TB ALLIANCE

TREAT TB MDR-TB Trials Capacity Building Series 10 July 2018

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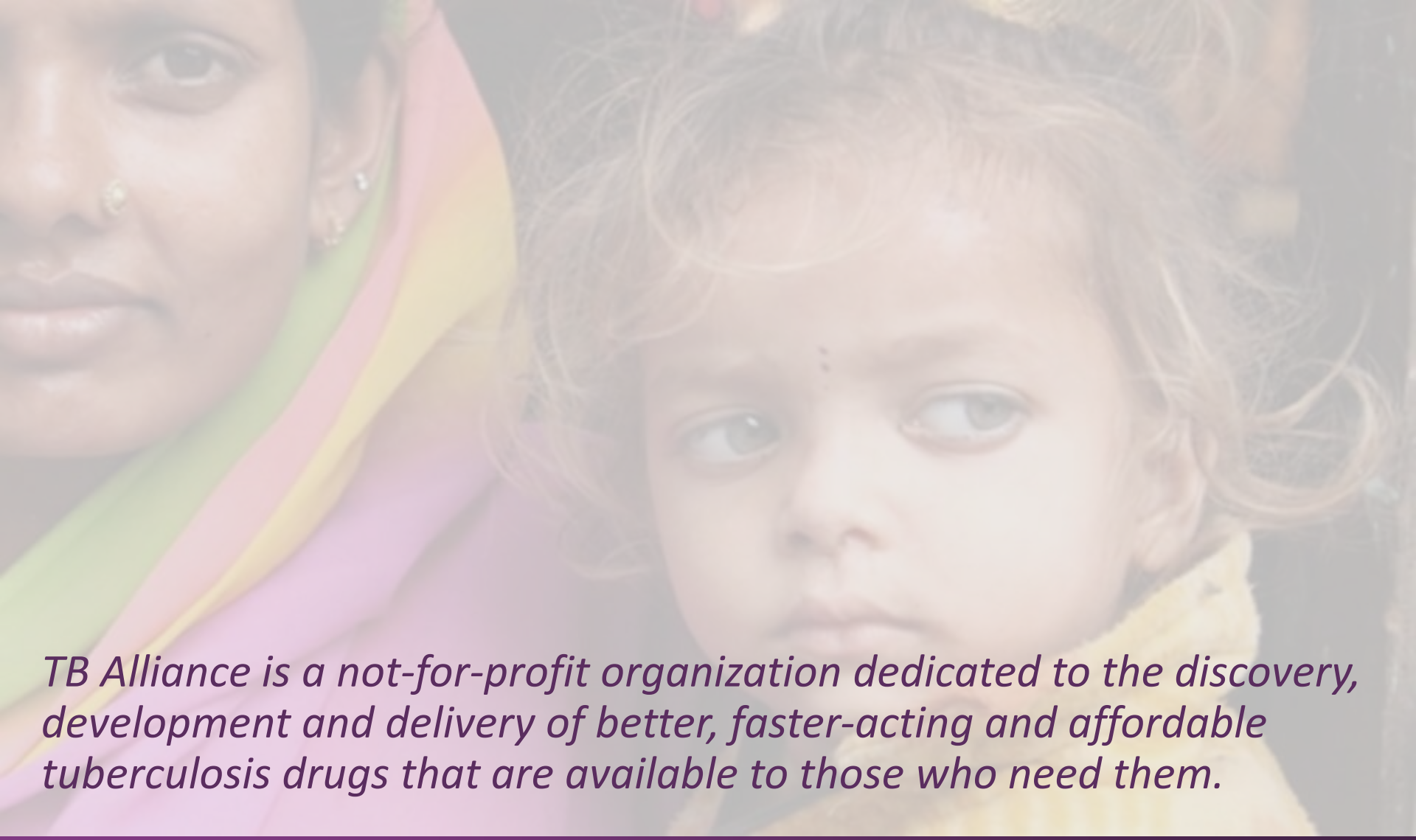
Sponsor Challenges: From Concept to Full Site Approval



TB Alliance is a not-for-profit organization dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those who need them.

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Outline of the Challenges

- Context of the TB Alliance Trials
- General Approach of TB Alliance to a New Site and Country
- Regulatory and Ethics Committee Approvals
- Challenges of Site Documents for Clinical Trial Applications
- Site Assessment and Challenges
  - Pre-study visits and site qualification
  - Contracts and budgets
- Laboratories
  - Safety Labs
  - Microbiology laboratories

TB Drug Development Pipeline As of May 2018*

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Discovery

Lead Identification

- **Clp-C/PIP2**
  Eli Lilly
  Harvard University
- **Energy Metabolism Inhibitors**
  AUCK/UIC
- **GHIT Hit ID Programs**
  - *OP-BIO*
  - *Daiichi Sankyo Novare*
  - *HyphaGenesis*
  - *Chugai*
- **GHIT Hit-to-Lead Program**
  Takeda
- **Natural Product Hit-to-Lead Program**
  Sanofi
- **PEPCK**
  Roche/TAMU
- **PknB**
  Schrödinger
- **POA Prodrugs**
  Yonsei
- **RNA Polymerase Inhibitors**
- **Whole Cell Hit-to-Lead Program**
  GSK

Lead Optimization

- **Arylsulfonamides**
  GSK
- **InhA Inhibitors**
- **Intracellular Phenotypic Hits**
  GSK
- **KasA**
  GSK
- **Macrolides**
  Sanofi
- **MmpL3 Inhibitors**
  Abbvie
- **Squaramides**
  Sanofi

Preclinical Development

- **Preclinical TB Regimen Development**
  JHU
- **TBAJ-587 / Diarylquinoline**
  Merck
- **TBI-223 / Oxazolidinone**
  IMM

Early Development

Phase 1

- **Optimization of Rifampicin in Children <5kg**
  Stellenbosch University
- **Sutezolid/ Oxazolidinone**
- **TBA-7371/ DprE1 Inhibitor**
  Eli Lilly/FNDR

Phase 2A

- **Linezolid Dose-Ranging Study**

Late Development

Phase 2B/2C

- **NC-005**
- **Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide** (BPaMZ)

Phase 3

- **NixTB**
- **Bedaquiline/ Pretomanid/ Linezolid** (BPaL)
- **ZeNix**
- **Bedaquiline/ Pretomanid/ Linezolid** (BPaL)

Phase 4 / Marketed Products

- **Optimized Pediatric Formulations**
- **Ethambutol**
  Macleods
- **Isoniazid**
  Macleods
- **Pyrazinamide**
  Macleods
- **Rifampicin/ Isoniazid**
  Macleods
- **Rifampicin/ Isoniazid/ Pyrazinamide**
  Macleods

* Clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.

TB Alliance Portfolio Partners

Abbvie
Chugai
Daiichi Sankyo Novare
Eli Lilly
Foundation for Neglected Disease Research (FNDR)
GlaxoSmithKline (GSK)
Harvard University
HyphaGenesis
Institute of Materia Medica (IMM)
IMPAACT
Johns Hopkins University (JHU)
Macleods Pharmaceuticals
Medical Research Council (MRC) at UCL
Médecins Sans Frontières (MSF)
Merck
US National Institutes of Health (NIH)
OP-BIO
Roche Pharmaceuticals
Sanofi
Schrödinger
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
Texas A&M University (TAMU)
University College London (UCL)
University of Auckland (AUCK)
University of Dundee (Dundee)
University of Illinois at Chicago (UIC)
Yonsei University

Approach to a New Site and Country

- Example of a new country, from personal experience
- Some key issues:
  - Can we get reliable information on the regulatory process and timelines in the country from our partners and friends?
  - How to identify potential investigators and sites?
  - How is the communication with potential investigators?
    - If an investigator is not good at communicating with us in the exploratory phase, we worry they will not be a good partner in the long run for a complex trial

The Regulatory Approval Process

- First, understand the regulatory authority and what is needed for a regimen with an investigational drug
  - Quality of the CTA submission dossier
  - What is needed in the submission templates?
  - Fully understand what the regulator is asking when questions are raised
    - Example from Russia
    - Need a regulatory partner who fully understands their local country
- Time delays in putting together the submission dossier
  - Local insurance
  - Final translated CRFs
  - Final site contract

The Regulatory Approval Process

- What is the total time from Submission of the CTA to site initiation?
  - Can be less than 1 month in the US, to over a year in some countries
  - Is Ethics Committee and Regulatory Authority in sequence or parallel?
  - Are other approvals needed, such as provincial or local public health departments?

Can we Influence the Regulatory Process?

- Meetings with regulators before the Trial Application is submitted
- Recent example from Tanzania
- Any examples from the audience?

Site Assessment and Challenges

- Approach to Site Evaluation and Qualification
  - Initial visit from TB Alliance Staff
    - My Key questions:
      - Will the PI communicate with the Sponsor/Medical Monitor during the study?
      - Will the PI truly follow the protocol and understand the concept of an “Isolated Positive” culture?
      - Will the site follow all participants through the full follow up period, with minimal losses to f/u?
  - Pre-study visit from CRO for site qualification
    - Challenges:
      - Does our partner CRO really understand the protocol and needs for a site?
      - Need for GCP training, SOP’s, etc.
  - Site Initiation visit

Required Site Documents

- ICF and Patient Materials Translated
  - ? How many local languages
  - ? Dialects of the local languages
  - Don’t forget anything – Patient Instruction Cards
- Approach to Site Budgets
  - What must be only on a per-participant basis vs for site development?
    - In general our trial budget cannot pay ongoing salaries but must be linked to services performed
  - Up front payments

Laboratories

- Safety Labs
  - Central Lab
    - Advantage of one budget, one set of reference ranges, standard reporting platform and export to database
  - Local Labs
    - Shorter turn around time, more familiar to the local staff

Laboratories - Microbiology

Very often the limiting factor to initiating a site!

- Can isolates or TB DNA be exported from the country to a trial central lab?
  - Typically MTB isolates are sub-cultured on LJ Slopes and shipped to London for:
    - MICs to the study drugs
    - Standard panel of phenotypic Drug Susceptibility Testing
    - Whole Genome Sequencing of baseline isolates and any late treatment failures or positive cultures in follow up
      - To determine relapse vs new infection
- Does the local / regional lab have the required equipment?
  - MGIT Incubators
  - Hain LPA capability when needed?

Laboratories - Microbiology

- Status of required SOPs, training in GCLP, Hazardous material handling
- Physical facility to provide staff/monitor safety and minimize cross-contamination
  - What standards to use?

Reminder

- Research on a new investigational drug for Marketing Authorization Approval requires trials at a different standard from academic studies
- Any trial of an investigational drug can turn in to a key trial for MAA
  - Example of the TB Alliance Nix-TB trial and the upcoming file for approval of pretomanid to be used with bedaquiline and linezolid for XDR TB and MDR intolerant/failures

TB Alliance Donors

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United States Agency for International Development

Thank You

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