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

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USAID FROM THE AMERICAN PEOPLE

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The Union International Union Against Tuberculosis and Lung Disease Health solutions for the poor

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Disclosures

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

Drug		Weight group		Duration
	Less than 33 kg	33 kg to 50 kg	More than 50 kg	
Moxifloxacin	400 mg	600 mg	800 mg	40 weeks
Clofazimine	50 mg	100 mg	100 mg	
Ethambutol	800 mg	800 mg	1200 mg	
Pyrazinamide	1000 mg	1500 mg	2000 mg	
Isoniazid	300 mg	400 mg	600 mg	16 weeks
Prothionamide	250 mg	500 mg	750 mg	
Kanamycin	15 mg per kilogramme body weight (maximum 1g)			

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

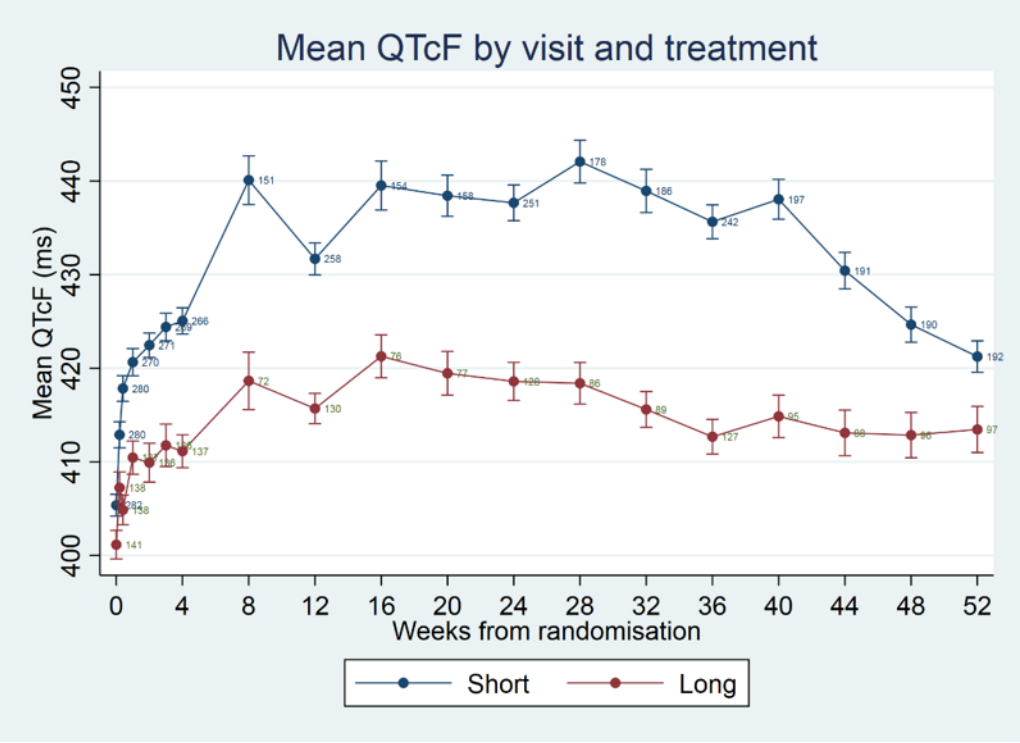
Why focus on ECG data?

- 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

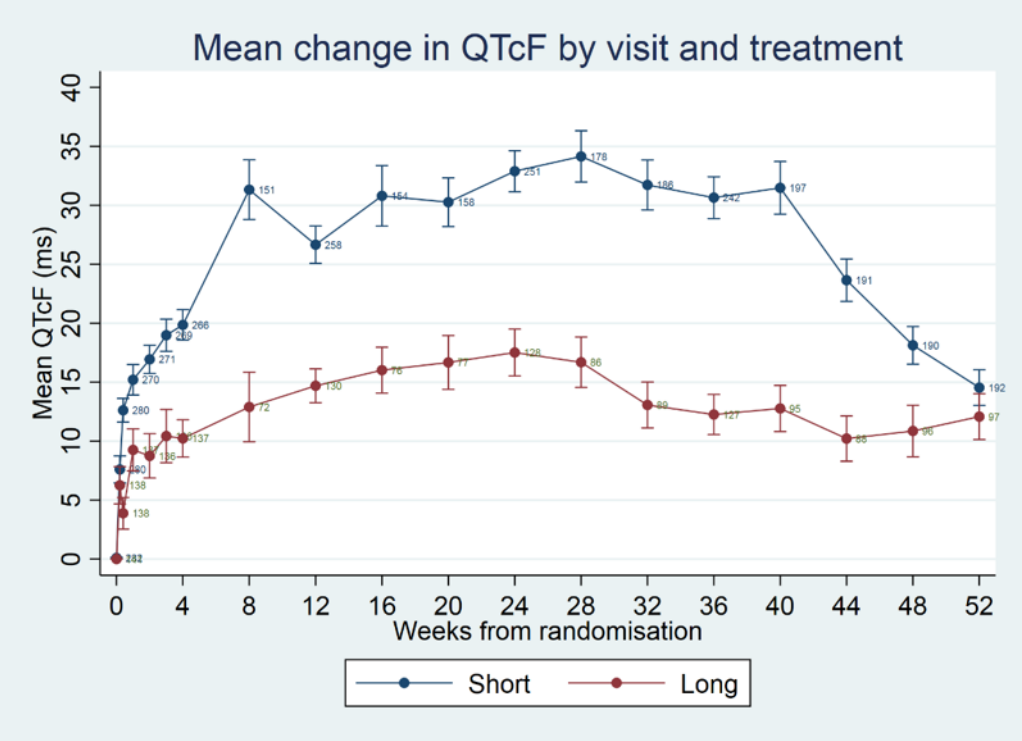
Mean (SE) QTcF by visit and treatment



Results shown are of patient monitoring up to the point of treatment change of more than one drug at which point they were censored

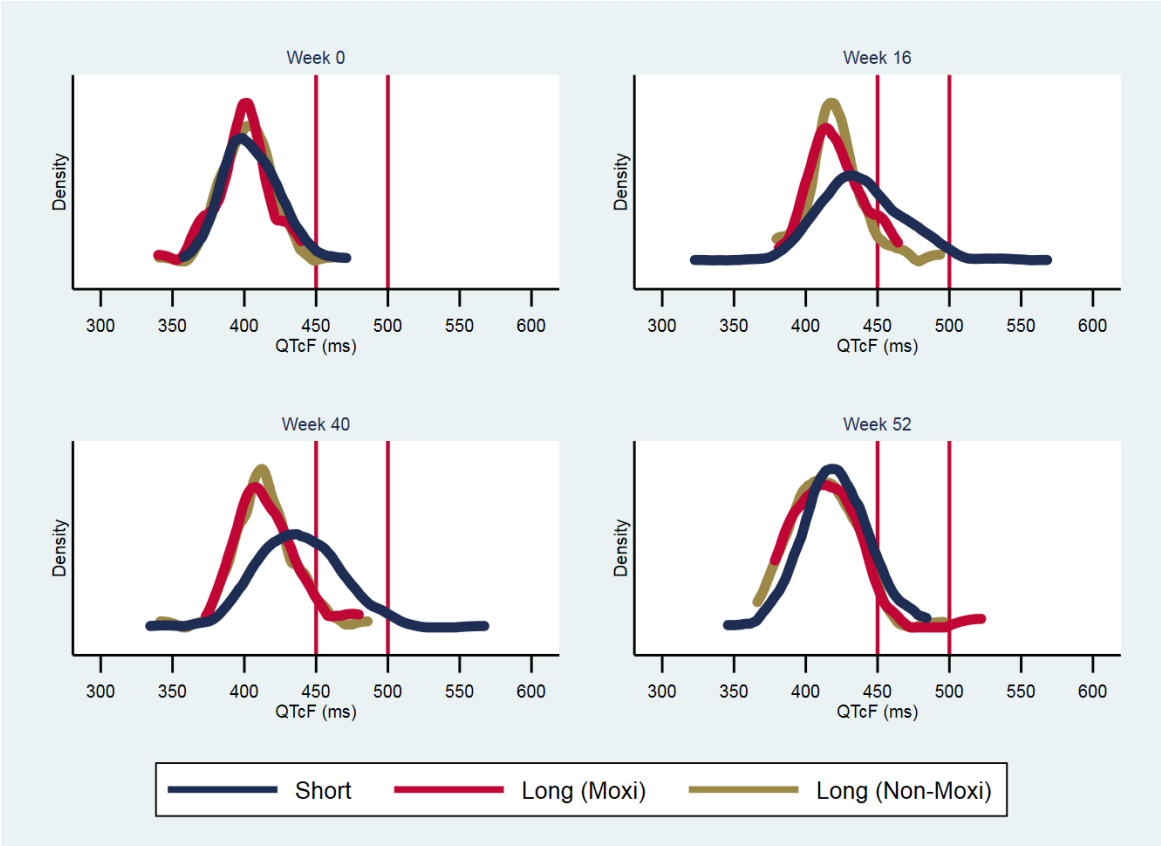
Bars indicate +/- 1 standard error

Mean (SE) change in QTcF from baseline

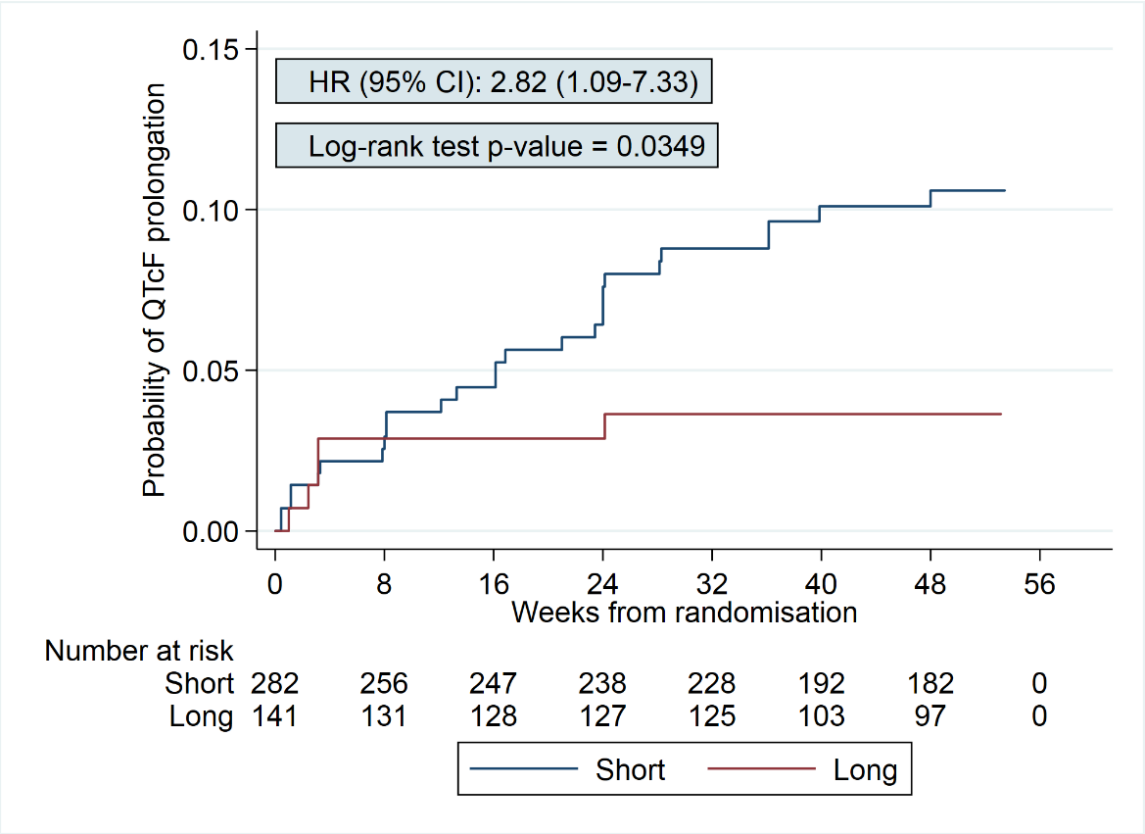


Bars indicate +/- 1 standard error

Distribution of QTcF by time



Time to QTcF exceeding ≥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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