Conflict of Interest

The author has declared no conflict of interest.

TB Practecal

Innovating MDR-TB Treatment

Early termination of randomisation into TB-PRACTECAL, a novel six month, all-oral regimen study.

Bern-Thomas Nyang'wa, Catherine Berry, Ilaria Motta, Emil Kazounis

This study was approved by the London School of Hygiene and Tropical Medicine Ethics Review Board (ERB) and the MSF Ethics Review Board, as well as national or regional ERB's at each trial site. Clinicaltrials.gov registry number, NCT02589782.

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

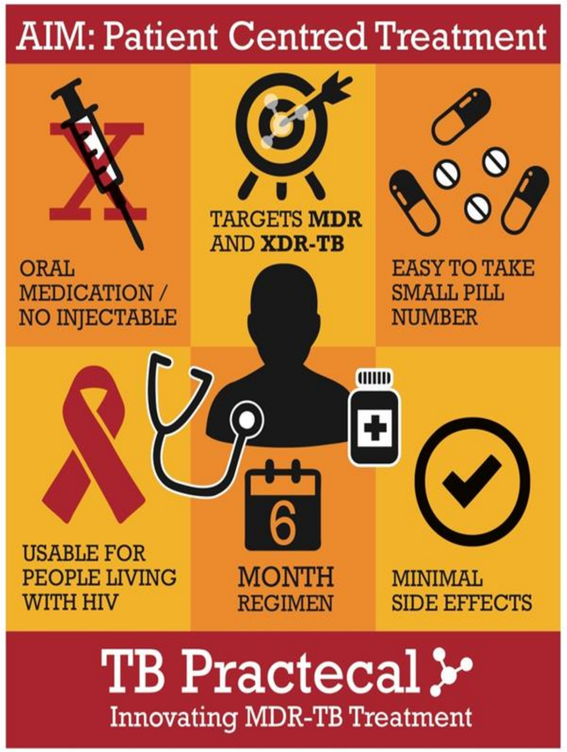
SCIENTIFIC DAYS

TB Practecal
Innovating MDR-TB Treatment

Principles for designing future regimens for multidrug-resistant tuberculosis

Grania Brigden,[a] Bern-Thomas Nyang'wa,[b] Philipp du Cros,[b] Francis Varaine,[c] Jennifer Hughes,[d] Michael Rich,[e] C Robert Horsburgh Jr,[f] Carole D Mitnick,[g] Eric Nuermberger,[h] Helen McIlleron,[i] Patrick PJ Phillips[j] & Manica Balasegaram[a]

- At least one new class
- At least three and max five effective drugs
- Effective against multidrug-resistant (MDR) and pre-extensively drug-resistant (XDR) strains
- 6-9 months, all oral
- Good side effect profile, limited monitoring
- Minimal interaction with antiretrovirals



MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

TB Practecal
Innovating MDR-TB Treatment

One day of MDR/ pre-XDR regimen today

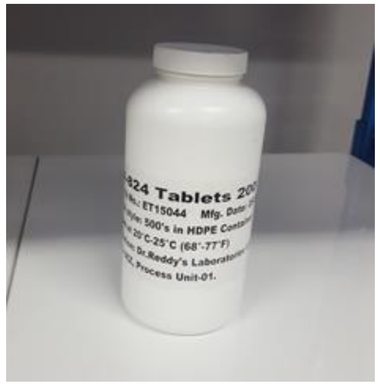
One day of TB PRACTECAL arm-1

‘A randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of drug regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug resistant tuberculosis’

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

TB Practecal
Innovating MDR-TB Treatment



Investigational arms:

1. Bedaquiline + Pretomanid + linezolid + moxifloxacin
2. Bedaquiline + Pretomanid + linezolid + clofazimine
3. Bedaquiline + Pretomand + linezolid
   - For 24 weeks

Control arm:

Locally accepted standard of care (SOC) which is consistent with the WHO recommendations for the treatment of M/XDR-TB

- For 36 - 96 weeks
- Included shorter MDR-TB regimen and bedaquiline / delaminid containing regimens

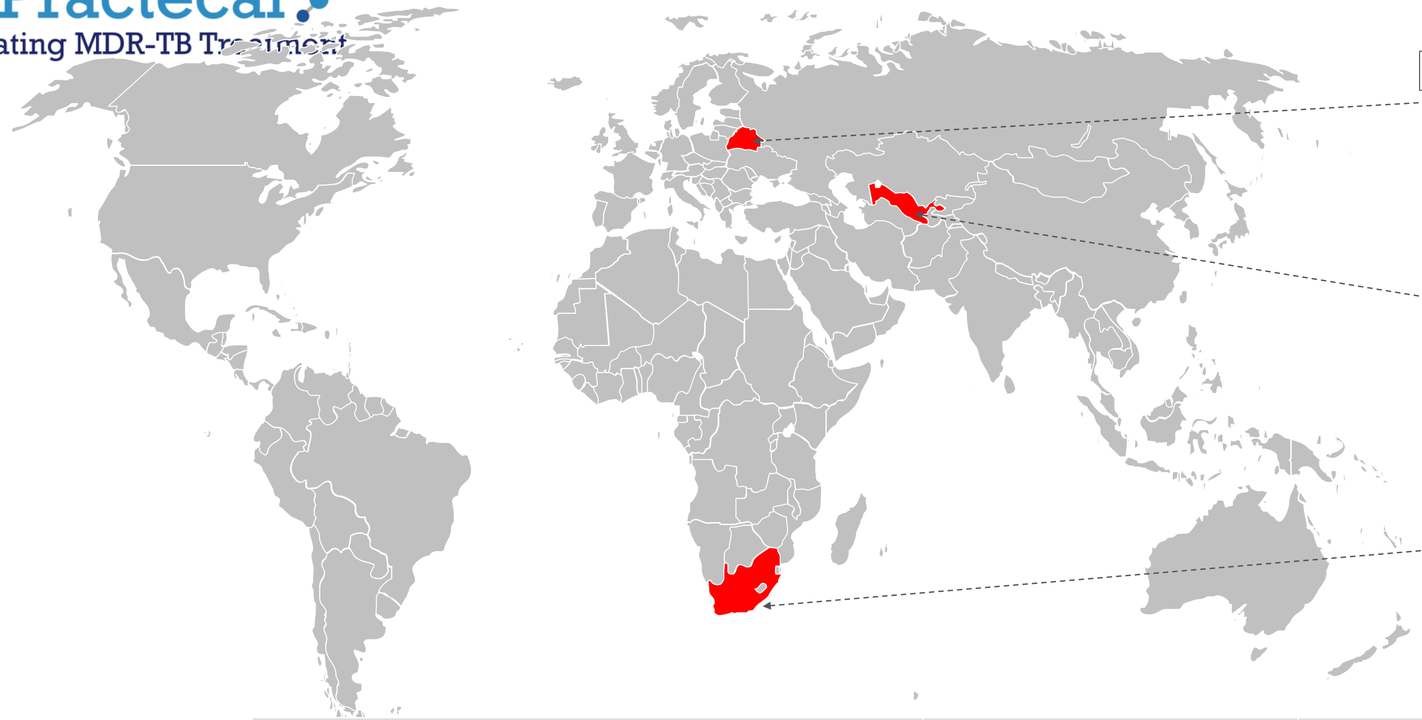
MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

Population

- ≥15 years of age
- Regardless of HIV status
- Microbiological test (molecular or phenotypic) confirming presence of M. tuberculosis
- Resistant to at least rifampicin by either molecular or phenotypic drug susceptibility test
- Can include pre-XDR (fluoroquinolone resistance)

TB Practecal
Innovating MDR-TB Treatment



02. MINSK - Site opened: Dec 2017

01 . NUKUS - Site opened Jan 2017

04. TASHKENT - Site opened Dec 2018

03. DORIS GOODWIN - Site opened Nov 2017

03b. DON MCKENZIE - Sub-Site opened Oct 2018

05. HELEN JOSEPH - Site opened Dec 2019

06. KING DINIZULU - Site opened Nov 2019

	Belarus	South Africa	Uzbekistan
% RR-TB among new cases*	38 (35-40)	3.4 (2.5-4.3)	12 (11-13)
Lab confirmed XDR-TB (2006 def)	344	406	602
HIV proportion amongst TB	7.1%	58%	4%
RR-TB treatment success rate	70%	60%	61%

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

*2020 Global Tuberculosis report, Accessed 7th May 2021

SCIENTIFIC DAYS

Stage 1

Primary objective:

- Identify regimens containing bedaquiline and pretomanid for further evaluation based on safety and efficacy outcomes after 8 weeks of treatment

Primary outcomes:

- Analysis at stage 1 was based on investigational arms only; no SOC
- The sample size of 60 participants per arm was based on the number required to detect:
    - a percentage culture conversion < 40% and / or
    - a percentage of treatment discontinuation for any cause and death >45% in an investigational arm.

TB Practecal
Innovating MDR-TB Treatment

Stage 2

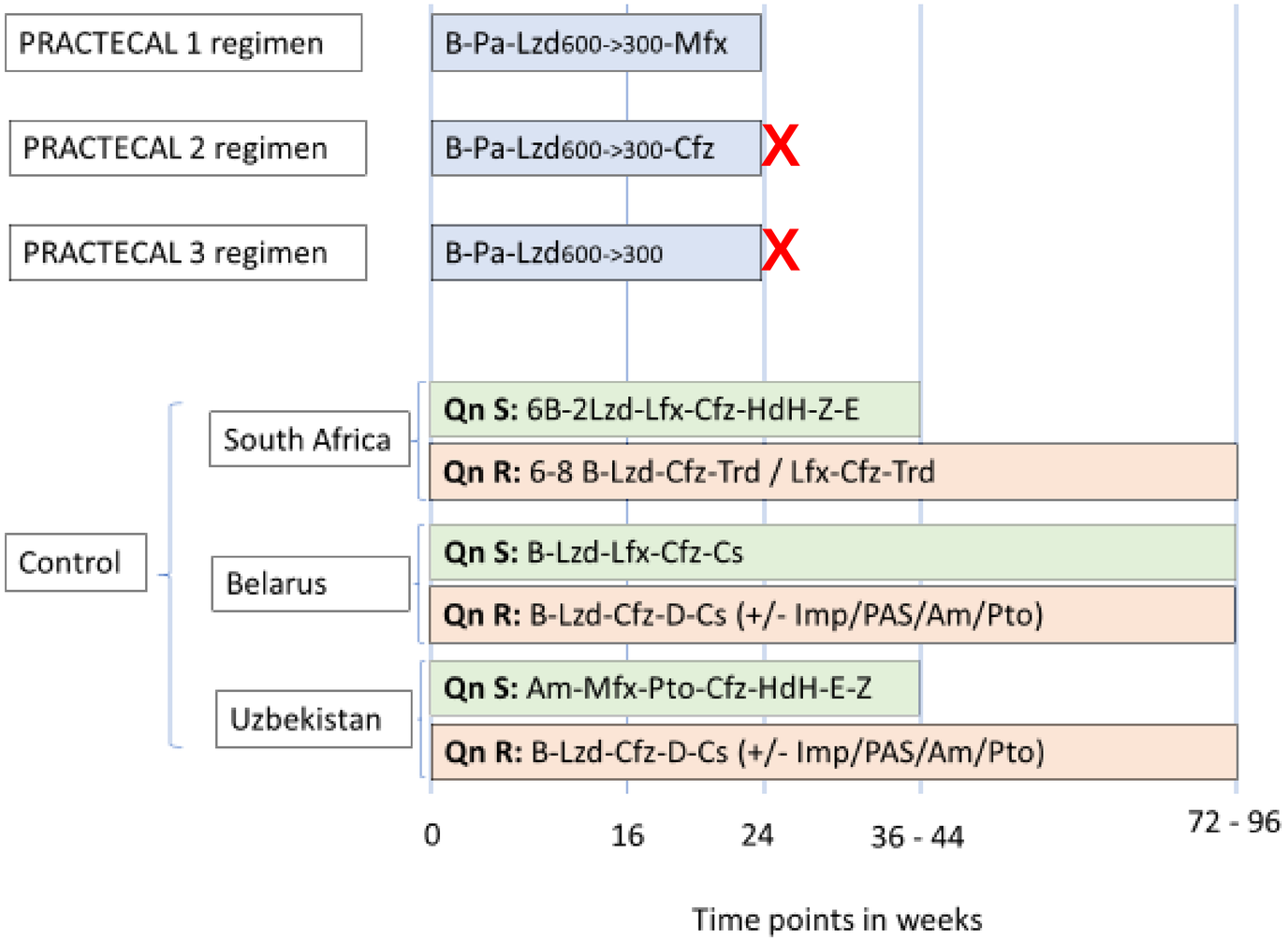
- Primary outcome: composite of death, treatment discontinuation, lost to follow up, treatment failure, recurrence or withdrawal
- 1 or 2 investigational arms compared against SOC
- Non-inferiority design
  - a delta of 12%
  - a conservative alpha of 1.7% (corresponding to 1-sided CI 98.3%)
  - 181 patients to give 85% power
  - Allowing for 10% non-assessable = 201 patients per arm

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

TB Practecal
Innovating MDR-TB

Stage 1 → 2 decision



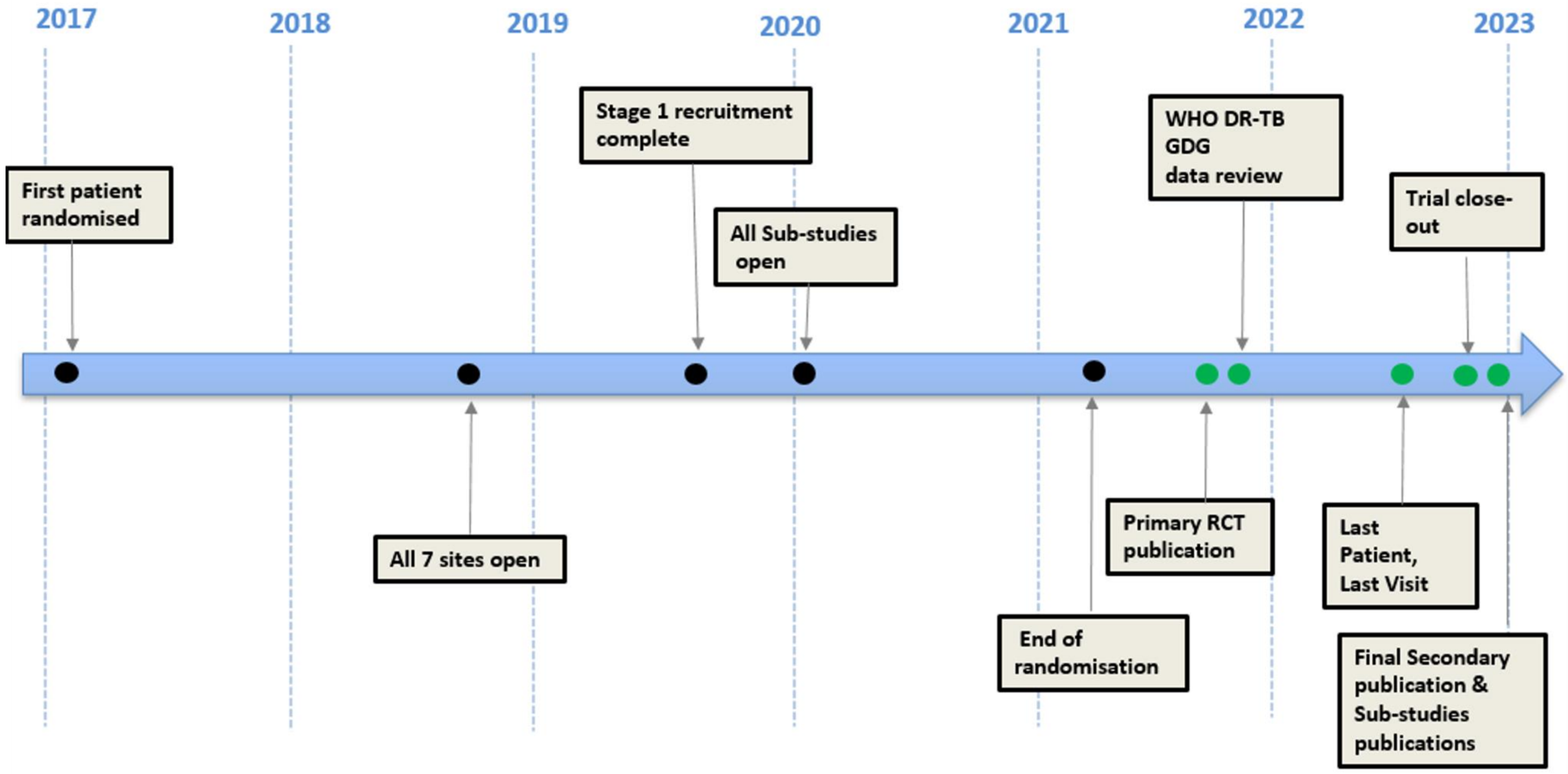
MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

TB Practecal
Innovating MDR-TB Treatment

Trial Milestones

TB Practecal
Innovating MDR-TB Treatment



MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

Data safety monitoring board (DSMB) review

- Review of safety and efficacy data February 2021.
  - data lock was 31 December 2020
- Data from:
  - 122 participants in the control arm
  - 120 in an experimental arm 1
  - with “late exclusions” removed from efficacy analyses.
- Data also provided for 229 participants in experimental arms 2 and 3, but these arms have been discontinued from enrollment in Stage 2 of the study.

DSMB Recommendation

- "Based on their review, the DSMB unanimously recommends termination of randomization of new participants in the trial.

- This recommendation is based primarily on guidance in the DSMB Charter that stopping might be considered if a difference between randomized arms of at least 3 standard deviations in the interim analysis of a major endpoint is achieved and the results have the potential to impact clinical practice."

TB Practecal
Innovating MDR-TB Treatment

DSMB Recommendation

- Specifically, the DSMB considers that this level of evidence was achieved favouring the experimental arm being evaluated in Stage 2 (PRACTECAL arm-1) versus the standard of care control arm for the primary outcome of percentage of study participants with an unfavourable outcome.

- The difference in the proportion of unfavourable outcomes was primarily driven by a higher rate of treatment discontinuations in the control arm.

Outcome	Arm 1	Control arm
Death	0	5
Recurrence	0	0
TB treatment failure	0	0

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

TB Practecal
Innovating MDR-TB Treatment

Outcomes/Conclusions

- On 18th March, 2021, recruitment was terminated, follow-up ongoing
- Completion of data checking, cleaning and update to provide to WHO
- TB-PRACTECAL regimen 1 and other 6-9 month regimens will be assessed by WHO in 2021 guidelines review
- MSF is currently developing guidance and collaborations to scale up the regimen

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS

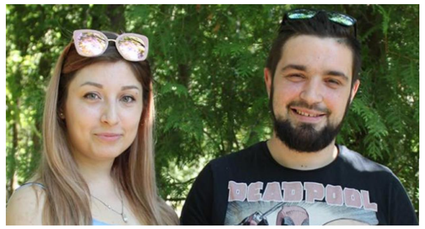
TB Practecal
Innovating MDR-TB Treatment

A Global Collaboration

- Médecins Sans Frontières
- Swiss Tropical & Public Health Institute
- London School of Hygiene and Tropical Medicine
- University College London
- Global Alliance for TB Drug Development
- Drugs for Neglected Diseases Initiative
- eResearch Technology, Inc.;
- Ministry of Health, Republic of Uzbekistan
- Ministry of Health, Belarus
- Republican Specialised Scientific Practical Medical Centre of Tuberculosis and Pulmonology (TBI)
- Republican Scientific and Practical Centre for Pulmonology and Tuberculosis (RSPCPT)
- TB & HIV Investigative Network (THINK)
- Clinical HIV Research Unit, Wits Health Consortium
- TDR, Special Programme for Research and Training in Tropical Diseases

With special acknowledgement of our participants

Questions?
TB-PRACTECAL@london.msf.org



MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

SCIENTIFIC DAYS