Population pharmacokinetics of bedaquiline (TMC207) and its M2 and M3 metabolites with efavirenz demonstrate reduced exposure

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Background

- Co-infection with tuberculosis (TB) and HIV is common
- Bedaquiline is an investigational anti-TB agent
- CYP3A4 activity is induced by efavirenz and bedaquiline is a substrate of CYP3A4

Objective: To develop a population model that describes the effect of efavirenz induction on the PK of bedaquiline and M2 and M3 metabolites after multiple doses.

M2 and M3 are less active in vitro against M. tuberculosis, monitor for safety reasons.
Methods:
Data from ACTG Study 5267

• 2 doses of 400 mg in 33 healthy volunteers

• PK sampling over 14 days after dose

• Bedaquiline, M2 and M3 assayed

• EFV started at day 15, PK measured at day 28

Dooley et al. J Acquir Immune Defic Syndr, 2012;59(5)
Methods: Limitations

• Given the long terminal half-lives, extrapolation from single dose to steady state is limited

• Potential differences in PK between healthy volunteers and patients

• Relationship between PK parameters and treatment response not well characterized, hence the clinical importance of a change is hard to assess
Methods: Model building

- Non-linear mixed effects models

- Software: NONMEM 7.2
  - Additional tools: PsN, Xpose4, Pirana

- Models selection based on:
  - Objective function value
  - Graphical analysis (goodness of fit plots and visual predictive checks)

- Evaluation of a range of structural assumptions
Results: Structural model

- Oral dose
  - N transit compartments
  - TMC207
  - M3
  - M2

= induction effect
Results:
Model features

• Simultaneous analysis

• Full induction effect starting after one week of EFV treatment

• No significant difference in the magnitude of the induction effect on bedaquiline and M2

• Estimated factor change in CL with induction:
  bedaquiline and M2: 2.07 (RSE 3.6%)
  M3: 1.12 (RSE 3.6%)

• Correlations between CL and induction effects for bedaquiline, M2 and M3
Results:
Visual predictive check

- Bedaquiline
- M2
- M3
- Bedaquiline + EFV
- M2 + EFV
- M3 + EFV

Log concentration (ng/mL) vs Time after dose (days)
Results:
Impact on exposure

\[ C_{SS,av} = \frac{F \cdot \text{Dose}}{CL \cdot \tau} \Rightarrow \text{Rel}_{C_{SS,av}} = \frac{C_{SS,av(EFV)}}{C_{SS,av}} = \frac{CL}{CL(EFV)} \]

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<tr>
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<th>Bedaquiline</th>
<th>M2</th>
<th>M3</th>
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<tbody>
<tr>
<td>( \text{Rel } C_{ss,av} ) (SE)</td>
<td>48 (1.9)%</td>
<td>48 (1.9)%</td>
<td>88 (3.7)%</td>
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<tr>
<td>( \text{Inter individual variability [CV] in } \text{Rel } C_{ss,av} ) (SE)</td>
<td>21 (2.7)%</td>
<td>29 (7.7)%</td>
<td>35 (9.8)%</td>
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Calculated from simulated (n=10000) individual CL values from each of 93 sets of parameter estimates obtained in a bootstrap of the primary model.
Results:
Alternative models

Evaluate different assumptions regarding:

• the fractions of bedaquiline converted to M2 and of M2 converted to M3
• the time for onset of induction
• the induction effect on bioavailability

The results were robust:
Bedaquiline, M2 and M3 exposures on EFV induction were estimated to between 48-64%, 48-60% and 85-110% respectively of the non-induced condition under all assumptions
Results:
Possible dose adjustments

Standard regimen:
- 2 weeks 400 mg QD + 22 weeks 200 mg thrice weekly (TIW)

Scenario:
- Patient diagnosed with TB and HIV simultaneously
- EFV treatment initialized at start of week 3 of bedaquiline treatment

Evaluated cases:
- Unchanged bedaquiline dosing
  - 2 weeks 400 mg QD + 22 weeks 200 mg TIW
- Alt. 1: Change dosing frequency
  - 2 weeks 400 mg QD + 22 weeks 200 mg QD
- Alt. 2: Increase dose
  - 2 weeks 400 mg QD + 22 weeks 400 mg TIW
Results:
Possible dose adjustments
Conclusions

• EFV may reduce the typical exposure to bedaquiline and M2 by up to 52% upon chronic co-administration

• The result was robust under a range of plausible model assumptions

• Simulations of dose adjustments suggest that alternative dosing strategies could mitigate the effects of EFV induction on bedaquiline, but these must be tested prospectively
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