CS-5015, **S**hortened Oral Treatment for **M**ultidrug-**R**esistant **T**uberculosis in Children (SMaRT Kids): A Phase III Randomized Multi-center Trial

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IMPAACT TB Scientific Committee

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Every breath counts

Background and Rationale (1)

- *1. Public health relevance:* Substantial global burden of MDR-TB in children
- *2. Improved treatment is needed:*
  - Outcomes better than adults, but could be improved
  - Current regimens long (9-18m), toxic (20% hearing loss) and poorly tolerated
  - Different implications for children – hearing loss, hospitalization - during critical periods of neurodevelopment, attachment
  - New WHO-recommended 9-12m regimen still contains injectable x 4m

Background and Rationale (2)

- *3. Need for efficacy trial in children*
  - Children tend to have paucibacillary TB (less severe)
    - Reasonably expected to respond better to treatment than adults
  - MDR-TB treatment outcomes
    - Adults – 50% successful outcome
    - Pediatric – 75-90% successful outcome

Background and Rationale (3)

- *Summary:*
  - Children may suffer disproportionately from existing treatment regimens…
  - …AND would be expected to respond better than adults to shorter, less intense regimens
  - Time is right –
    - More children being diagnosed
    - New and repurposed treatments becoming available
- *Assertion:* Children with probable and confirmed MDR-TB stand to substantially benefit from an efficacy trial of a shortened all-oral regimen

Population

- Inclusion
  - Children 0 to <15 years of age;
  - Probable or confirmed pulmonary or extrapulmonary MDR/RMR-TB, and MDR-TB with additional resistance to injectables or fluoroquinolones (i.e. pre-XDR and XDR-TB)
  - HIV-infected and uninfected
  - Written informed consent (and assent).
- Exclusion
  - Probable or confirmed Stage 2 or 3 TB meningitis or spinal TB.

Challenges relative to adult trials

- Confirmed vs probable often not known at time of diagnosis
- May not always know DST at time of diagnosis
- Cannot delay treatment until diagnosis
- Lack of microbiologic endpoints in some

Design

- *Design:* Randomized, open-label two-arm phase III non-inferiority efficacy trial
  - Other designs carefully considered – MAMS, Phase II, DOOR
  - Primarily powered for confirmed disease
    - Confirmed TB - expected to have more severe disease, potentially respond less well
    - Expect to be powered also for probable group – less severe disease, may respond better

Intervention

- Children with MDR/RMR randomized 1:1 to control vs intervention arms
- Children with preXDR/XDR assigned to an observational arm

Table. Proposed treatment regimens by drug-resistance profile and study arm

MDR/RMR TB	
Intervention	2 mo DLM (once daily), CFZ, hdLZD, LFX, PZA / 4 mo DLM (once daily), CFZ, sdLZD, LFX, PZA
Control	4-6 mo KAN/AMK, LFX, PTO/ETO, CFZ, PZA, hdINH, EMB / 5-6 mo LFX, CFZ, PZA, EMB
preXDR/XDR-TB	
Single arm	6 mo DLM (once daily), CFZ, hdLZD, PZA, LFX (if FQN-susc) or PAS (if FQN-res)

Objectives (1)

- *Primary Objectives*
  - To compare efficacy of an all-oral 6-month treatment regimen vs. the regimen currently recommended by WHO, for children with *confirmed* MDR/RMR-TB
  - To compare efficacy of an all-oral 6-month treatment regimen vs. the regimen currently recommended by WHO, for children with *probable* MDR/RMR-TB
  - To compare the safety and tolerability of an all-oral 6-month treatment regimen vs. the regimen currently recommended by WHO, for children with probable and confirmed MDR/RMR-TB

Objectives (2)

- *Secondary Objectives*
  - Others: PK, acceptability, cost-effectiveness
- *Exploratory Objectives*
  - To characterize treatment outcomes of an all-oral treatment regimen for children with pre-XDR and XDR-TB.
  - To characterize the safety of an all-oral treatment regimen for children with pre-XDR and XDR-TB.
  - Others – biomarkers, novel trial design [desirability of outcome rankings (DOOR)]

Sample Size

- Efficacy: 648 to demonstrate non-inferior efficacy of interventional arm among confirmed MDR/RMR-TB with 80% power
  - Assumptions:
    - 12% non-inferiority margin
    - 85% (ctrl) and 87% (int) successful outcomes
    - 40% of children with confirmed diagnosis
    - 25% non-evaluable – (LTFU, preXDR/XDR)
  - 93% power in probable MDR/MDR-TB group
  - 260 confirmed cases, 390 probable cases
  - 192 evaluable confirmed MDR-TB cases

Endpoints

- *Primary outcomes:*
  - Cure or probable cure without relapse, 18 months after initiating treatment in children with *confirmed* MDR/RMR-TB
  - Cure or probable cure without relapse, 18 months after initiating treatment in children with *probable* MDR/RMR-TB
  - ≥ Grade 3 AEs (using DAIDS 2014 criteria), which are at least possibly related to anti-TB treatment in all children with MDR/RMR-TB, evaluated 12 months after treatment initiation

Feasibility (1): Potential Sites

- Desmond Tutu TB Centre (DTTC), Stellenbosch University, Cape Town
- Klerksdorp Matlosana, PHRU, WITS Health Consortium (N. Martinson) and Sizwe Hospital (F. Conradie)
- De La Salle Health Sciences Institute and Angelo King Medical Research Center, Philippines (M. Frias)
- GHESKIO, Haiti (V. Rouzier)
- BJMC-JHU Clinical trials research site, India (A. Gupta, C. Valvi)
- Additional sites participating in the A5300/I2003 Phoenix preventive therapy trial (n=20)
- All sites participating in IMPAACT P1108 and 2005 will be solicited for participation.

Feasibility (2): Duration

- 36 months to complete enrolment
  - 18 participants/month
  - Depends on number, capacity of sites
- 60 months to complete follow-up

Potential impact

- Result in changed international guidance for MDR-TB treatment in children
- The proposed trial will also:
  - Provide needed information on microbiological and clinical/radiological treatment response in children with TB
  - Generate crucial pediatric experience with novel/repurposed TB drugs which are the future of TB treatment, even if in different regimens
  - Build international capacity for pediatric TB trials
  - Catalyze diagnosis and treatment of children with MDR-TB, which is grossly under-diagnosed in many settings
- Ambitious

Additional Considerations

- Different design
  - Primarily evaluate efficacy in combined population of probable and confirmed MDR/RMR-TB
  - 346 to demonstrate non-inferior efficacy of interventional arm among combined confirmed/probable MDR/RMR-TB with 90% power
- Benefit
  - Smaller, more feasible trial
  - Results sooner in this rapidly evolving landscape
- Risks
  - Not powered for efficacy in children with confirmed (more severe) disease

Conclusion

- Questions?
- Comments?
- Thank you.