# *TRUNCATE-TB: A Treatment Strategy for Rifampicin-Susceptible Tuberculosis*

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Paton N, Cousins C, Suresh C et al. *N Engl J Med* 2023;388:873-87.

# Overview of talk

- Trial Rationale
- Trial design and implementation
- Results
- Summary and implications of findings

# Trial Rationale

# TRUNCATE-TB Rationale

- Current global standard treatment for DS-TB is 6m regimen (2RHZE/4RH)
- First established in 1980s
- 95% cure rate for DS-TB in trials
- Decreases to ≤ 85% under programme conditions (non-adherence, default)

# TRUNCATE-TB Rationale

**Table 1.11** Short-course chemotherapy studies of smear-negative pulmonary tuberculosis in Hong Kong. Patients with negative cultures or with drug-sensitive cultures initially.

| Study no. (date of start) | Initial culture results | Regimen | Duration (months) | Patients assessed for relapse | Relapse rate (%) follow-up for 2 years* | Relapse rate (%) follow-up for 5 years* | Reference |
|---|---|---|---|---|---|---|---|
| 1 (1976) | Negative | SC† | – | 176 | 53 (40) | 57 (41) | 212 |
| | | SHRZ | 2 | 165 | 7 (4) | 11 (6) | 213 |
| | | SHRZ | 3 | 162 | 4 (2) | 7 (3) | 214 |
| | | 3SPH/$S_2H_2$ | 12 | 160 | 1 (0) | 2 (1) | |
| | Positive | SHRZ | 2 | 72 | 22 (15) | 32 (23) | |
| | | SHRZ | 3 | 69 | 12 (9) | 13 (10) | |
| | | 3SPH/$S_2H_2$ | 12 | 78 | 1 (0) | 5 (1) | |
| 2 (1978) | Negative | SHRZ | 3 | 364 | 2 | 6 (3) | 215 |
| | | $S_3H_3R_3Z_3$ | 3 | 345 | 3 | 8 (3) | |
| | | $S_3H_3R_3Z_3$ | 4 | 325 | 2 | 4 (1) | |
| | Positive | SHRZ | 4 | 157 | 3 | 3 (3) | |
| | | $S_3H_3R_3Z_3$ | 4 | 136 | 1 | 2 (1) | |
| | | $S_3H_3R_3Z_3$ | 6 | 166 | 2 | 5 (2) | |

* Percentage bacteriologically confirmed in parentheses.
† Selective chemotherapy group. Treatment started when bacteriological or radiographic evidence of activity occurred during follow-up.

Fox Int J Tubercl Lung Dis 1999

Regimens of less than six months for treating tuberculosis (Review)

Gelband H

THE COCHRANE COLLABORATION®

- With standard 6m Rx we're over-treating the majority to prevent relapse in a minority

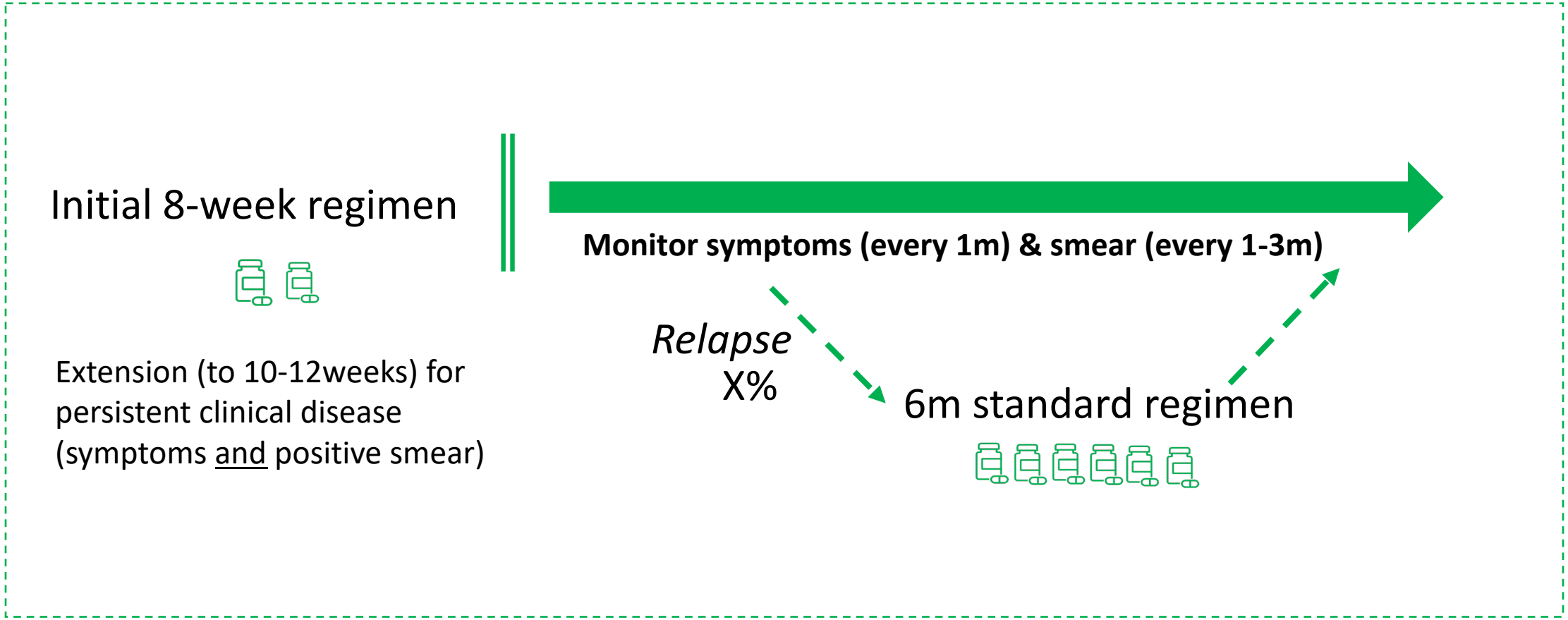
# TRUNCATE-TB Rationale

Overall outcomes may be as good (or better) in programme setting if:

- Treat everyone with a shorter duration needed for the majority
- Shift resources to ensure early detection and re-treatment of relapses in the minority

→ Potential advantages for people with tuberculosis and for programmes

# The TRUNCATE-TB Strategy



# Trial design and implementation

# TRUNCATE-TB Trial design

***Standard treatment (strategy)***

24w standard treatment

**Monitor symptoms & smear**

**vs**

***TRUNCATE strategy***

8w initial regimen

+/- Extension (to 10-12w) for persistent clinical disease

**Monitor symptoms & smear**

*Relapse* X%

6m Standard regimen

**Primary outcome:**
Unsatisfactory clinical outcome at **W96**
- Died or
- Active TB or
- On TB treatment

**Secondary outcomes:**

***Participant-centred:***
Total time on treatment, acceptability, motivation, QoL

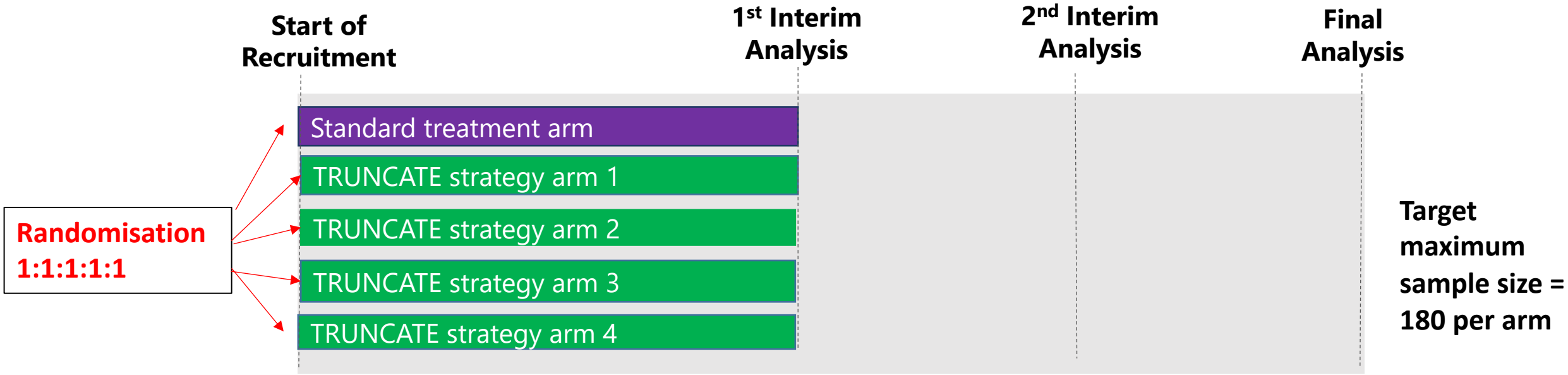
***Safety:***
Adverse events
Respiratory disability

***Programme-centred:***
Adherence, default, new drug resistance, estimated transmission risk

# *Trial Regimens*

| | | | | | | |
|---|---|---|---|---|---|---|
| **Standard Treatment** | 24w | Rifampicin 10mg/kg | Isoniazid | Pyrazinamide (first 8w) | Ethambutol (first 8w) | |
| TRUNCATE STRATEGY | | | | | | |
| **hRIF/LZD** | 8w | ↑ Rifampicin 35 mg/kg | Isoniazid | Pyrazinamide | Ethambutol | Linezolid 600mg |
| **hRIF/CFZ** | 8w | ↑ Rifampicin 35 mg/kg | Isoniazid | Pyrazinamide | Ethambutol | Clofazimine 200mg |
| **RPT/LZD** | 8w | Rifapentine 1200mg | Isoniazid | Pyrazinamide | Levofloxacin 1000mg | Linezolid 600mg |
| **BDQ/LZD** | 8w | Bedaquiline 400/200mg | Isoniazid | Pyrazinamide | Ethambutol | Linezolid 600mg |

# Multi-arm multi-stage design




**Stopping guidelines at interim analysis:**

High rate of early relapse (>20%)

Time to culture conversion worse than control (HR < 0.9)

Poor tolerability/toxicity

# Eligibility Criteria

**Selected inclusion criteria**

- Age 18 to 65 years
- Clinical symptoms consistent with pulmonary TB and/or evidence of pulmonary TB on CXR
- Sputum GeneXpert test positive

**Selected exclusion criteria**

- Presence of rifampicin resistance on Gene Xpert
- Previous active TB disease
- Extra-pulmonary TB
- Severe clinical PTB
- Sputum smear 3+ *
- Cavity size >4cm on screening CXR*
- HIV positive*
- Poorly-controlled diabetes
- Cardiac disease
- Severe chronic lung disease
- Peripheral neuropathy

*Removed/modified in stage 3 of trial

# Trial schedule

Telephone visits

| VISIT TIMING[1] | SCREENING | D0 | W1 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W36 | W48 | W60 | W72 | W84 | W96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Eligibility criteria | X | X | | | | | | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | | | | | | | |
| CLINICAL EVALUATION | | | | | | | | | | | | | | | | | | |
| Medical history & demographics | X | X | | | | | | | | | | | | | | | | |
| Symptoms | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication review and adherence | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HEALTHCARE UTILISATION & QOL | | | | | | | | | | | | | | | | | | |
| Healthcare utilisation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| EQ-5D | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| MOS-HIV | | X | | | | | | | | | | | | | | | | X |
| Patient acceptability questionnaire | | | | | | | | | | | | | | X | | | | X |
| Socioeconomic evaluation | | X | | | | | | | | | | | | | | | | X |
| INVESTIGATIONS | | | | | | | | | | | | | | | | | | |
| ECG[2] | X | X | X | | X | | X | | | | | | | | | | | |
| CXR[3] | X | X | | | | | X | | | | | | | | | | | X |
| Spirometry | | | | | | | X | | | | | | | X | | | | X |
| URINE | | | | | | | | | | | | | | | | | | |
| Pregnancy test | X | | | | X | | X | | | | | | | | | | | |
| Urine for storage[4] | | X | | | X | | X | | | | | X | | | | | | |
| SPUTUM | | | | | | | | | | | | | | | | | | |
| Smear[5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liquid culture[6] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| GeneXpert test[7] | X | | | | | | X | | | | | | | | | | | |
| Drug susceptibility tests[8] | | X | | | | | X | | | | | | | | | | | |
| BLOOD | | | | | | | | | | | | | | | | | | |
| Standard safety monitoring[9] | X | X | X | X[10] | X | X[10] | X | X[10] | | | | | | | | | | |
| HIV test[11] (and CD4 count)[12] | X | | | | | | | | | | | | | | | | | |
| Drug levels (PK)[13] | | X | | | X | | X | | | | | X | | | | | | |
| Plasma and RNA storage[14] | | X | | | X | | X | | | | | X | | | | | | |

Clinic visits 2 weekly

Clinic visits 4 weekly

Clinic visits 12 weekly + telephone visits monthly

# Trial schedule

Telephone visits

| VISIT TIMING[1] | SCREENING | D0 | W1 | W2 | W4 | W6 | W8 | W10 | W12 | W16 | W20 | W24 | W36 | W48 | W60 | W72 | W84 | W96 |
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| CLINICAL EVALUATION | | | | | | | | | | | | | | | | | | |
| Medical history & demographics | X | X | | | | | | | | | | | | | | | | |
| Symptoms | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication review and adherence | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HEALTHCARE UTILISATION & QOL | | | | | | | | | | | | | | | | | | |
| Healthcare utilisation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| EQ-5D | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| MOS-HIV | | X | | | | | | | | | | | | | | | | X |
| Patient acceptability questionnaire | | | | | | | | | | | | | | X | | | | X |
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| ECG[2] | X | X | X | | X | | X | | | | | | | | | | | |
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| Spirometry | | | | | | | X | | | | | | | X | | | | X |
| URINE | | | | | | | | | | | | | | | | | | |
| Pregnancy test | X | | | | X | | X | | | | | | | | | | | |
| Urine for storage[4] | | X | | | X | | X | | | | | X | | | | | | |
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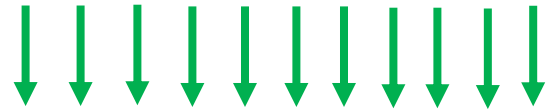
| Plasma and RNA storage[14] | | X | | | X | | X | | | | | X | | | | | | |

# Trial schedule

Telephone visits



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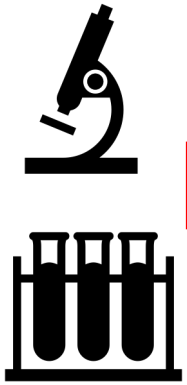

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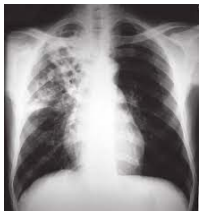

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| Eligibility criteria | X | X | | | | | | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | | | | | | | |
| CLINICAL EVALUATION | | | | | | | | | | | | | | | | | | |
| Medical history & demographics | X | X | | | | | | | | | | | | | | | | |
| Symptoms | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication review and adherence | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HEALTHCARE UTILISATION & QOL | | | | | | | | | | | | | | | | | | |
| Healthcare utilisation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
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| MOS-HIV | | X | | | | | | | | | | | | | | | | X |
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| Socioeconomic evaluation | | X | | | | | | | | | | | | | | | | X |
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| ECG[2] | X | X | X | | X | | X | | | | | | | | | | | |
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| Spirometry | | | | | | | X | | | | | | | X | | | | X |
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| Pregnancy test | X | | | | X | | X | | | | | | | | | | | |
| Urine for storage[4] | | X | | | X | | X | | | | | X | | | | | | |
| SPUTUM | | | | | | | | | | | | | | | | | | |
| Smear[5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liquid culture[6] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| GeneXpert test[7] | X | | | | | | X | | | | | | | | | | | |
| Drug susceptibility tests[8] | | X | | | | | X | | | | | | | | | | | |
| BLOOD | | | | | | | | | | | | | | | | | | |
| Standard safety monitoring[9] | X | X | X | X[10] | X | X[10] | X | X[10] | | | | | | | | | | |
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| Drug levels (PK)[13] | | X | | | X | | X | | | | | X | | | | | | |
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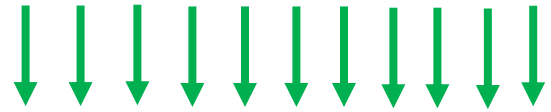

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Eligibility criteria | X | X | | | | | | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | | | | | | | |
| CLINICAL EVALUATION | | | | | | | | | | | | | | | | | | |
| Medical history & demographics | X | X | | | | | | | | | | | | | | | | |
| Symptoms | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication review and adherence | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HEALTHCARE UTILISATION & QOL | | | | | | | | | | | | | | | | | | |
| Healthcare utilisation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
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| Patient acceptability questionnaire | | | | | | | | | | | | | | X | | | | X |
| Socioeconomic evaluation | | X | | | | | | | | | | | | | | | | X |
| INVESTIGATIONS | | | | | | | | | | | | | | | | | | |
| ECG[2] | X | X | X | | X | | X | | | | | | | | | | | |
| CXR[3] | X | X | | | | | X | | | | | | | | | | | X |
| Spirometry | | | | | | | X | | | | | | | X | | | | X |
| URINE | | | | | | | | | | | | | | | | | | |
| Pregnancy test | X | | | | X | | X | | | | | | | | | | | |
| Urine for storage[4] | | X | | | X | | X | | | | | X | | | | | | |
| SPUTUM | | | | | | | | | | | | | | | | | | |
| Smear[5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liquid culture[6] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| GeneXpert test[7] | X | | | | | | X | | | | | | | | | | | |
| Drug susceptibility tests[8] | | X | | | | | X | | | | | | | | | | | |
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| Drug levels (PK)[13] | | X | | | X | | X | | | | | X | | | | | | |
| Plasma and RNA storage[14] | | X | | | X | | X | | | | | X | | | | | | |

# Analysis of the primary outcome

- Compare each complete (full sample size) TRUNCATE strategy arm with standard treatment arm on **% unsatisfactory outcome**
  - Death
  - Active TB disease at week 96
  - On treatment at week 96
- Estimate 97.5% confidence interval for the difference (multiplicity adjustment for 2 comparisons)
- Non-inferiority declared if limit of 97.5% CI is < 12%
- Main analysis done in an intention to treat population (excluded only those randomised in error)

# TRUNCATE-TB sites

18 trial sites, 5 countries

**INDONESIA**
21 Universitas Padjadjaran, Bandung
22 Universitas Hasanuddin, Makassar
23 Dr Soetomo Hospital, Surabaya
24 Universitas Indonesia, Jakarta
25 Dr Moewardi Hospital, Solo
26 Dr Saiful Anwar Hospital, Malang

**THAILAND**
31 King Chulalongkorn Memorial Hospital, Bangkok
32 Central Chest Institute of Thailand, Nonthaburi
33 Taksin Hospital, Bangkok

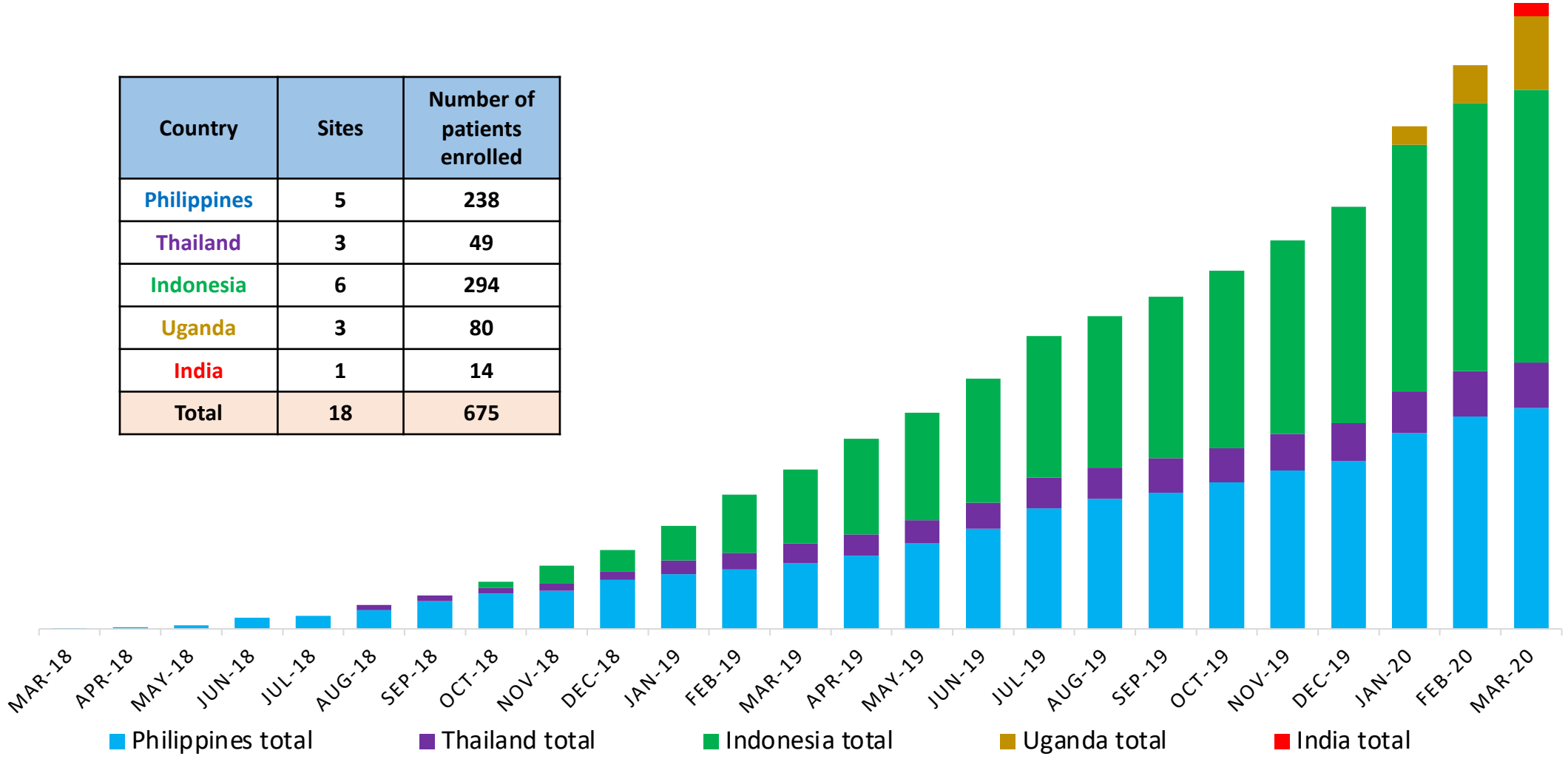
**PHILIPPINES**
41 Lung Center of Philippines, Quezon City
42 Quezon Institute, Quezon City
43 De La Salle Health Sciences Institute, Cavite
44 Perpetual Succour Hospital, Cebu
45 Tropical Disease Foundation, Makati City

**INDIA**
61 NITRD, New Delhi

**UGANDA**
71 Infectious Diseases Institute, Kampala
72 Joint Clinical Research Centre, Lubowa
73 Joint Clinical Research Centre, Mbrara


# Trial Recruitment

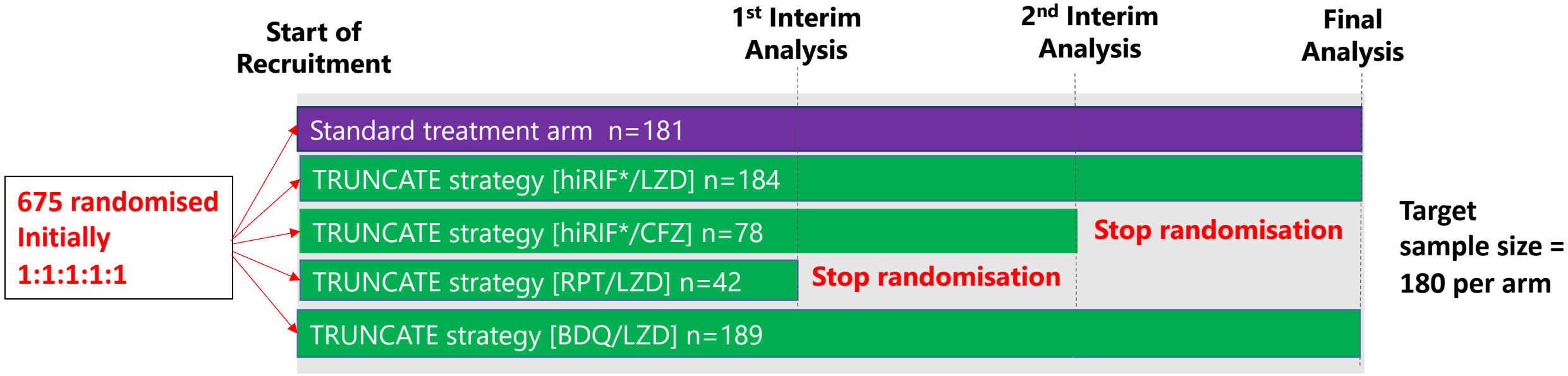
| Country | Sites | Number of patients enrolled |
|---|---|---|
| Philippines | 5 | 238 |
| Thailand | 3 | 49 |
| Indonesia | 6 | 294 |
| Uganda | 3 | 80 |
| India | 1 | 14 |
| Total | 18 | 675 |




…Last patient last visit 20Jan2022

# Results

# Recruitment to arms – adaptive changes




**IDMC Stopping guidelines at interim analyses:**

High rate of early relapse (>20%)

Time to culture conversion worse than control (HR < 0.9)

Poor tolerability/toxicity

**TSC Stopping decisions:**

TRUNCATE strategy [RPT/LZD]: high pill burden and new regulatory guidance on quinolone toxicity

TRUNCATE strategy [hRIF/CFZ]: regulator refused to allow CFZ importation

*hRIF dose decreased from 35mg/kg (first 88 enrolled) to 20mg/kg (subsequent 96 enrolled) in the hiRIF/LZD arm following drug induced liver injury event

# Retention in trial

- Screened: 1179
  - 504 excluded (170 negative GeneXpert, 334 other reasons)
- Randomised in trial: 675
  - Randomised in error and immediately withdrawn: 1
- Intention to treat population: 674
  - Lost to follow-up or withdrawal: 4 (0.6%)
  - Died before week 96: 10 (1.5%)
- Alive and under follow-up at W96: 660
  - Evaluated at W96: 660
  - 643 (97%) in person
  - 17 (3%) by telephone

# Baseline characteristics (1)

| Characteristic | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | TRUNCATE strategy (hRIF/CFZ) (N=78) | TRUNCATE strategy (RPT/LZD) (N=42) | TRUNCATE strategy (BDQ/LZD) (N=189) | Overall (N=674) |
|---|---|---|---|---|---|---|
| Male sex – no. (%) | 66% | 61% | 62% | 60% | 61% | 62% |
| | | | | | | |
| Age group – no. (%) | | | | | | |
| <35 yr | 57% | 59% | 65% | 62% | 50% | 57% |
| 35-50 yr | 33% | 31% | 27% | 26% | 37% | 32% |
| ≥50 – 65 yr | 10% | 10% | 8% | 12% | 13% | 11% |
| | | | | | | |
| Country – no. (%) | | | | | | |
| Indonesia | 43% | 40% | 49% | 55% | 43% | 44% |
| Philippines | 34% | 36% | 41% | 36% | 33% | 35% |
| Thailand | 6% | 8% | 10% | 10% | 6% | 7% |
| Uganda † | 15% | 14% | 0 | 0 | 14% | 12% |
| India † | 2% | 3% | 0 | 0 | 3% | 2% |
| | | | | | | |
| Median BMI (range) -kg/$m^2$ | 19 (14-29) | 19 (14-33) | 19 (14-29) | 18 (12-25) | 19 (13-30) | 19 (12-33) |

# Baseline characteristics (2)

| Characteristic | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | TRUNCATE strategy (hRIF/CFZ) (N=78) | TRUNCATE strategy (RPT/LZD) (N=42) | TRUNCATE strategy (BDQ/LZD) (N=189) | Overall (N=674) |
|---|---|---|---|---|---|---|
| CXR cavitation present | 52% | 55% | 47% | 55% | 56% | 54% |
| CXR proportion lung affected | | | | | | |
| <25% | 25% | 34% | 36% | 29% | 28% | 30% |
| 25-50% | 52% | 47% | 46% | 57% | 52% | 50% |
| >50% | 23% | 19% | 18% | 14% | 20% | 20% |
| | | | | | | |
| WHO smear grade | | | | | | |
| Negative | 26% | 31% | 33% | 29% | 26% | 28% |
| Scanty | 15% | 15% | 15% | 17% | 13% | 15% |
| 1+ | 21% | 26% | 32% | 32% | 28% | 26% |
| 2+ | 24% | 20% | 10% | 17% | 20% | 20% |
| 3+ | 14% | 8% | 9% | 5% | 13% | 11% |
| | | | | | | |
| Xpert MTB/RIF result | | | | | | |
| Very low | 14% | 13% | 11% | 8% | 9% | 12% |
| Low | 23% | 28% | 30% | 30% | 28% | 27% |
| Medium | 42% | 46% | 42% | 40% | 40% | 42% |
| High | 21% | 13% | 17% | 22% | 23% | 19% |

# TB treatment - initial

## Standard treatment arm

- 98% completed initial 24-week treatment
- 2% did not complete initial treatment (defaulted or died)

## TRUNCATE strategy arms (overall)

- 91.5% completed initial ultra-short treatment (mean 58 days)
  - 56 days in 80%
  - 57-70 days in 9%
  - 71 -84 days in 3%
- 6% switched
  - 1% switched to standard treatment after W12
  - 5% switched to standard treatment before completing initial 8-week treatment
- 2% did not complete initial treatment (defaulted, withdrew or died)

# TB treatment - re-treatment

## Standard treatment arm

- 3% had re-treatment

## TRUNCATE strategy arms (overall)

- 17% had re-treatment
  - 23% hRIF/LZD
  - 13% in hRIF/CFZ
  - 19% in RPT/LZD
  - 13% in BDQ/LZD

# Primary efficacy outcome, ITT population: TRUNCATE strategy (hRIF/LZD) arm

| Outcome | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | Adjusted difference (97.5% CI) |
|---|---|---|---|
| **Unsatisfactory outcome – no. (%)** | **7 (3.9)** | **21 (11.4)** | **7.2 (1.7 –13.2)** |
| On tuberculosis treatment at W96 | 2 (1.1) | 8 (4.3) | - |
| Tuberculosis disease activity at W96 | 1 (0.6) | 4 (2.2) | - |
| Death before W96 | 2 (1.1) | 5 (2.7) | - |
| Telephone evaluation W96 – insufficient evidence of disease clearance when last seen | 2 (1.1) | 3 (1.6) | - |
| No evaluation W96 - insufficient evidence of disease clearance when last seen | 0 | 1 (0.5) | - |
| **Participants with unassessable outcome – no. (%)** | **1 (0.6)** | **1 (0.5)** | **-** |
| Single positive culture at W96 | 0 | 1 (0.5) | - |
| Death (not related to tuberculosis) | 1 (0.6) | 0 | - |
| No evaluation W96 – evidence of disease clearance when last seen | 0 | 0 | - |
| **Participants with satisfactory outcome – no. (%)** | **173 (95.6)** | **162 (88.0)** | **-** |

# Primary efficacy outcome, sensitivity analyses: TRUNCATE strategy (hRIF/LZD) arm

| **Unsatisfactory outcome – no (%)** | **Standard treatment (N= 181)** | **TRUNCATE strategy (hiRIF/LZD) (N=184)** | **Adjusted difference (97.5% CI)** |
|---|---|---|---|
| ITT population | 7 (3.9) | 21 (11.4) | 7.2 (1.7 –13.2) |
| Assessable population | 7/180 (3.9) | 21/183 (11.5) | 7.5 (1.7 to 13.2) |
| Per-protocol population | 6/177 (3.4) | 17/160 (10.6) | 6.9 (0.9 to 12.8) |

# Primary efficacy outcome, ITT population: TRUNCATE strategy (BDQ/LZD) arm

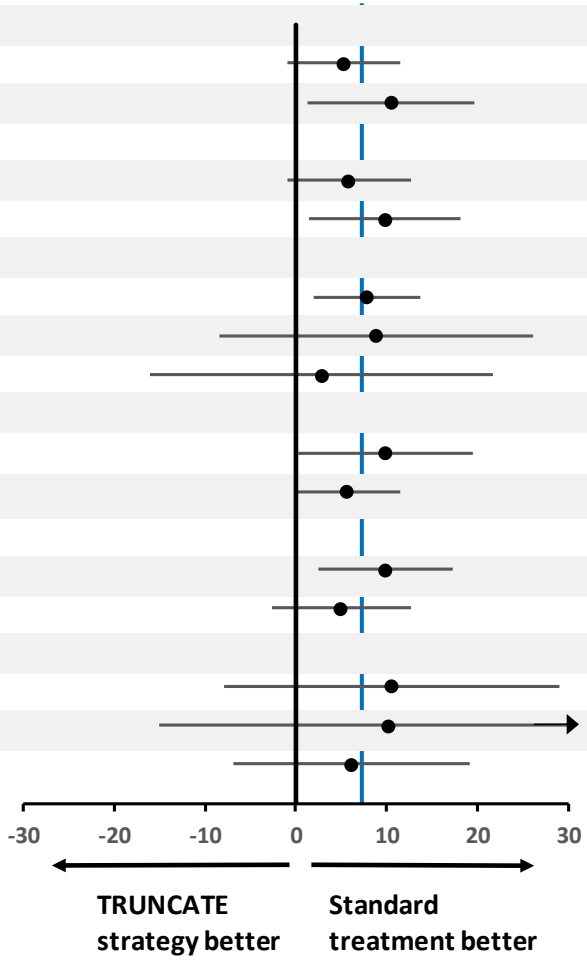
| Outcome | Standard treatment (N= 181) | TRUNCATE strategy (BDQ/LZD) (N=189) | Adjusted difference (97.5% CI) |
|---|---|---|---|
| **Unsatisfactory outcome – no. (%)** | **7 (3.9)** | **11 (5.8)** | **0.8 (-3.4 to 5.1)** |
| On tuberculosis treatment at W96 | 2 (1.1) | 5 (2.6) | - |
| Tuberculosis disease activity at W96 | 1 (0.6) | 3 (1.6) | - |
| Death before W96 | 2 (1.1) | 1 (0.5) | - |
| Telephone evaluation W96 – insufficient evidence of disease clearance when last seen | 2 (1.1) | 1 (0.5) | - |
| No evaluation W96 - insufficient evidence of disease clearance when last seen | 0 | 1 (0.5) | - |
| **Participants with unassessable outcome – no. (%)** | **1 (0.6)** | **2 (1.1)** | - |
| Single positive culture at W96 | 0 | 0 | - |
| Death (not related to tuberculosis) | 1 (0.6) | 0 | - |
| No evaluation W96 – evidence of disease clearance when last seen | 0 | 2 (1.1) | - |
| **Participants with satisfactory outcome – no. (%)** | **173 (95.6)** | **176 (93.1)** | - |

# Primary efficacy outcome, sensitivity analyses: TRUNCATE strategy (BDQ/LZD) arm

| **Unsatisfactory outcome – no (%)** | **Standard treatment (N= 181)** | **TRUNCATE strategy (BDQ/LZD) (N=189)** | **Adjusted difference (97.5% CI)** |
|---|---|---|---|
| ITT population | 7 (3.9) | 11 (5.8) | 0.8 (-3.4 to 5.1) |
| Assessable population | 7/180 (3.9) | 11/187 (5.9) | 0.8 (-3.4 to 5.1) |
| Per-protocol population | 6/177 (3.4) | 9/176 (5.1) | 0.9 (-3.3 to 5.1) |

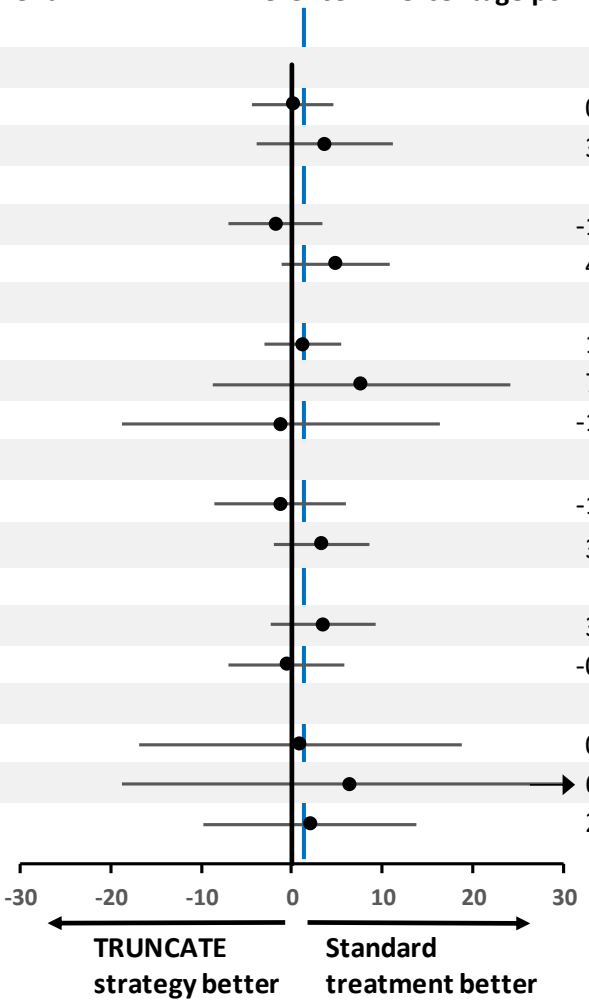
# Subgroup analysis: TRUNCATE strategy (hRIF/LZD) arm

| Subgroup | TRUNCATE strategy | Standard treatment | Difference in Percentage points (95% CI) |
|---|---|---|---|
| | No of patients/total no. (%) | | |
| Sex | | | |
| Male | 11/113 (9.7) | 5/119 (4.2) | 5.3 (-0.9 to 11.5) |
| Female | 10/71 (14.1) | 2/62 (3.2) | 10.5 (1.4 to 19.7) |
| Age | | | |
| <35 years | 11/109 (10.1) | 5/104 (4.8) | 5.8 (-1.0 to 12.7) |
| ≥35-65 years | 10/75 (13.3) | 2/77 (2.6) | 9.9 (1.6 to 18.2) |
| Country | | | |
| Indonesia or Philippines | 15/139 (10.8) | 4/139 (2.9) | 7.9 (2.1 to 13.8) |
| Uganda | 4/25 (16) | 2/28 (7.1) | 8.9 (-8.4 to 26.1) |
| India or Thailand | 2/20 (10) | 1/14 (7.1) | 2.9 (-16.0 to 21.7) |
| Body Mass Index | | | |
| <18.5 kg/$m^2$ | 13/80 (16.3) | 5/79 (6.3) | 10.0 (0.4 to 19.6) |
| ≥18.5 kg/$m^2$ | 8/104 (7.7) | 2/102 (2) | 5.7 (-0.0 to 11.4) |
| CXR | | | |
| No Cavitation | 10/83 (12) | 1/87 (1.1) | 9.9 (2.6 to 17.3) |
| Cavitation | 11/101 (10.9) | 6/94 (6.4) | 5.0 (-2.7 to 12.7) |
| WHO smear grade | | | |
| Negative | 7/57 (12.3) | 1/46 (2.2) | 10.6 (-8.0 to 29.1) |
| Scanty or 1+ | 7/76 (9.2) | 0/65 (0) | 10.3 (-15.0 to 35.6) |
| 2+ or 3+ | 7/51 (13.7) | 5/69 (7.2) | 6.1 (-6.8 to 19.1) |



# Subgroup analysis: TRUNCATE strategy (BDQ/LZD) arm

| Subgroup | TRUNCATE strategy | Standard treatment | Difference in Percentage points (95% CI) |
|---|---|---|---|
| | No of patients/total no. (%) | | |
| Sex | | | |
| Male | 5/116 (4.3) | 5/119 (4.2) | 0.1 (-4.4 to 4.6) |
| Female | 6/73 (8.2) | 2/62 (3.2) | 3.6 (-3.9 to 11.2) |
| Age | | | |
| <35 years | 4/95 (4.2) | 5/104 (4.8) | -1.8 (-7.0 to 3.4) |
| ≥35-65 years | 7/94 (7.4) | 2/77 (2.6) | 4.8 (-1.1 to 10.7) |
| Country | | | |
| Indonesia or Philippines | 6/145 (4.1) | 4/139 (2.9) | 1.3 (-3.0 to 5.5) |
| Uganda | 4/27 (14.8) | 2/28 (7.1) | 7.7 (-8.8 to 24.1) |
| India or Thailand | 1/17 (5.9) | 1/14 (7.1) | -1.3 (-18.8 to 16.3) |
| Body Mass Index | | | |
| <18.5 kg/$m^2$ | 4/76 (5.3) | 5/79 (6.3) | -1.3 (-8.5 to 6.0) |
| ≥18.5 kg/$m^2$ | 7/113 (6.2) | 2/102 (2) | 3.3 (-2.0 to 8.6) |
| CXR | | | |
| No Cavitation | 5/81 (6.2) | 1/87 (1.1) | 3.4 (-2.4 to 9.2) |
| Cavitation | 6/108 (5.6) | 6/94 (6.4) | -0.6 (-7.0 to 5.9) |
| WHO smear grade | | | |
| Negative | 1/50 (2) | 1/46 (2.2) | 0.9 (-16.8 to 18.7) |
| Scanty or 1+ | 4/77 (5.2) | 0/65 (0) | 6.4 (-18.7 to 31.6) |
| 2+ or 3+ | 6/62 (9.7) | 5/69 (7.2) | 2.0 (-9.8 to 13.8) |



# Participant-centred secondary outcomes

| | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | TRUNCATE strategy (BDQ/LZD) (N=189) |
|---|---|---|---|
| Total treatment days to week 96 | 180.2 ± 37.9 | 105.7 ± 80.1 | 84.8 ± 65.3 |
| Quality of life (MOS-HIV) | | | |
| Mental health summary score | 57.5 ± 0.5 | 57.5 ± 0.5 | 57.8 ± 0.5 |
| Physical health summary score | 56.7 ± 0.5 | 56.8 ± 0.5 | 56.7 ± 5.6 |
| Illness-related missed work or study – days | 2.6 ± 9.1 | 3.3 ± 9.4 | 3.1 ± 12.9 |
| Body weight | | | |
| Change from baseline – kg | 5.8 ± 4.8 | 5.6 ± 4.7 | 6.1 ± 4.8 |
| Change from baseline - % | 11.9 ± 10.0 | 11.4 ± 9.8 | 12.1 ± 9.8 |

# Participant acceptability

| | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | TRUNCATE strategy (BDQ/LZD) (N=189) |
|---|---|---|---|
| **Motivation** | | | |
| Motivation score | 6.2 ± 3.9 | 8.0 ± 3.0 | 8.1 ± 2.9 |
| **Recommendation to others** | | | |
| 2-month treatment (%) | NA | 72% | 78% |
| 6-month treatment (%) | NA | 29% | 14% |
| No preference (%) | NA | 9% | 8% |

# Safety outcomes

| | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | P value | TRUNCATE strategy (BDQ/LZD) (N=189) | P value |
|---|---|---|---|---|---|
| Any grade 3 or 4 adverse event – no. (%) | 29 (16.0) | 32 (17.4) | 0.664 | 30 (15.9) | 0.666 |
| Any serious adverse event – no. (%) | 11 (6.1) | 18 (9.8) | 0.168 | 14 (7.4) | 0.530 |
| Death no. (%) | 3 (1.7) | 5 (2.7) | 0.724 | 1 (0.5) | 0.362 |
| | | | | | |
| Respiratory disability at W96 | | | | | |
| MRC breathlessness scale ≥ 3 – no. (%) | 0 | 2.7 (1.5) | 0.122 | 2.7 (1.4) | 0.499 |
| FEV1 < 50% of Predicted value | 24.3 (13.4) | 20.5 (11.1) | 0.597 | 22.4 (11.8) | 0.378 |

# Safety outcomes

| | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | P value | TRUNCATE strategy (BDQ/LZD) (N=189) | P value |
|---|---|---|---|---|---|
| Any grade 3 or 4 adverse event – no. (%) | 29 (16.0) | 32 (17.4) | 0.664 | 30 (15.9) | 0.666 |
| Any serious adverse event – no. (%) | 11 (6.1) | 18 (9.8) | 0.168 | 14 (7.4) | 0.530 |
| Death no. (%) | 3 (1.7) | 5 (2.7) | 0.724 | 1 (0.5) | 0.362 |
| | | | | | |
| Respiratory disability at W96 | | | | | |
| MRC breathlessness scale ≥ 3 – no. (%) | 0 | 2.7 (1.5) | 0.122 | 2.7 (1.4) | 0.499 |
| FEV1 < 50% of Predicted value | 24.3 (13.4) | 20.5 (11.1) | 0.597 | 22.4 (11.8) | 0.378 |

# Programme-centred secondary outcomes

| | Standard treatment (N= 181) | TRUNCATE strategy (hRIF/LZD) (N=184) | TRUNCATE strategy (BDQ/LZD) (N=189) |
|---|---|---|---|
| Treatment adherence | | | |
| Adherence over first 56 days - % | 98.8 ± 5.5 | 95.9 ± 10.0 | 98.4 ± 6.6 |
| Default within first 56 days – no. (%) | 1 (0.6) | 3 (1.6) | 1 (0.5) |
| | | | |
| Relapse-associated transmission risk | | | |
| Transmission risk period – days | 0.5 ± 4.3 | 2.4 ± 8.3 | 3.2 ± 14.1 |
| New exposed household contacts – no. | 0.01 ± 0.15 | 0.01 ± 0.10 | 0.06 ± 0.4 |
| | | | |
| Acquired drug resistance - no. (%) | 0 | 0 | 2 (1.1) |

# Programme-centred secondary outcomes

| | **Standard treatment (N= 181)** | **TRUNCATE strategy (hRIF/LZD) (N=184)** | **TRUNCATE strategy (BDQ/LZD) (N=189)** |
|---|---|---|---|
| Treatment adherence | | | |
| Adherence over first 56 days - % | 98.8 ± 5.5 | 95.9 ± 10.0 | 98.4 ± 6.6 |
| Default within first 56 days – no. (%) | 1 (0.6) | 3 (1.6) | 1 (0.5) |
| | | | |
| Relapse-associated transmission risk | | | |
| Transmission risk period – days | 0.5 ± 4.3 | 2.4 ± 8.3 | 3.2 ± 14.1 |
| New exposed household contacts – no. | 0.01 ± 0.15 | 0.01 ± 0.10 | 0.06 ± 0.4 |
| | | | |
| Acquired drug resistance - no. (%) | 0 | 0 | 2 (1.1) |

# Acquired drug resistance

**Participant 1**

- Baseline INH resistance
- Missed 14 days (12 consecutive) of all drugs during the first 4 weeks
- Relapsed at W52 with new phenotypic resistance to BDQ (and CFZ) [with compatible mutations]
- Retreatment with standard treatment (with quinolone added) was successful.

**Participant 2**

- No baseline drug resistance
- Adherent to initial 8-week treatment
- Relapsed at W36 with new phenotypic resistance to BDQ (and CFZ) [with compatible mutations]
- Retreatment with standard treatment was successful.

No acquired drug resistance in the other TRUNCATE strategy or standard treatment arm

# Summary

## The TRUNCATE strategy was:

- ✓ **Non-inferior** to standard treatment on clinical outcome at week 96 (with initial BDQ/LZD, but not with initial hRIF/LZD) - consistent in subgroup analyses
- ✓ **Safe** – no excess severe/serious AEs, death, respiratory disability
- ✓ Resulted in **substantial reduction in overall days** on treatment
- ✓ Had **low risk of drug resistance** (only with BDQ regimen)

# Implications of the findings

- Alternatives to over-treating the large majority of people with TB can be successful
- Important new research direction, with the promise to improve outcomes for patients and programmes

# Further work

- **Ongoing analyses from the TRUNCATE-TB trial will further enhance our understanding:**
  - Strategy implementation and health economics
  - Safety, efficacy and PK-PD of the regimens tested
  - Analysis of biomarkers (standard and new)

- **TRUNCATE strategy may be refined in future to improve outcomes using:**
  - Alternative drug regimens (short duration, well tolerated)
  - Alternative monitoring approaches (biomarkers to decide Rx cessation; or improve relapse detection)

- **Need implementation studies of TRUNCATE strategy in broader populations (especially including HIV+)**

# Acknowledgements

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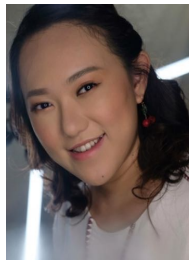

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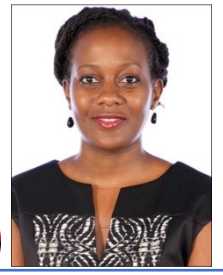
TRUNCATE TB



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