QT prolongation and its evolution over time in the STREAM 1 trial

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No disclosures or conflicts of interest to declare
Introduction

• STREAM Stage 1
• Regimen similar to Bangladesh regimen (Aung KJ et al. IJTLD 2014)
• Phase 3 non-inferiority RCT for rifampicin resistant TB
• Short 9-11 month regimen (n=282)

  versus

• Long 20-24 month WHO 2011 control regimen (n=142)
## Short 9-11 month regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight group</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 33 kg</td>
<td>400 mg</td>
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<tr>
<td>Clofazimine</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Less than 33 kg</td>
<td>50 mg</td>
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<tr>
<td>Ethambutol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 33 kg</td>
<td>800 mg</td>
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<tr>
<td>Pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 33 kg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Less than 33 kg</td>
<td>300 mg</td>
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<tr>
<td>Prothionamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 33 kg</td>
<td>250 mg</td>
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<tr>
<td>Kanamycin</td>
<td></td>
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<tr>
<td></td>
<td>Less than 33 kg</td>
<td>15 mg per kilogramme body weight (maximum 1g)</td>
</tr>
</tbody>
</table>
Long 20-24 month regimen

• Patients received local version of the WHO 2011 regimen
• Fluoroquinolone was either 400mg moxifloxacin or 750mg levofloxacin
• Neither clofazimine or bedaquiline were part of allocated regimen
Why focus on ECG data?

• Moxifloxacin 400mg dose known to prolong QT interval
• Short regimen uses 600 mg and 800 mg moxifloxacin with clofazimine
• Long duration even with “short” course
• Prolonged QT asymptomatic but can quickly progress to Torsade de pointes, ventricular fibrillation and ultimately sudden cardiac death
Monitoring

- Patients with QT/QTcF ≥500ms at screening were excluded
- Patients had 4-weekly ECG monitoring up to 52 weeks
- If QT/QTcF ≥500 ms the fluoroquinolone was temporarily withheld
- Management algorithm:
  - attempt to reintroduce moxifloxacin at 400mg dose
  - if unsuccessful switch to levofloxacin
  - if still unsuccessful clofazimine dose reduced or later stopped
Results shown are of patient monitoring up to the point of treatment change of more than one drug at which point they were censored.

Bars indicate +/- 1 standard error.
Mean (SE) change in QTcF from baseline

Bars indicate +/- 1 standard error
Distribution of QTcF by time

Week 0

Week 16

Week 40

Week 52

Density vs. QTcF (ms)

Short  Long (Moxi)  Long (Non-Moxi)
Time to QTcF exceeding $\geq 500$ ms threshold
Summary

- Mean QTcF changes were greater on the Short regimen
  - Max. difference 24ms at week 28
- Mean QTcF differences between treatment arms had returned to less than 10ms by week 52
- QTcF ≥500 ms 10% Short regimen v 4 % Long regimen; HR (95% CI); 2.82 (1.09-7.33) log-rank test p = 0.034
Conclusions

- There was more QT prolongation on the Short regimen, with twice as many participants having QT/QTcF ≥500ms; this occurred throughout treatment.
- QTcF increase resolved by week 52, after almost all patients on the Short regimen had completed treatment.
- Patients on the Long regimen continued treatment for at least 18 months; any effect of treatment on QTcF would still be present at week 52.
- Density plots demonstrate the Short regimen alters the QTcF distribution to a greater extent than the Long regimen.
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