Child & Adolescent TB Working Group

SHINE

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

Partners: Universiteit iYunivesithi Stellenbosch University 100 1918 2018 — forward together · saam vorentoe · masiye phambili; Mujhu Research Collaboration; The University of Zambia; National Institute of Medical Research; B.J. Medical College Poona; University of Cape Town · iYunivesithi yaseKapa · Universiteit van Kaapstad; MRC Medical Research Council — Smarter Studies Global Impact Better Health; UCL; Radboudumc

Funders: UKRI Medical Research Council; Funded by NIHR National Institute for Health Research; UKaid from the British people; wellcome; EDCTP; TB Alliance

BACKGROUND

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 2. Marais BJ et al. CID 2006 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)

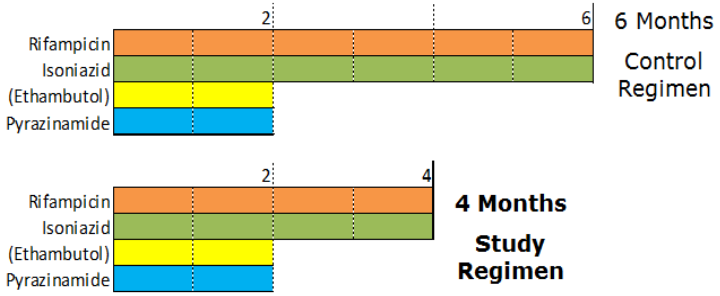
Randomisation (1:1)

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

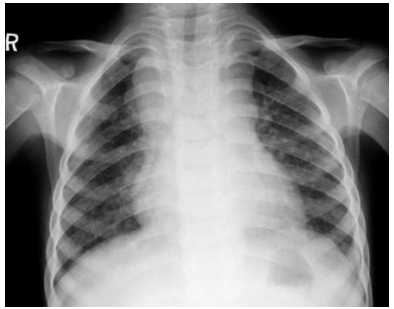
PARTICIPATING SITES

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)

ANALSYIS 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

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- Non-adherent to allocated treatment, “80-120%” rule

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Adjudicated to have TB at baseline, assumed 80% of all children

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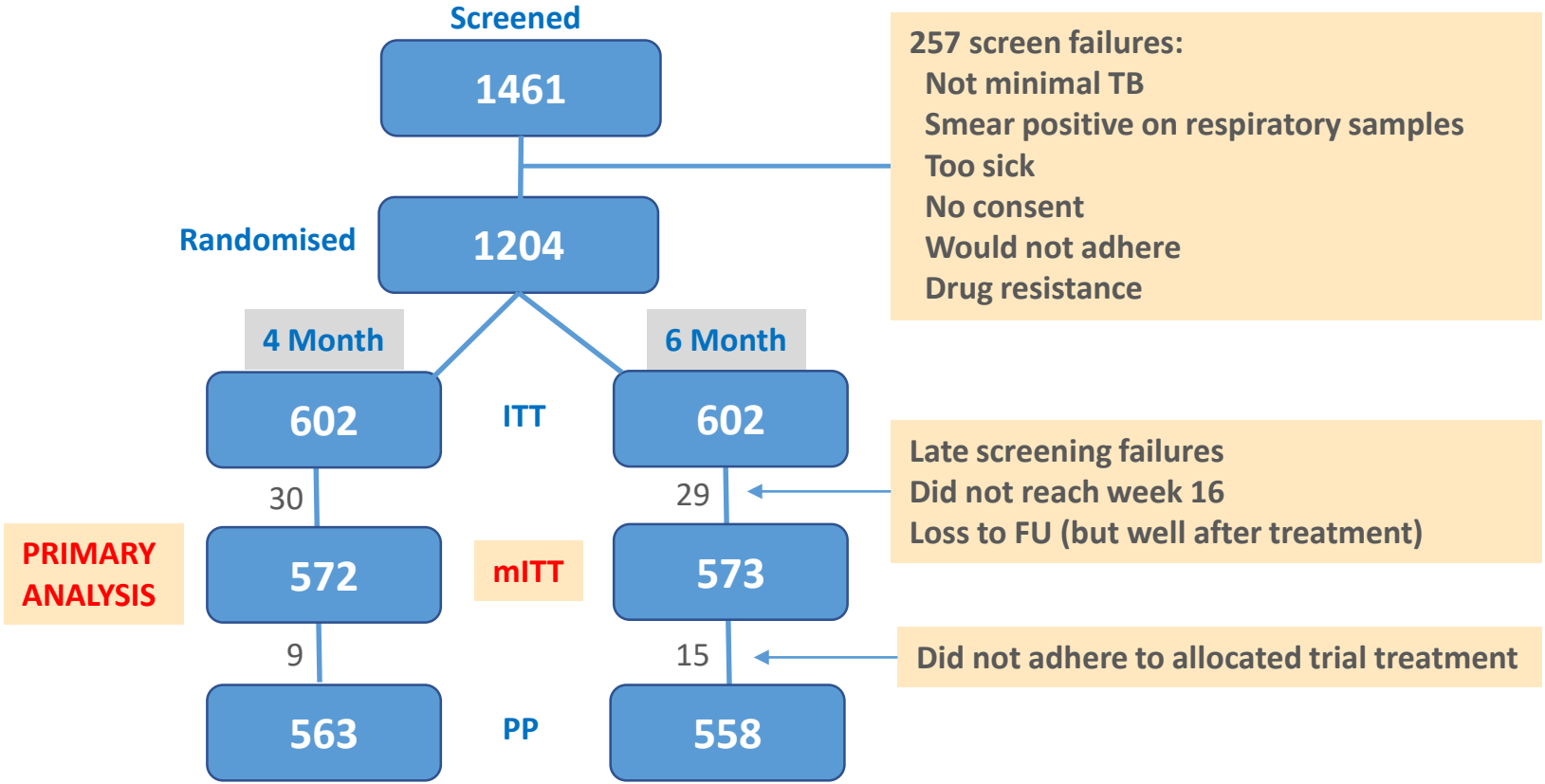
Sample size
6% non-inferiority margin
8% events in control arm
90% power, 5% 2-sided

RESULTS

CONSORT DIAGRAM



BASELINE CHARACTERISTICS

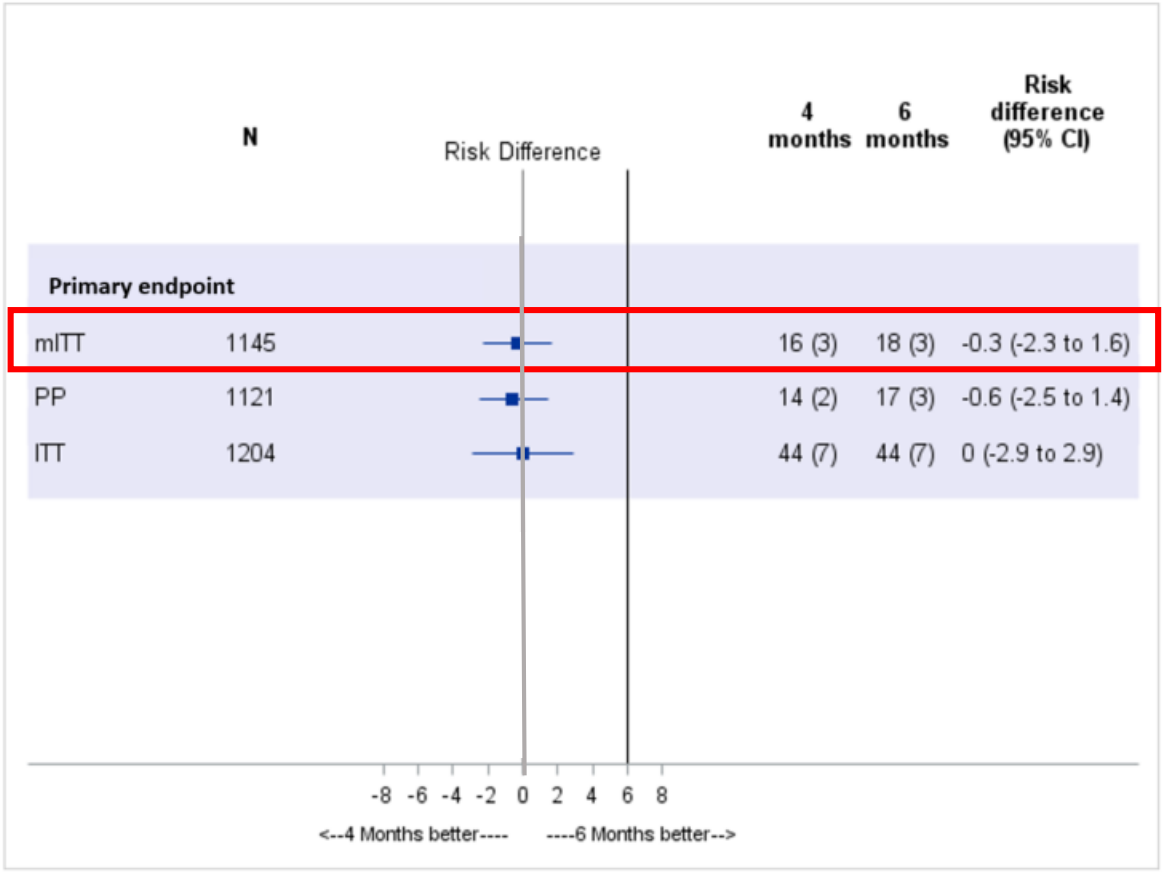
	4 Months N=602	6 Months N=602
Age (years), median, range	3.4 (2 months, 15 years)	3.5 (2 months, 15 years)
Sex, n(%) female	297 (49)	286 (48)
Ethnicity, n (%)		
Black	460 (76)	460 (76)
Indian	75 (12)	74 (12)
Other	67 (11)	68 (11)
HIV status, n (%) positive	65 (11)	62 (10)
Weight-for-age Z score, median,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

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



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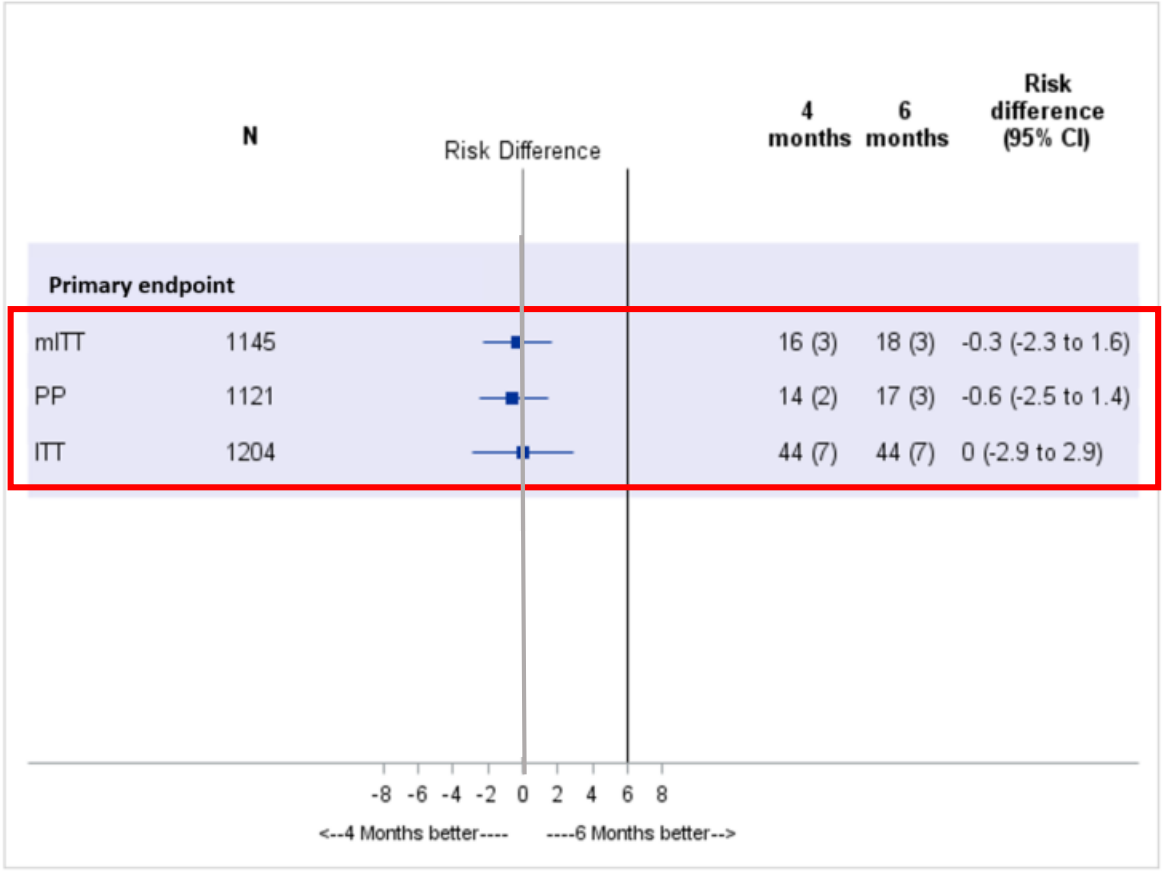

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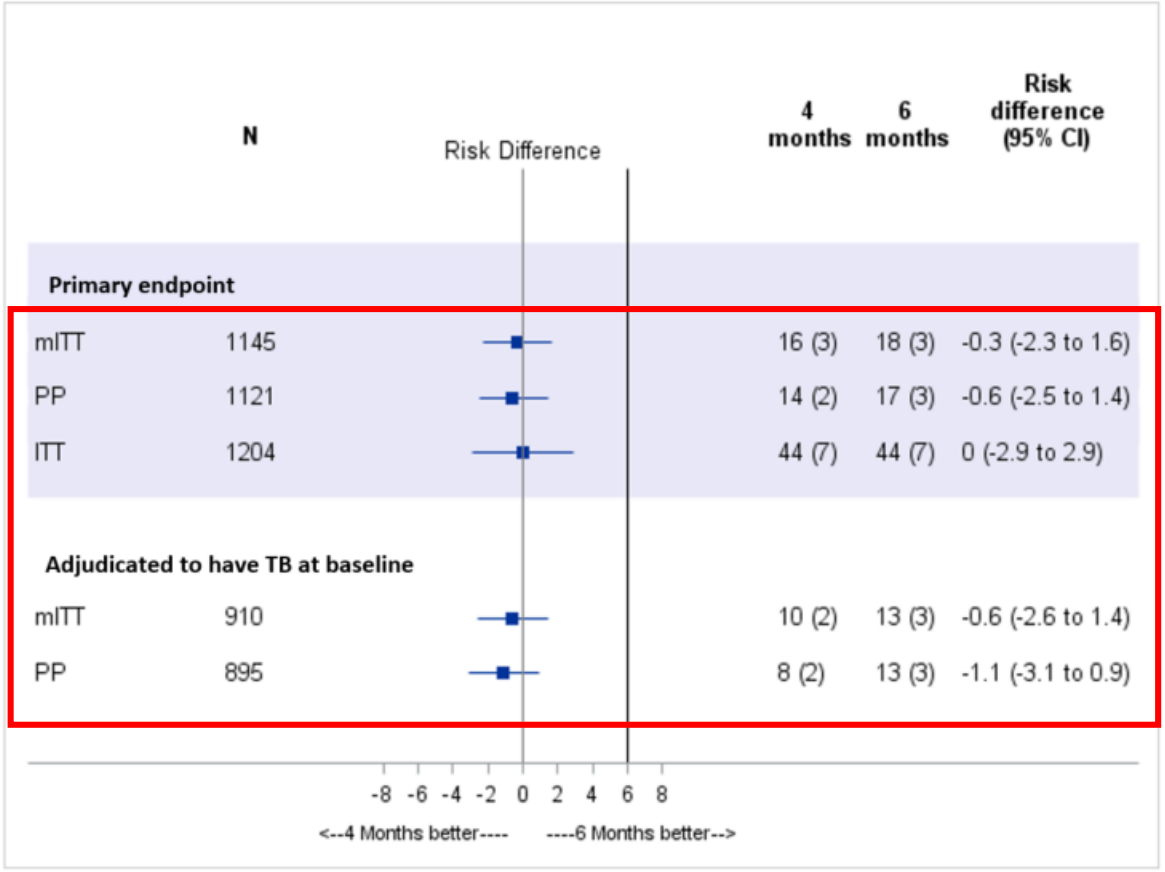
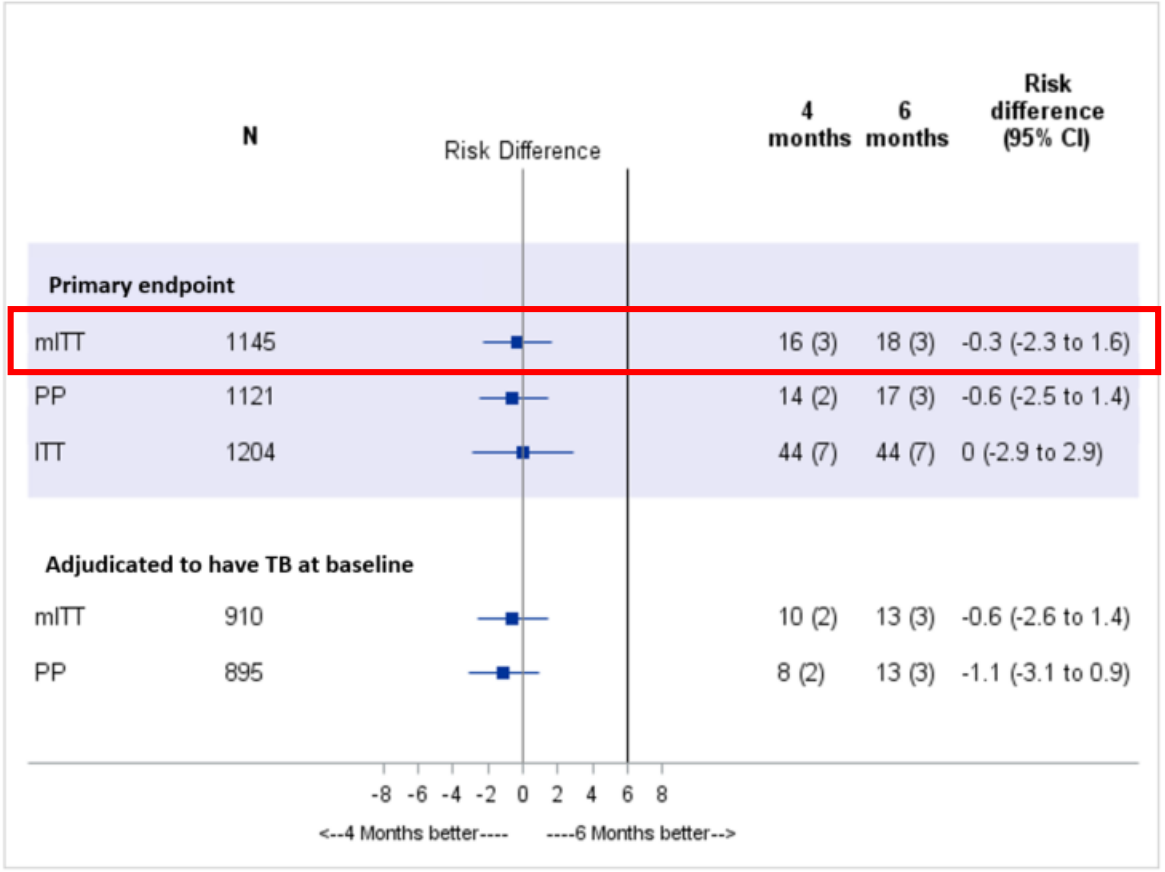


Endpoint Review Committee (ERC) adjudication of TB at baseline

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

PRIMARY EFFICACY



34 unfavourable outcomes (mITT):

	4 Month N=16	6 Month N=18
Death from any cause (after week 16)	7	12
LTFU during treatment (after week 16)	0	1
TB recurrence	6	4
Treatment extension (treatment failure)	2	0
Restart/change of treatment (treatment failure)	1	1

PRIMARY SAFETY ON-TREATMENT ADVERSE EVENTS GRADE ≥3

	4 Months N=602	6 Months N=602
Total number of ≥ Grade 3 AEs	49	66
Children with at least 1 AE *Deaths*	47 (8) *8*	48 (8) *9*
After week 16 Total number of AEs	14	14
Children with at least 1 AE *Deaths*	14 (2) *2*	12 (2) *0*

	4 Months	6 Months
Adverse reactions (AR)	**5**	**11**

11 / 16 adverse reactions were raised liver enzymes

Most reactions occurred in first 8 weeks

SUMMARY AND CONCLUSIONS

- 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

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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. Zyambo, C. Tembo, S. Kunda, E. Shingalili, T. Chipoya, F. Mwanakalanga, E. Chambula, J. M. Hankombo, M. Malama Kalumbi
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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

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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***
- A method for baseline adjudication of tuberculosis diagnosis in children in a therapeutic clinical trial: experience from SHINE ***(EP02-112-21): 21 October 2020***
- Caregivers' beliefs in anti-tuberculosis medicines in the African/Indian SHINE trial ***(EP15-241-22): 22 October 2020***

THANK YOU

SHINE

Investigators' meeting
Lusaka, Zambia