New treatments and approaches to Tuberculosis

Tuberculosis Symposium – Eastern Europe and Central Asia

RA Ministry of Health and Médecins Sans Frontières

TB trials for new treatment combinations: end TB and PRACTECAL

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Overview

- Why do we need Clinical Trials?
- What clinical Trials are planned
- MSF Trial Initiative
  - end TB
  - PRACTECAL

We have new drugs so why do we need Clinical Trials?

New drugs ≠ New regimens

- Still treating with multiple drugs
- Usually still with injectables or intravenous
- Long duration
- Not sure optimal combination

New MDR-TB treatment regimes

Principles for designing future regimens for multidrug-resistant tuberculosis

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- At least one new class
- At least 3 and max 5 effective drugs
- Effective against MDR and XDR strains
- 6 -9 months
- Oral
- Simple dosing schedule
- Good side effect profile, limited monitoring
- Minimal interaction with antiretrovirals

Good Clinical Practice (GCP) Guidelines

- International ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects
- Lays out the responsibilities of the ethics committees, sponsors and investigators.

Good Clinical Practice (GCP) Guidelines

- Ethical principles: Declaration of Helsinki
- Favourable benefit(s) vs. risk(s)
- Subject's rights
- Adequate supporting data
- Scientifically sound protocol
- Independent ethics committee oversight
- Medical care by qualified investigator
- Qualified personnel
- Informed consent
- Record-keeping
- Subject confidentiality
- GMP manufacturing of the investigational product
- Quality assurance & monitoring

Clinical Trial Landscape

Trial Name (Funding Source)	Duration Experimental Regimen	Experimental Arms	
C213 Delamanid Phase 3 Trial (Otsuka)	24 mths	6 mths Dlm + OBR	Completed follow up for primary end point
Delamanid safety study children	24 mths	6 mths Dlm + OBR (6-17 yr old)	Enrolling
STREAM I Trial (MRC)	9 mth	Comparison std WHO regimen vs 9 mth modified Bangladesh regimen	85% enrolled
STREAM II Trial	6-9 mths	Comparison of short bedaquiline-containing regimens against the WHO and Bangladesh regimen	Expected to being enrolling 1Q15

Clinical Trial Landscape

Trial Name (Funding Source)	Duration Experimental Regimen	Experimental Arms	
PRACTECAL	6 mths	3 regimens with Bdq+Prt+Lzd	Protocol Finalised Expected start Q3 2015
end TB	9 mths	Novel, no inj, regimens 4-5 drugs with Bdq and/or Dlm	Protocol near finalised
Bedaquiline/PA -824/PZA (GATB NC-005)	8-week SSCC Study of Bedaquiline plus PA-824 plus PZA	Study of B/PA/Z for drug-susceptible TB; has one arm enrolling patients with MDR-TB that adds Moxifloxacin to B-PA-Z	Expected to begin enrolling in 4Q14
NiX-TB	6-9 mths	Prt, Lzd, Bdq	Salvage regimen for XDR TB
PA-824/moxi/PZA (GATB NC-006)	4 or 6 months	Prt/M/Z for DS-TB; 1 arm with MDR-TB (susc. to FQ and Z)	Expected to begin enrolling 4Q14

Clinical Trial Landscape

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Bedaquiline/PA -824/PZA (GATB NC-005)	8-week Study	Study of Bdq/Prt/Z for DS-TB; 1 arm with MDR-TB adds Mfx	Expected to begin enrolling in 4Q14
DDI of bedaquiline + delamanid (ACTG A5343)	Safety, Tolerability, & Pharmacokin etics Study	Bedaquiline and delamanid Drug-drug interactions and combined QT effects	Expected to begin enrolling in 1Q15
NExT Trial	6-9 mths	Injection free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high dose INH, and PZA	Open labelled RCT Waiting for MCC approval, expected enrollment at 5 sites in South Africa

MSF MDR-TB Clinical Trial Initiative

- 2 MDR TB clinical trials
  - end TB
  - PRACTECAL
- Novel short course regimens without injectables
- Using new and repurposed drugs

TB Trial Initiative

- PRACTECAL

University College of London

Uzbekistan national institute of Tuberculosis

- end TB

PRACTECAL Trial overview

- Adults with pulmonary MDR and XDR-TB
- Open label, 4 parallel arms, randomised and controlled
- Multicentre, phase II-III trial
- Adaptive 2 stage design with a seamless transition

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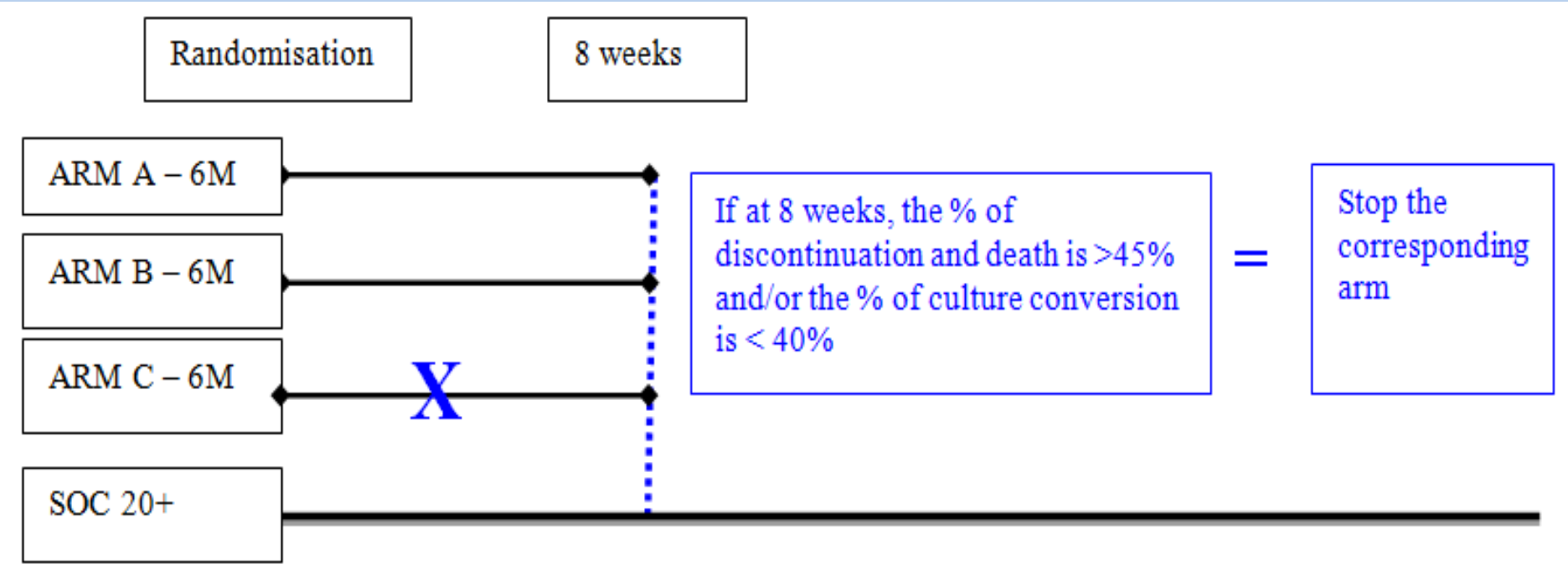

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- Multicentre, phase II-III trial
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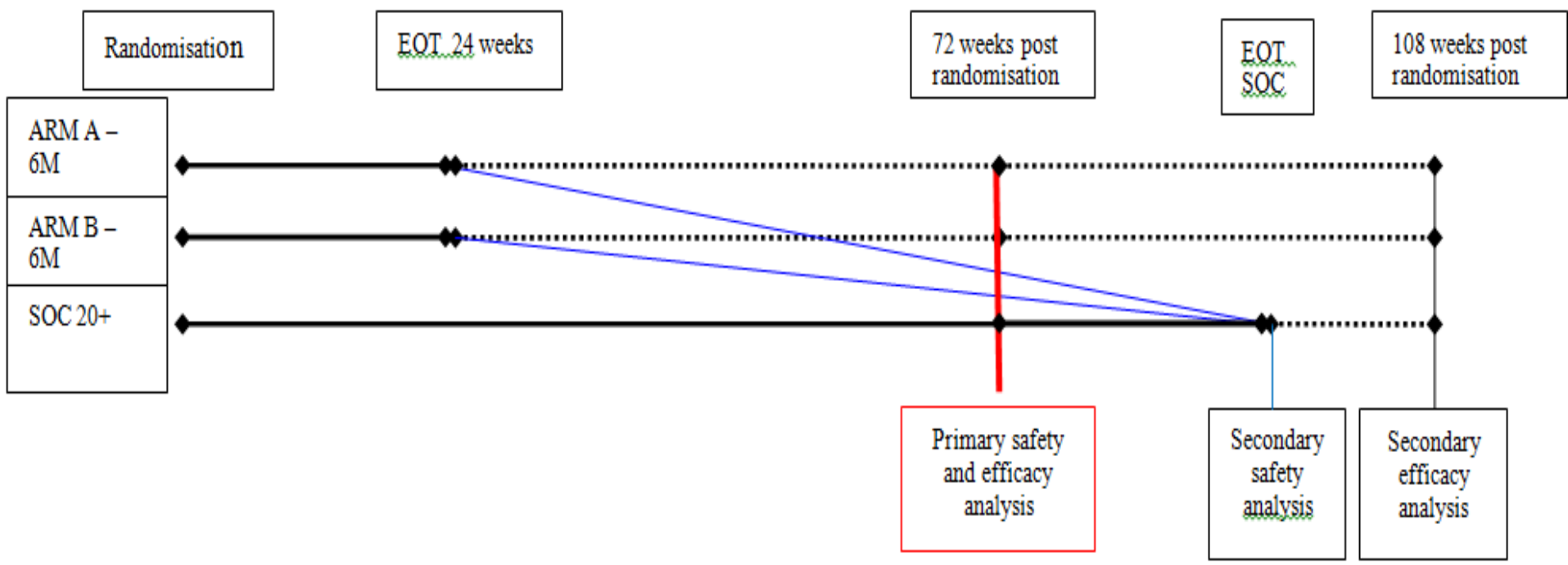

PRACTECAL Trial Arms

- **Intervention arms:**

1. Bedaquiline + PA-824 + linezolid + moxifloxacin
2. Bedaquiline + PA-824 + linezolid + clofazimine
3. Bedaquiline + PA-824 + linezolid

- **Control arm:** Locally accepted standard of care which is consistent with the WHO recommendations for the treatment of M/XDR-TB

Summary end TB trial: Regimen optimization

- Phase III pragmatic, open-label, multicentric trial in 2 parts
  - Part I: test different 36-week regimens with 1 new drug (Bdq or Dlm) in patients with MDR, sensitive to FQs
  - Part 2: test different regimens combining 2 new drugs (Bdq AND Dlm) in patients with MDR, including FQ resistant patients

- Part I will be implemented while awaiting results of DDI study

- Randomization in this study will be adapted to outcome: bad outcomes on a regimen will result in decreased randomization to that regimen allowing the trial to progress quicker

end TB: Experimental 9-month Regimens (Part I)

#	Bdq	Dlm	Cfz	Lzd	FQ	Z
1	Bdq			Lzd	Mfx	Z
2	Bdq		Cfz	Lzd	Lfx	Z
3		Dlm		Lzd	Mfx	Z
4		Dlm	Cfz	Lzd	Lfx	Z
5		Dlm	Cfz		Lfx	Z

Bdq=bedaquiline, Dlm=delamanid, Cfz=clofazamine, Lzd=linezolid, FQ=fluoroquinolone, Z=pyrazinamide

Expected outputs MSF TB Trial Initiative (end TB and PRACTECAL)

- Short, safe and effective regimens that can be used in treating both MDR and XDR – TB
- The effect on safety and efficacy of adding Mfx or Cfz to a back bone of B+Pa+Lzd
- Cardiac specific safety of the new drugs (Bdq, Dlm, Prt) in combinations
- Tolerability of the new regimens
- Pharmacokinetic data of the new drugs when administered in combination regimen

Conclusions

- Important that we don't just have new drugs but also research to inform better combinations and potential shorter duration
- Several new MDR TB drug combination trials starting or about to start
- MSF and partners have started an MDR TB Trial Initiative – 2 trials