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

Partners:

Funders:

BACKGROUND

More than one million children develop tuberculosis (TB) annually and almost 20% of them die [1,2]

Two-thirds have non-severe TB which is paucibacillary and may benefit from shorter treatment [3,4]

Children have been historically excluded from clinical efficacy trials of anti TB treatment with extrapolation of results from adult trials, which mostly include smear positive respiratory disease

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 2021 2. PJ Dodd et al. Lancet Glob Health, 2017 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)

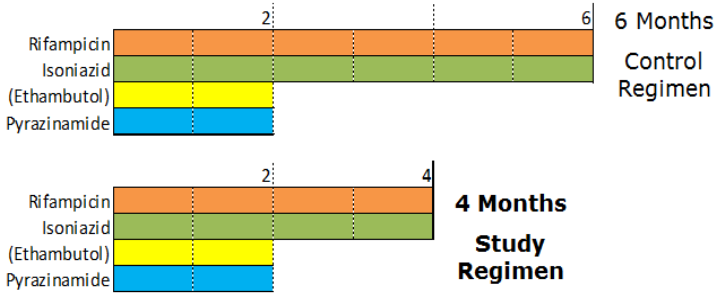
Randomisation (1:1)

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

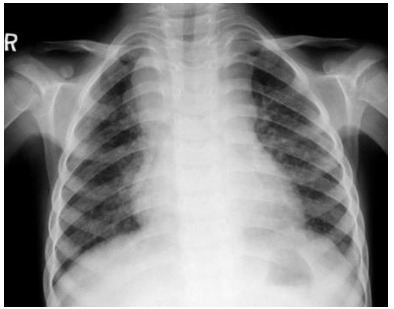
PARTICIPATING SITES

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

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

Coordination:
MRC CTU at UCL, London, UK

TRIAL POPULATION



SHINE

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, minimal or no parenchymal abnormality on CXR.
- Smear negative on gastric aspirate, other respiratory sample.

TRIAL POPULATION

Main Exclusion Criteria:

- Smear positive respiratory sample
- Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB
- Premature (<37 weeks) and aged less than 3 months
- Pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. liver or kidney disease, peripheral neuropathy, cavitation
- Known contact with drug resistant adult source case (including mono-resistant TB)
- Known drug resistance in the child

PRIMARY ENDPOINTS

Primary efficacy outcome:

Unfavourable status by 72 weeks defined as

- **Composite of TB events (treatment failure, extension and recurrence)**
- **Loss to follow up during treatment**
- **Death from any cause**

Primary Safety outcome:

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

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

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

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- Statistical power of trial determined on the basis of a key subgroup analysis involving children adjudicated to have TB at baseline, assumed 80% of all children.

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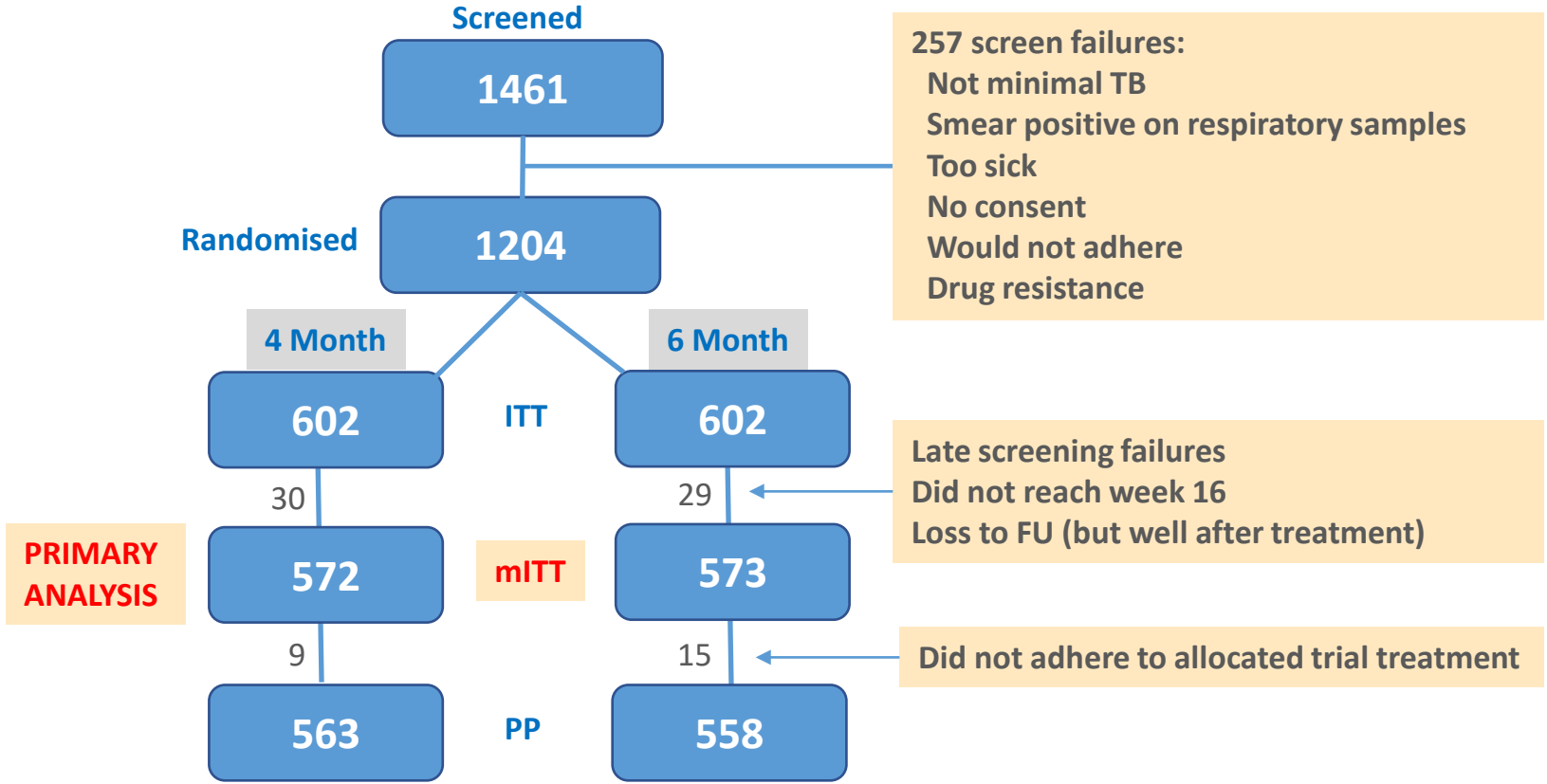
We calculated that enrolment of 1200 children will provide trial with 90% power to detect nonnoninferiority at a two sided significance level of 5% assuming
10% loss to follow up
6% non-inferiority margin
8% events in control arm.

RESULTS

CONSORT DIAGRAM



BASELINE CHARACTERISTICS

		16 weeks (N=602)	24 weeks (N=602)	Total (N=1204)
Sex N (%)	Female	297 (49)	286 (48)	583 (48)
Age (Years)	Median (IQR), (Min,Max)	3.4 (1.5, 6.9), (2m, 15y)	3.5 (1.5, 7.1), (2m, 15y)	3.5 (1.5, 7.0), (2m, 15y)
Site country				
	South Africa	156 (26)	159 (26)	315 (26)
	Uganda	188 (31)	188 (31)	376 (31)
	Zambia	183 (30)	181 (30)	364 (30)
	India	75 (12)	74 (12)	149 (12)
HIV status, N (%)	Positive	65 (11)	62 (10)	127 (11)
WHO weight band (kg), N (%)	3-3.9	0	3 (1)	3 (<1)
	4-7.9	86 (14)	92 (15)	178 (15)
	8-11.9	162 (27)	152 (25)	314 (26)
	12-15.9	126 (21)	116 (19)	242 (20)
	16-24.9	142 (24)	153 (25)	295 (25)
	≥25	86 (14)	86 (14)	172 (14)

BASELINE CHARACTERISTICS (CONTINUED)

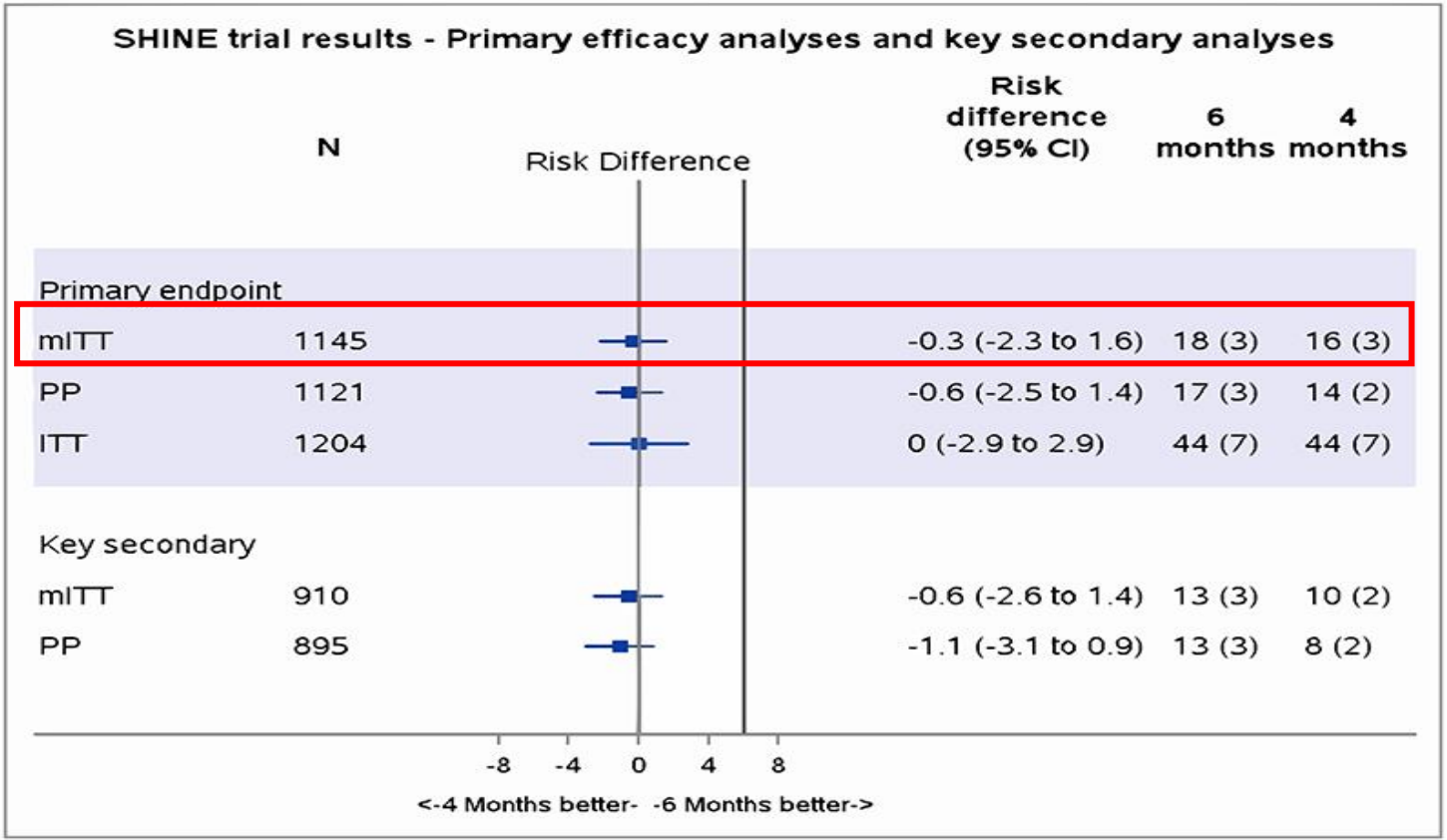
		16 weeks (N=602)	24 weeks (N=602)	Total (N=1204)
Clinical Presentation N (%)	Respiratory	398 (66)	406 (67)	804 (67)
	Mixed respiratory and peripheral TB	182 (30)	171 (28)	353 (29)
	Peripheral lymph node TB	19 (3)	21 (3)	40 (3)
	Other ¥	3 (1)	4 (1)	7 (1)
MTB culture and Xpert MTB/RIF results θ N (%)	Total (culture positive for MTB (MGIT or LJ) OR Xpert MTB/RIF positive)	85 (14)	80 (13)	165 (14)
	TB culture positive only	40 (7)	40 (7)	80 (7)
	Xpert MTB/RIF positive only	14 (2)	5 (1)	19 (2)
	TB culture positive AND Xpert MTB/RIF positive	31 (5)	35 (6)	66 (5)

ADHERENCE TO RANDOMISED DURATION AND RETENTION

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

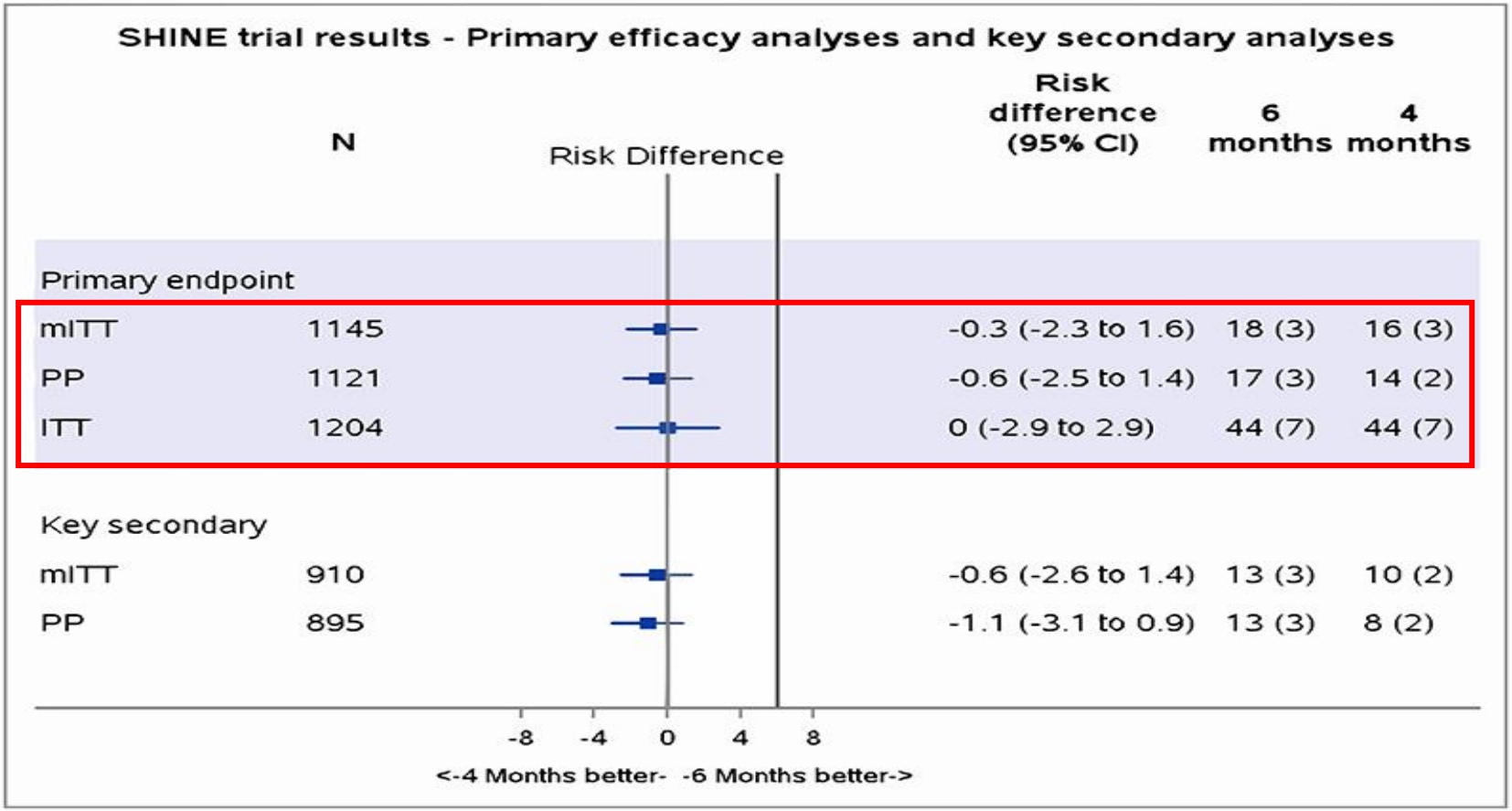
95% retention at week 72 across both arms

PRIMARY EFFICACY



PRIMARY EFFICACY

SHINE trial results - Primary efficacy analyses and key secondary analyses



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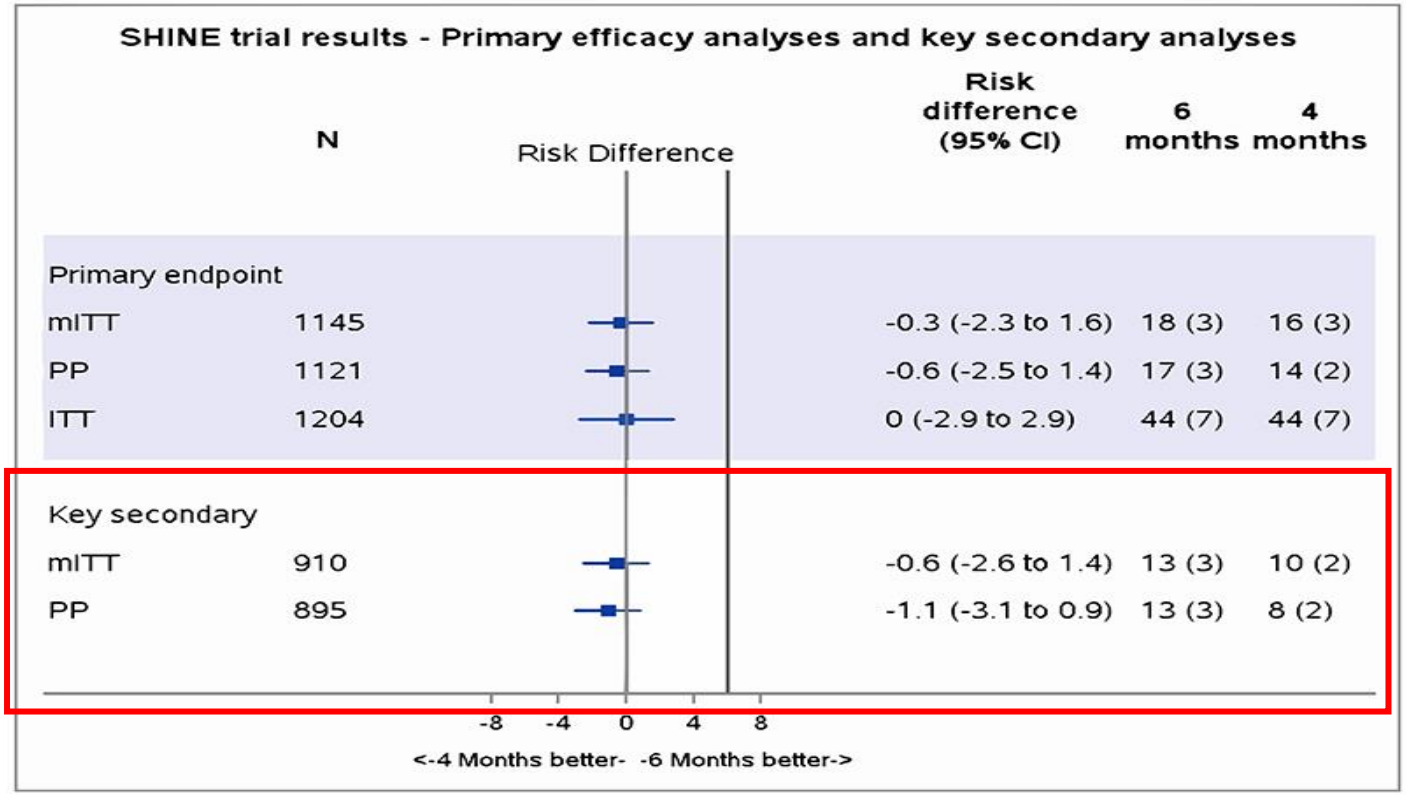
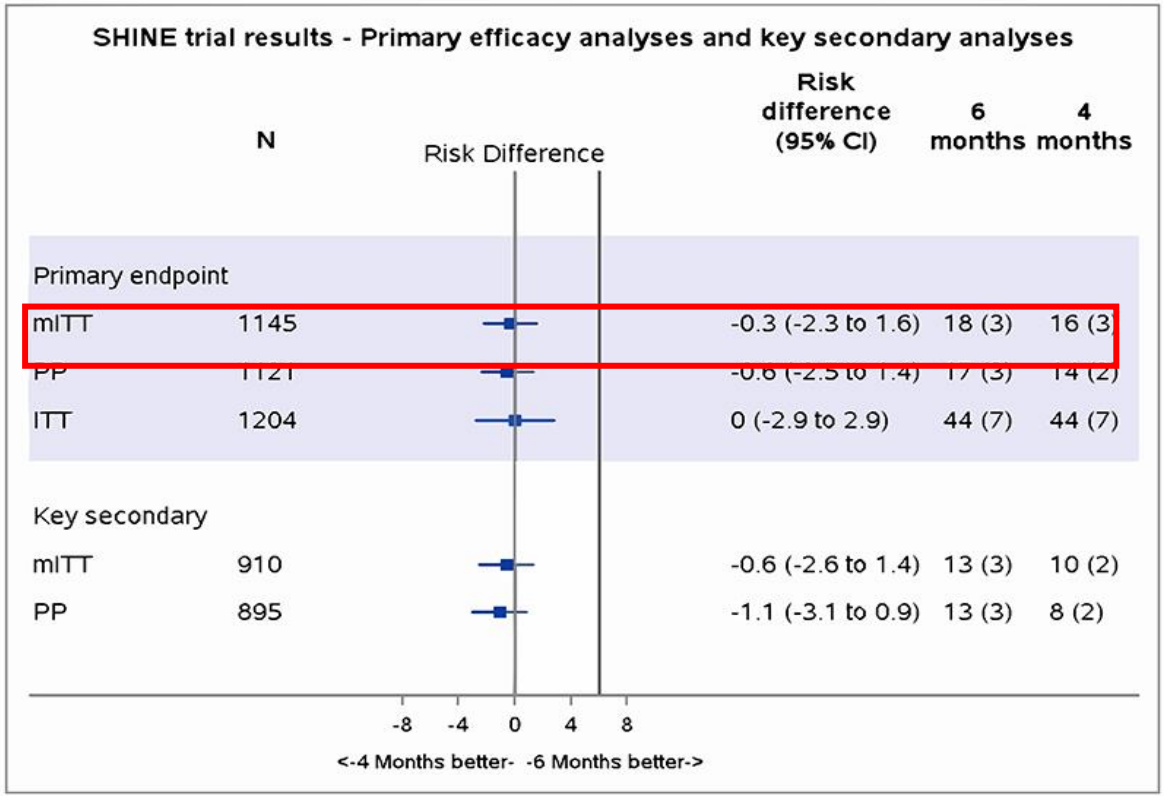


Endpoint Review Committee (ERC) adjudication of TB at baseline

~ 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 ENDPOINTS

Timing	Randomised	16 weeks (N=602)	24 weeks (N=602)	Total (N=1204)
Overall	**DAIDS grade 3, 4 or 5 adverse events**	**49**	**66**	**115**
	Participants with at least one DAIDS grade 3, 4 or 5 adverse event ¤	47 (8)	48 (8)	95 (8)
Before week 16	Grade 3, 4 or 5 adverse events	35	52	87
	Participants with at least one grade 3, 4 or 5 adverse event	33 (5)	40 (7)	73 (6)
After week 16	Grade 3, 4 or 5 adverse events	14	14	28
	Participants with at least one grade 3, 4 or 5 adverse event	14 (2)	12 (2)	26 (2)
Overall	No. of adverse drug reactions ¥ on treatment and within 30 days of completing treatment	6 (1)	11 (2)	17 (1)

- 115 grade≥3 adverse events on treatment or for up to 30 days post treatment, similar across arms.
- There were 17 grade 3 or 4 adverse reactions including 11 hepatic events

SERIOUS ADVERSE EVENTS AND DEATHS

Timing	Randomised	16 weeks (N=602)	24 weeks (N=602)	Total (N=1204)
Overall	**SAEs**	**88**	**104**	**192**
	Participants with at least one SAE ¤	**75 (12)**	**75 (12)**	**150 (12)**
Before week 16	SAEs	35	50	85
	Participants with at least one SAE	33	40	73
After week 16	SAEs	53	54	107
	Participants with at least one SAE	47	44	91
Total	**No. of Deaths**	**12**	**19**	**31**
Before week 16	Deaths	5	6	11
	Deaths considered related to TB	3	2	5
After week 16	Deaths	7	13	20
	Deaths considered related to TB	2	6	8

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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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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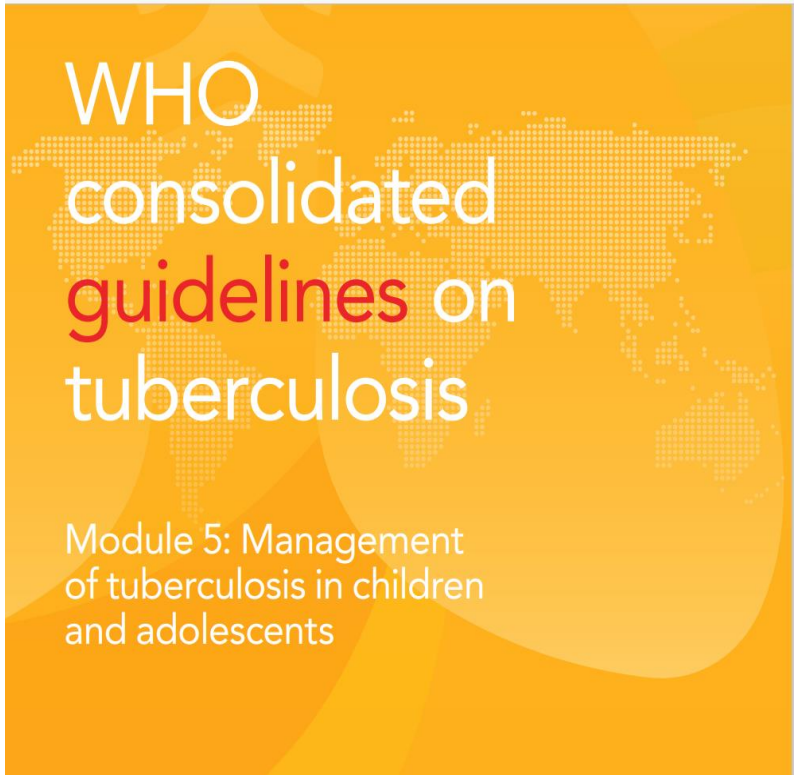
Conclusion:

Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, non-severe, smear-negative tuberculosis

WHO guidelines March 2022 : Recommendations



5.1. Treatment shortening in children and adolescents with non-severe TB

Recommendation:

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.

(Strong recommendation, moderate certainty of evidence)

Remarks

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.
- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.
- The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV,[26] or of isoniazid resistance.[27]

THANK YOU