Shorter Treatment for Minimal Tuberculosis in Children: Main Findings from the SHINE Trial

A phase III randomised open trial comparing 4 vs 6 months treatment in children (+/- HIV) with smear-negative non-severe TB in Africa and India

Dr. Priyanka Raichur & Dr Aarti Kinikar on behalf of the SHINE trial team

Annual meeting of the Child and Adolescent TB working group
October 16, 2020
Estimated 1.1 million children <15 years develop tuberculosis (TB) annually\(^1\)

Two-thirds have non-severe TB which is paucibacillary and may benefit from shorter treatment\(^2,3\)

A meta-analysis of treatment duration trials in adults suggests 4-month drug regimens are efficacious in adults with paucibacillary TB who had <2+ sputum smear grade or non-cavitary disease \(^4\)

SHINE Trial is the first Phase III paediatric RCT to evaluate whether the standard 6 months of treatment can be reduced to 4 months in children with smear-negative non-severe (minimal) TB

1. WHO. Global tuberculosis report 2019
3. Wiseman CA et al. PIDJ 2012
4. Imperial MZ et al. Nat Med 2018
TRIAL DESIGN

Children aged <16 years with minimal TB (n=1200)

Randomisation (1:1)

6 month (n=600)
- Intensive phase: 8 weeks
- Continuation phase: 16 weeks

4 month (n=600)
- Intensive phase: 8 weeks
- Continuation phase: 8 weeks

72 weeks follow-up for primary outcome assessment

Nested PK substudies undertaken in selected centres

All anti-TB drugs prescribed as per WHO 2010 dosing guidelines using new weight bands
PARTICIPATING SITES

Clinical sites:
Kampala, Uganda
Lusaka, Zambia
Cape Town, South Africa
Pune, India
Chennai, India

PK substudies:
UCT, Cape Town, SA
Nijmegen, Netherlands
Chennai, India

Coordination:
MRC CTU at UCL, London, UK
TRIAL POPULATION

Main inclusion criteria:

- Age 0-16 years, weight ≥ 3kg
- No known drug resistance
- Clinical decision to treat with 1st line Rx
- Symptomatic but non-severe TB
- Smear-negative on respiratory samples
  - GeneXpert positive allowed
- Not treated for TB in previous 2 years
- Known HIV infection status

Non-severe TB
- extrathoracic lymph node TB
- intrathoracic lymph node TB with no significant airway obstruction
- uncomplicated forms of pulmonary TB, confined to one lobe and with no cavities
PRIMARY ENDPOINTS

Primary efficacy outcome:

Unfavourable outcomes

- TB treatment failure
- TB recurrence
- Death of any cause by 72 weeks
- On-treatment loss-to-follow-up

Primary Safety outcome:

Grade 3-5 adverse events on treatment (plus 30 days)
Analysis populations

**Modified ITT (mITT) = All excluding:**
- Late screening failures
- Did not reach week 16
- Completed treatment, well, lost before week 72
ANALYSIS POPULATIONS AND SAMPLE SIZE ASSUMPTIONS

Analysis populations

**Modified ITT (mITT) = All excluding:**
- Late screening failures
- Did not reach week 16
- Completed treatment, well, lost before week 72

**Per-Protocol (PP) = mITT excluding:**
- Non-adherent to allocated treatment, “80-120%” rule

**Intent-to-treat (ITT) = All randomised**
ANALYSIS POPULATIONS AND SAMPLE SIZE ASSUMPTIONS

Analysis populations

Modified ITT (mITT) = All excluding:
  o Late screening failures
  o Did not reach week 16
  o Completed treatment, well, lost before week 72

Per-Protocol (PP) = mITT excluding:
  o Non-adherent to allocated treatment, “80-120%” rule

Intent-to-treat (ITT) = All randomised

Trial powered on
Key secondary analysis
Adjudicated to have TB at baseline, assumed 80% of all children
Analysis populations

**Modified ITT (mITT) = All excluding:**
- Late screening failures
- Did not reach week 16
- Completed treatment, well, lost before week 72

**Per-Protocol (PP) = mITT excluding:**
- Non-adherent to allocated treatment, “80-120%” rule

**Intent-to-treat (ITT) = All randomised**

Trial powered on
Key secondary analysis
Adjudicated to have TB at baseline, assumed 80% of all children

Sample size
6% non-inferiority margin
8% events in control arm
90% power, 5% 2-sided
RESULTS
CONSORT DIAGRAM

1461

Screened

1204

Randomised

602

4 Month

30

602

ITT

572

9

573

6 Month

29

558

PP

257 screen failures:
Not minimal TB
Smear positive on respiratory samples
Too sick
No consent
Would not adhere
Drug resistance

Late screening failures
Did not reach week 16
Loss to FU (but well after treatment)

Did not adhere to allocated trial treatment

PRIMARY ANALYSIS
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>4 Months N=602</th>
<th>6 Months N=602</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median, range</strong></td>
<td>3.4 (2 months, 15 years)</td>
<td>3.5 (2 months, 15 years)</td>
</tr>
<tr>
<td><strong>Sex, n(%) female</strong></td>
<td>297 (49)</td>
<td>286 (48)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>460 (76)</td>
<td>460 (76)</td>
</tr>
<tr>
<td>Indian</td>
<td>75 (12)</td>
<td>74 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>67 (11)</td>
<td>68 (11)</td>
</tr>
<tr>
<td><strong>HIV status, n (%) positive</strong></td>
<td>65 (11)</td>
<td>62 (10)</td>
</tr>
<tr>
<td><strong>Weight-for-age Z score, median, IQR</strong></td>
<td>-1.20 (-2.12,-0.29)</td>
<td>-1.12 (-2.10,-0.37)</td>
</tr>
<tr>
<td><strong>TB Symptoms, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough &gt; 2 weeks</td>
<td>370 (61)</td>
<td>373 (62)</td>
</tr>
<tr>
<td>Fever</td>
<td>308 (51)</td>
<td>306 (51)</td>
</tr>
<tr>
<td>Poor feeding/appetite</td>
<td>311 (52)</td>
<td>311 (52)</td>
</tr>
<tr>
<td><strong>Local chest X-ray, n (%) Abnormal</strong></td>
<td>563 (94)</td>
<td>559 (93)</td>
</tr>
<tr>
<td>Typical of TB</td>
<td>340 (60)</td>
<td>368 (66)</td>
</tr>
<tr>
<td><strong>Microbiologically confirmed TB, n(%)</strong></td>
<td>85 (14)</td>
<td>80 (13)</td>
</tr>
</tbody>
</table>
ADHERENCE TO RANDOMISED DURATION AND RETENTION

94% of participants adhered to their allocated randomised duration (similar in both arms)

95% retention at week 72 across both arms
# PRIMARY EFFICACY

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>N</th>
<th>Risk Difference</th>
<th>4 months</th>
<th>6 months</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>1145</td>
<td></td>
<td>16 (3)</td>
<td>18 (3)</td>
<td>-0.3 (-2.3 to 1.6)</td>
</tr>
<tr>
<td>PP</td>
<td>1121</td>
<td></td>
<td>14 (2)</td>
<td>17 (3)</td>
<td>-0.6 (-2.6 to 1.4)</td>
</tr>
<tr>
<td>ITT</td>
<td>1204</td>
<td></td>
<td>44 (7)</td>
<td>44 (7)</td>
<td>0 (-2.9 to 2.9)</td>
</tr>
</tbody>
</table>
PRIMARY EFFICACY

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>N</th>
<th>Risk Difference</th>
<th>4 months</th>
<th>6 months</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>1145</td>
<td>-0.3 (-2.3 to 1.6)</td>
<td>16 (3)</td>
<td>18 (3)</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>1121</td>
<td>-0.6 (-2.5 to 1.4)</td>
<td>14 (2)</td>
<td>17 (3)</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>1204</td>
<td>0 (-2.9 to 2.9)</td>
<td>44 (7)</td>
<td>44 (7)</td>
<td></td>
</tr>
</tbody>
</table>
## PRIMARY EFFICACY

Endpoint Review Committee (ERC) adjudication of TB at baseline

~ 80% of children (as assumed in sample size) – similar in both arms
### PRIMARY EFFICACY

#### 34 unfavourable outcomes (mITT):

<table>
<thead>
<tr>
<th>Outcome</th>
<th>4 Month N=16</th>
<th>6 Month N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause (after week 16)</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>LTFU during treatment (after week 16)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TB recurrence</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Treatment extension (treatment failure)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Restart/change of treatment (treatment failure)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N</th>
<th>4 months</th>
<th>6 months</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>1145</td>
<td>16 (3)</td>
<td>18 (3)</td>
<td>-0.3 (-2.3 to 1.6)</td>
</tr>
<tr>
<td>PP</td>
<td>1121</td>
<td>14 (2)</td>
<td>17 (3)</td>
<td>-0.6 (-2.6 to 1.4)</td>
</tr>
<tr>
<td>ITT</td>
<td>1204</td>
<td>44 (7)</td>
<td>44 (7)</td>
<td>0 (-2.9 to 2.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>910</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>895</td>
<td></td>
</tr>
</tbody>
</table>

---

**<---4 Months better----  ----6 Months better--->**
## PRIMARY SAFETY ON-TREATMENT ADVERSE EVENTS GRADE ≥3

<table>
<thead>
<tr>
<th></th>
<th>4 Months N=602</th>
<th>6 Months N=602</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of ≥ Grade 3 AEs</strong></td>
<td>49</td>
<td>66</td>
</tr>
<tr>
<td><strong>Children with at least 1 AE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>47 (8)</td>
<td>48 (8)</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><strong>After week 16</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total number of AEs</strong></td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td><strong>Children with at least 1 AE</strong></td>
<td>14 (2)</td>
<td>12 (2)</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

11 / 16 adverse reactions were raised liver enzymes

Most reactions occurred in first 8 weeks
SHINE Trial found that the 4 months treatment was as good as the standard 6 month treatment for children with minimal TB

- Few unfavourable outcomes in both arms (3% vs 3%)
- The results were consistent across all the analyses performed
- Few treatment related side-effects and similar in both arms

- Two thirds of children with TB could potentially be safely and effectively treated with 4 months of treatment
- Reducing the length of treatment could make treatment easier for children and caregivers, as well as reduce costs to families and the health system
- Guideline and policy makers should consider moving to 4 months of treatment for children with minimal TB
ACKNOWLEDGEMENTS

SHINE study participants and their families
Study teams in Zambia, Uganda, South Africa, and India:
• University Teaching Hospital, Children’s Hospital, Lusaka, Zambia: C. Chabala, V. Mulenga, J. Lungu, M. Kapasa, K. Zimba, K. Zymbo, C. Tembo, S. Kunda, E. Shingalili, T. Chipoya, F. Mwanakalanga, E. Chambula, J. M. Hankombo, M. Malama Kalumbi
• Makerere University - Johns Hopkins University Research Collaboration, Kampala, Uganda: E. Wobudeya, P. Musoke, R. Mboizi, W. Nansamba, G. Businge
• Desmond Tutu TB Centre, Stellenbosch University, South Africa: A. C.Hesseling, M. Palmer, M. M. van der Zalm, J. Workman, A.M. Demers, H.S. Schaal, E. Walters, W. Zimri, G. Hoddinott
• Byramjee Jeejeebhoy Government Medical College, Pune, India: A. Kinikar, V. Mave, A. P. Raichur, A. Nijampurkar, S. Khan
• Indian Council of Medical Research, National Institute for Research in Tuberculosis, Chennai, India: S. Hissar, J. Bency, P.K. Bhavani, G. Prathiksha, D. Baskaran, V. Mythily, H. Kumar, S. Elilarasi, S. Balaji, M.A. Aravind, J. Ganesh

Division of Clinical Pharmacology, University of Cape Town: H. McIlreron
Radboud University Medical Center, Nijmegen, The Netherlands: R. Aarnoutse
Endpoint Review Committee: S. Welch, S. Graham, J. Seddon, E. Whittaker, S. Anderson, L. Grandjean
Independent Data Monitoring Committee: T. Peto, A. Mwinga, K. Fielding
Trial Steering Committee: P. Mugyenyi, J. Darbyshire, P. Clayden, P. Donald, V. Singh, M. Grzemska, S. Swaminathan
Funders: Joint Global Health Trials Scheme of the Department for International Development, UK (DFID), the UK Department of Health and Social Care (DHSC), the Wellcome Trust, and the Medical Research Council (MRC UK), Grant number MR/L004445/1; EDCTP2 program supported by the European Union; and TB Alliance.
Sponsor: University College London, UK
Trial drugs: Manufactured by Macleods Pharmaceuticals Ltd.
SHINE AT THE 2020 INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE CONFERENCE

Oral presentations:

• Shorter treatment for minimal tuberculosis in children: main findings from the SHINE trial
  *(LB-2056-24): 24 October, 15:00-16:20 CEST*

• Diagnostic utility of microbiological and histopathological testing in the diagnosis of Paediatric TB lymphadenitis in Indian children screened for the SHINE trial
  *(OA-34-711-24): 24 October 2020, 11-12:20 CEST*

Poster Presentations

• Utility of colour vision testing for screening for ethambutol-associated ocular toxicity in children treated for TB in the SHINE trial *(EP02-114-21): 21 October 2020*

