STREAM Trial Update

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on behalf of the STREAM Trial Management Group
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Outline

• STREAM Stage 1
  – Background
  – Current status

• STREAM Stage 2
  – Regimen selection
  – Design
  – Timeframe
STREAM Stage 1

- The STREAM trial compares, in a non-inferiority design, the effectiveness of a 9-month regimen based closely on the one described by Van Deun\(^1\) with the locally used WHO approved regimen for MDR-TB.

- Regimen A  
  WHO approved regimen

- Regimen B  
  9-month regimen

STREAM Stage 1 objectives

The primary objectives of Stage 1 of the STREAM trial are:

• To assess whether the proportion of patients with a favourable efficacy outcome at 27 months (120 weeks) on the 9-month regimen (Regimen B) is not inferior to that on the WHO approved MDR-TB regimen (Regimen A)

• To compare the proportion of patients who experience grade 3 or greater adverse events, during treatment or follow-up, on Regimen B as compared to Regimen A
Stage 1: current status

- Enrolment to Stage 1 commenced: July 2012
- Six sites in Ethiopia, South Africa, Viet Nam and Mongolia
- 330 of target of 400 patients enrolled
- Intake completion expected: early 2015
- Last patient visit: Q3 2017
- Results from Stage 1 expected: Q4 2017 / Q1 2018
STREAM Stage 2

• Early in 2013 in recognition of the progress made to date in STREAM and noting the provisional licensing of the first new drug for TB for almost 50 years we were asked to consider:

  – is it possible to include additional regimens to the current STREAM trial?

  – if so, what would be the appropriate regimens to evaluate?
Additional regimens proposed for Stage 2

• After extensive discussions between the study team, the local investigators and other experts it was agreed that the primary interest to patients and programmes would be:

  – a fully oral 9-month regimen
  – a 6-month simplified regimen

• Both of these regimens would include bedaquiline
New STREAM Stage 2 Regimens

• In Regimen C, the fully oral regimen, kanamycin is replaced by bedaquiline and moxifloxacin by levofloxacin

• In Regimen D prothionamide is replaced by bedaquiline, moxifloxacin is replaced by levofloxacin, ethambutol is removed, the dose of isoniazid is increased, and the duration of the isoniazid and kanamycin is reduced to 8 weeks (total duration is reduced from 40 to 28 weeks)
Primary objectives in Stage 2

• The primary objectives of Stage 2 are:
  – To assess whether the proportion of patients with a favourable efficacy outcome on Regimen C, the fully oral regimen, is not inferior to that on Regimen B at 76 weeks (18 months)
  – To assess whether the proportion of patients with a favourable efficacy outcome on Regimen D, the 6-month regimen, is not inferior to that on Regimen B at 76 weeks (18 months)
The control regimen in Stage 2

• Regimen B (the 9-month regimen studied in Stage 1) was selected as the control regimen for Stage 2 although the results of Stage 1 will not be available before Q3 of 2017.

• In recognition of concerns about the possibility that Regimen B might not be found to be non-inferior to Regimen A it has been decided to continue to enrol patients to Regimen A.

• Secondary objectives include the comparisons of Regimen C and Regimen D to Regimen A; these will be particularly important if Regimen B is found to be inferior to Regimen A.
Stage 2 timeframe

• We plan to complete enrolment to Stage 2 in 3 years

• If enrolment begins in Q1 of 2015

• Last patient enrolled Q1 of 2018 (approx time of Stage 1 results)

• Last patient reaches 76 week post-randomisation Q3 of 2019

• Primary endpoint results of Stage 2 Q1 of 2020

• Last patient completes long term follow-up Q3 of 2020
Summary

• STREAM Stage 1 has been successfully implemented to date and is on track to reach recruitment target by Q1 2015

• STREAM Stage 2 will evaluate two additional shortened treatment regimens for MDR-TB adding important data to the evidence base for future treatment guidelines