R&D Update

Carl M. Mendel, M.D.

SHA Meeting

Kuala Lumpur

November 16, 2012

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB Alliance Strategic Focus

- R&D portfolio progression
  - Novel regimen development
  - Impact
- Delivering products to markets
  - Unified DS/DR development path
  - Controlled trials in XDR-TB as alternative to approvals based on 2-mo data
  - Planning for pediatric studies of new regimens
- Partnering / sustainable funding models

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Nov 2012

New Drug Discovery			Preclinical Development	Clinical Development	Regimen Development	
TARGET OR CELL-BASED SCREENING	LEAD IDENTIFICATION	LEAD OPTIMIZATION		CLINICAL PHASE I	CLINICAL PHASE II	CLINICAL PHASE III
Topoisomerase I Inhibitors *AZ/NYMC*	Whole-Cell Hit to Lead Program *GSK*	Mycobacterial Gyrase Inhibitors *GSK*	TBA-354 *U. of Auck/ U. Ill Chi*		New Drugs	Moxifloxacin (+ H, R, Z) *Bayer* Enrollment completed
TB Drug Discovery Portfolio *NITD*		THPP Series *GSK*	Preclinical TB Regimen Testing *JHU/U. Ill Chi*		New Drugs	Moxifloxacin (+ R, Z, E) *Bayer* Enrollment completed
	Energy Metabolism Inhibitors *AZ/U. Penn*	Pyrazinamide Analogs *Yonsei*				
	Folate Biosynthesis Inhibitors *AZ*	Diarylquinolines *Jan/U. of Auck*			Novel Regimens	PA-824/Moxifloxacin/ Pyrazinamide
	Whole-Cell Hit to Lead Program *AZ*	Riminophenazines *IMM/BTTTRI*			Novel Regimens	TMC207/ PA-824/ Pyrazinamide
					Novel Regimens	TMC207/PA-824/ Clofazamine
					Novel Regimens	TMC207 /Pyrazinamide/ Clofazamine
	RNA Polymerase Inhibitors *AZ*	DprE Inhibitors *Scripps*			Novel Regimens	TMC207/PA-824/ Pyrazinamide/ Clofazamine
	Gyrase B Inhibitors *AZ*	Macrolides *Sanofi*				
	ATP Synthase Inhibitors *Scripps*	Cyclopeptides *Sanofi*			Regimen Building Blocks	PA-824/Pyrazinamide
		Whole-Cell Leads *Sanofi*			Regimen Building Blocks	TMC207 /Pyrazinamide

Novel TB regimen development

Our R&D Partners					
AZ	AstraZeneca	JHU	Johns Hopkins University	U. of Auck	University of Auckland
Bayer	Bayer Healthcare AG	NITD	Novartis Institute for Tropical Diseases	U. Ill Chi	University of Illinois at Chicago
BTTTRI	Beijing Tuberculosis and Thoracic Tumor Research Institute	Novartis	Novartis Pharmaceutical	U. Penn	University of Pennsylvania School of Medicine
GSK	GlaxoSmithKline	NYMC	New York Medical College	Yonsei	Yonsei University
IMM	Institute of Materia Medica	Sanofi	sanofi-aventis		
Jan	Janssen (of Johnson & Johnson)	Scripps	Scripps Research Institute		

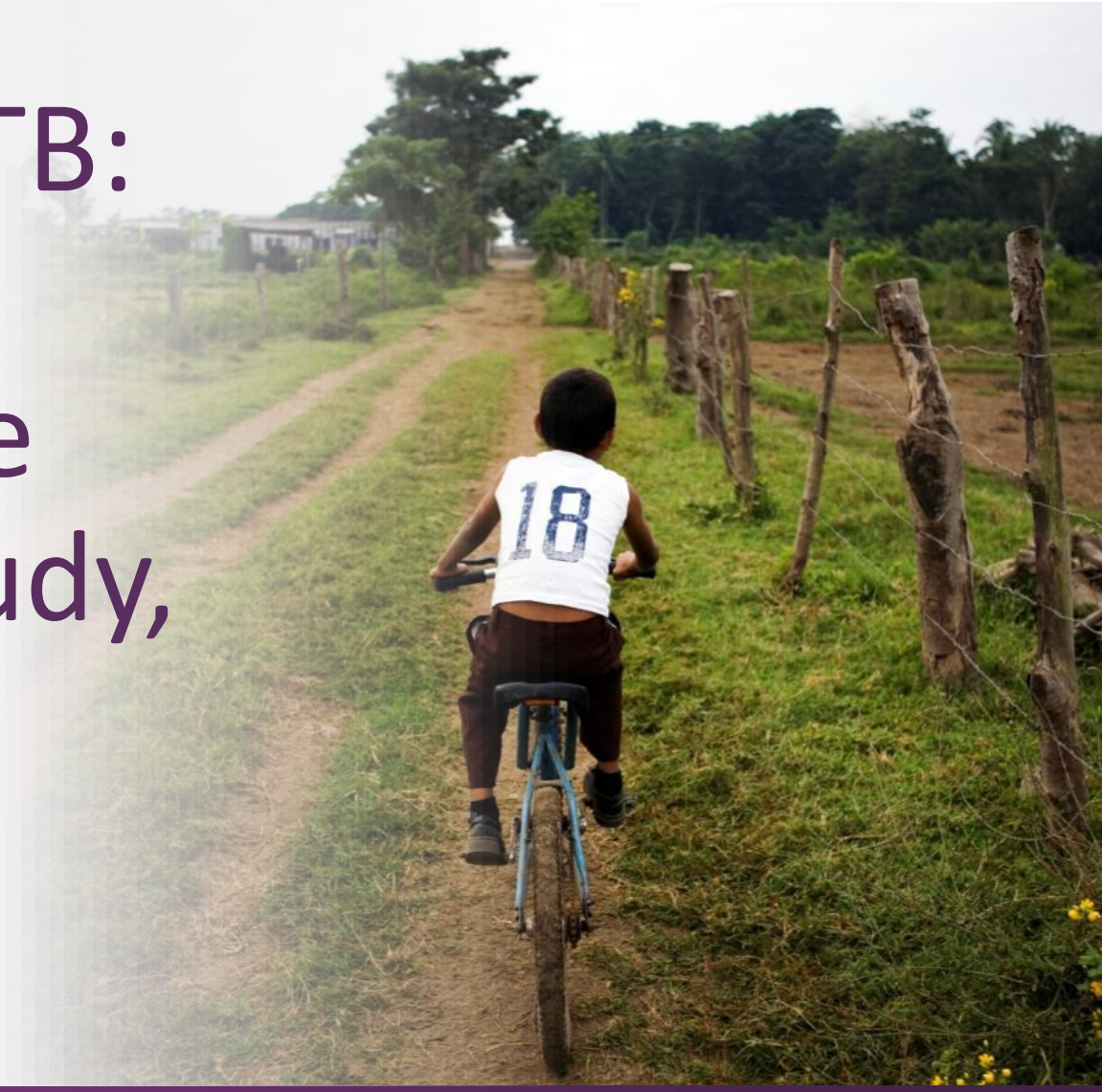
Key New TB Alliance R&D Initiatives

"NiX-TB"

New Chemical Entities (N) in (i) XDR-TB (X-TB) = NixTB

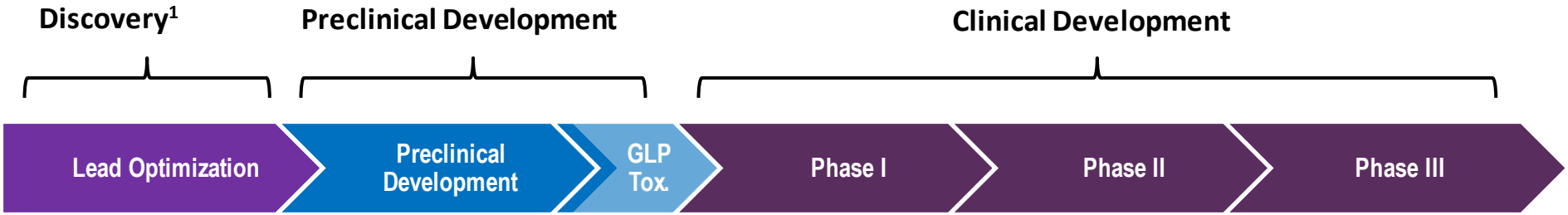
Planning for pediatric studies of novel regimens

XDR- / TDR-TB: Proposed Collaborative "Rescue" Study, NiX-TB



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Global TB Drug Pipeline



Lead Optimization

- Diarylquinoline
- InhA Inhibitors
- LeuRS Inhibitors
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Riminophenazines
- Ruthenium (II) complexes
- Spectinamides
- Translocase-1 Inhibitors

Preclinical Development

- CPZEN-45
- DC-159a
- Q201
- SQ609
- SQ641

GLP Tox.

- BTZ043
- TBA-354

Phase II

- AZD5847
- Bedaquiline (TMC-207)
- Linezolid
- Novel Regimens[2]
- PA-824
- Rifapentine
- SQ-109
- Sutezolid (PNU-100480)

Phase III

- Delamanid (OPC-67683)
- Gatifloxacin
- Moxifloxacin
- Rifapentine

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[1] Ongoing projects without a lead compound series can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

[2] Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated November 2010 and completed in 2011 with promising results. The second clinical trial (NC002) of this regimen was launched in March 2012 and will test the efficacy of the regimen in drug-sensitive and multidrug-resistant patients. The third clinical trial (NC003) will evaluate PA-824, TMC-207, pyrazinamide and clofazimine in combinations and is scheduled to begin September 2012.

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: August 10, 2012

Background

- DS-TB is a curable disease
- MDR-TB is a curable disease with treatment options
- XDR- / TDR-TB is a disease where existing treatment options are poor
  - Optimal therapy should consist of at least 3 effective drugs to which M.tb is susceptible
  - New chemical entities without pre-existing resistance are currently in development, but not yet available
  - Aim is to help XDR-TB patients now under carefully controlled conditions while advancing understanding of entirely novel regimen

NiX-TB

- Foundation: a number of drugs without pre-existing resistance could have promising data by END2013
  - Bedaquiline, delamanid, PA-824, sutezolid, SQ109
  - Clofazimine?
- Proposal: initiate global study of combinations of NCEs in patients with XDR-/TDR-TB at select centers with aim of cure
  - Potential collaborators: Tibotec, Otsuka, TB Alliance, Pfizer, Sequella
  - Once collaborators have committed, mouse relapse data of combination(s) to predict duration of treatment
  - By providing complete regimen, prevent emergence of resistance
  - Pre-approval study; not intended for MDR-TB or to expand access beyond XDR
- Not compassionate use: highly selected centers, more intensive data collection, long-term follow up with definitive outcomes, learn to use regimen, learnings to be rapidly incorporated into treatment

Questions

- Would the risk/benefit ratio in XDR-TB patients justify such an “accelerated” approach?
- Could we justify putting a regimen together for definitive treatment with two drugs that have 2- to 6-month data and one with only 2-week data?
  - Bedaquiline/PA-824/sutezolid

Thank you!

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT