **QD**: Once daily; **TIW**: three times a week
Methods

Pharmacokinetics of BDQ and its main metabolite

Characterization of the relationship between BDQ/M2 exposure & QT

Methods

Drug effect

**Effect of BDQ**

\[
\frac{E_{\text{max},\text{BDQ}} \cdot \text{Conc}_{\text{BDQ}}}{EC_{50,\text{BDQ}} + \text{Conc}_{\text{BDQ}}}
\]

**Effect of M2**

\[
\frac{E_{\text{max},\text{M2}} \cdot \text{Conc}_{\text{M2}}}{EC_{50,\text{M2}} + \text{Conc}_{\text{M2}}}
\]

**Competitive model**

\[
\frac{E_{\text{max},\text{M2}} \cdot \text{Conc}_{\text{M2}}}{EC_{50,\text{M2}} \cdot \left(1 + \frac{\text{Conc}_{\text{BDQ}}}{EC_{50,\text{BDQ}}}\right) + \text{Conc}_{\text{M2}}} + \frac{E_{\text{max},\text{BDQ}} \cdot \text{Conc}_{\text{BDQ}}}{EC_{50,\text{BDQ}} \cdot \left(1 + \frac{\text{Conc}_{\text{M2}}}{EC_{50,\text{M2}}}\right) + \text{Conc}_{\text{BDQ}}}
\]

**Competitive full agonist & antagonist model**

\[
\frac{E_{\text{max},\text{M2}} \cdot \text{Conc}_{\text{M2}}}{EC_{50,\text{M2}} \cdot \left(1 + \frac{\text{Conc}_{\text{BDQ}}}{EC_{50,\text{BDQ}}}\right) + \text{Conc}_{\text{M2}}}
\]
Methods

Drug effect

**Effect of BDQ**

\[ \frac{E_{\text{max},BDQ} \times \text{Conc}_{BDQ}}{EC_{50,BDQ} + \text{Conc}_{BDQ}} \]

**Effect of M2**

\[ \frac{E_{\text{max},M2} \times \text{Conc}_{M2}}{EC_{50,M2} + \text{Conc}_{M2}} \]

**Competitive model**

\[ \frac{E_{\text{max},M2} \times \text{Conc}_{M2}}{EC_{50,M2} \left(1 + \frac{\text{Conc}_{BDQ}}{EC_{50,BDQ}}\right) + \text{Conc}_{M2}} + \frac{E_{\text{max},BDQ} \times \text{Conc}_{BDQ}}{EC_{50,BDQ} \left(1 + \frac{\text{Conc}_{M2}}{EC_{50,M2}}\right) + \text{Conc}_{BDQ}} \]

**Competitive full agonist & antagonist model**

\[ \frac{E_{\text{max},M2} \times \text{Conc}_{M2}}{EC_{50,M2} \left(1 + \frac{\text{Conc}_{BDQ}}{EC_{50,BDQ}}\right) + \text{Conc}_{M2}} \]

\[ \Delta \text{OFV} = -1255 \]

\[ \Delta \text{OFV} = -159 \]

OFV

109 664

108 568

108 409

C208

C209

robustness of the results
**Results**

**Interpretation**

QTcF = QTcF<sub>wo</sub> TB treatment + $\text{Study}_{shift}$ + \[ \frac{E_{max,M2} \times C_{o,n,M2}}{1 + \frac{C_{BDQ}}{EC_{50,BDQ}} \times EC_{50,M2} + C_{o,n,M2}} \]

Background TB treatment effect
Exposure effect

Typical profiles in C208 study at predicted steady state
Results

Visual Predictive Checks

The solid and dashed lines show the 50\textsuperscript{th} (median) and 5\textsuperscript{th}/95\textsuperscript{th} percentiles of the observed data. The areas are the 95\% confidence intervals for the corresponding percentiles based on the simulated data. Dashed red vertical lines represent the different safety grades of abnormal QT corrected interval, based on the ICH E14 Guidance (CHMP/ICH/2/04; May 2005).
Conclusion

The QTcF interval prolongation was explained by an effect of the background regimen and M2 exposure, with bedaquiline antagonizing the effect of M2.

Further consideration
- Confirmation with other data
  - Placebo effect
  - Circadian rhythm, time dependency
  - Concomitant drugs with QT liability

Perspectives
- Integrated dose-exposure-efficacy-safety analysis
  - taking into account drug-drug interactions

➢ Simulation of optimized regimens
Acknowledgement

Patients involved in clinical trials
TMC207-C208 & TMC207-C209

Uppsala Pharmacometric Group

UPPSALA
UNIVERSITET
Thank you

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I do not have any conflict of interest to declare