


FIGHTBACK

Integration of Drug Development Tools and Strategic Regulatory Approaches to Accelerate TB Regimen Development

CPTR Meeting, Washington, DC 20 March 2017

LAM as a Pharmacodynamic Biomarker and Potential TB Drug Development Tool


Otsuka

TB innovation for tomorrow.

What is a Critical Path Innovation Meeting (CPIM) ?

Critical Path Innovation Meeting (CPIM)

- CPIMs are administered through the FDA's Office of Translational Science, within the Center for Drug Evaluation and Research
- A CPIM is broad in scope and serves as an opportunity for general discussion of challenges in drug development and innovative strategies to address them
- Purpose is to foster discussion of the science, medicine, and regulatory aspects of innovations in drug development
- Requests for CPIMs may come from anyone with a role in drug development (industry, government, PPP, academia, advocacy)
- Appropriate FDA experts from CDER offices and other Centers will participate as resources and time permit
- Meeting discussions are nonbinding on FDA and other participants

CPIM Details

Critical Path to TB Drug Regimens

Examples of CPIM Topics

- Potential biomarkers not ready for formal Qualification Program
- Emerging technologies (non-manufacturing) or new uses of existing technologies
- Novel clinical trial designs and methods

A CPIM does **not** provide

- Advice or a discussion of the regulatory pathway of a particular product
- Discussion of the qualification of particular biomarker, clinical outcome assessment, or animal model

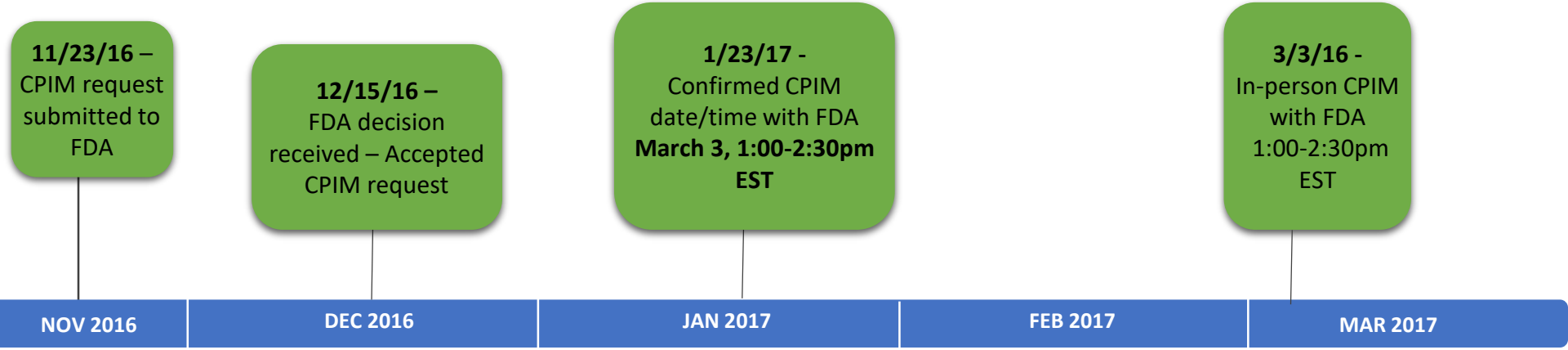
CPIM Details (continued)

Critical Path to TB Drug Regimens

- The CPIM is expected to provide FDA with exposure to innovative methods and techniques that may have value in drug development
- Information package containing the meeting objective, proposed agenda, presentation slides, and attendees is submitted to FDA in advance of the CPIM
- Meetings are typically held in person at FDA and are 60-90 minutes in length
- Outcomes include CDER's perspectives and advice on:
  - Potential for use of proposed new tools and methods in drug development
  - Issues to consider in pursuing the work
  - Pursuing joint efforts through existing consortia, or the potential to form new consortia
  - Recommendations for public workshops or other avenues for engaging with the wider scientific community
- CPIM summary issued by FDA within 60 days of meeting

CPIM Information from FDA: http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm395888.htm

LAM CPIM Request Timeline



Next Steps:

- Feedback from FDA is expected by May 3, 2017.
- Input received from FDA in the meeting will be used to inform future qualification plans for this biomarker.

What we presented for the CPIM

The Opportunity

High unmet medical need for real-time assessment of efficacy in TB drug development trials

- Field requires a tool that:
  - Assesses Early Bactericidal Activity (EBA) and Sputum Culture Conversion (SCC) in real-time, allowing for quick decision making
  - Reduces cost associated with delayed results in development of drugs for TB, a therapeutic area with limited treatment options and few commercial incentives
  - Can be easily utilized in varying clinical trial settings
  - Is not affected by contamination or drug carry-over effect

Current Landscape: Sputum Culture as a Surrogate Endpoint in TB Drug Development

Both FDA and EMA guidelines recommend the following microbiologic endpoints for clinical trials:

- Early Bactericidal Activity (EBA)
  - Over 14 days
  - Quantitative colony forming unit (cfu) counts of sputum viable tubercle bacilli on solid media
  - Time to detection (TTD) on liquid media
- Sputum Culture Conversion (SCC)
  - Either solid or liquid media, or both
  - Proportion at 2 months or time to conversion
  - Proportion at 6 months or time to conversion
  - Proportion of sustained conversion
  - 2 month SCC can be used for MDR-TB accelerated approval (21 CFR part 314, subpart H)

14-day EBA is Useful: Challenging to Conduct

- Time delay and resource requirement
  - ~ 4-6 weeks for cfu count
  - Quantitative culture requires serial dilutions of sputum, and weekly reading of plates, resulting in high work load
  - MGIT-TTD requires a separate sample processing
  - Limited number of labs can perform such work
  - Risk of contamination
  - Drug carry-over (over-estimate of efficacy)
  - TTD has its own challenges
    - Detection uses automated systems, such as MGIT, but TTD is not a direct measure of cfu counts
    - During treatment, viable bacilli may grow slower, resulting in inaccurate measure of viable bacilli
    - Results require up to 1-2 weeks; only semi-quantitative

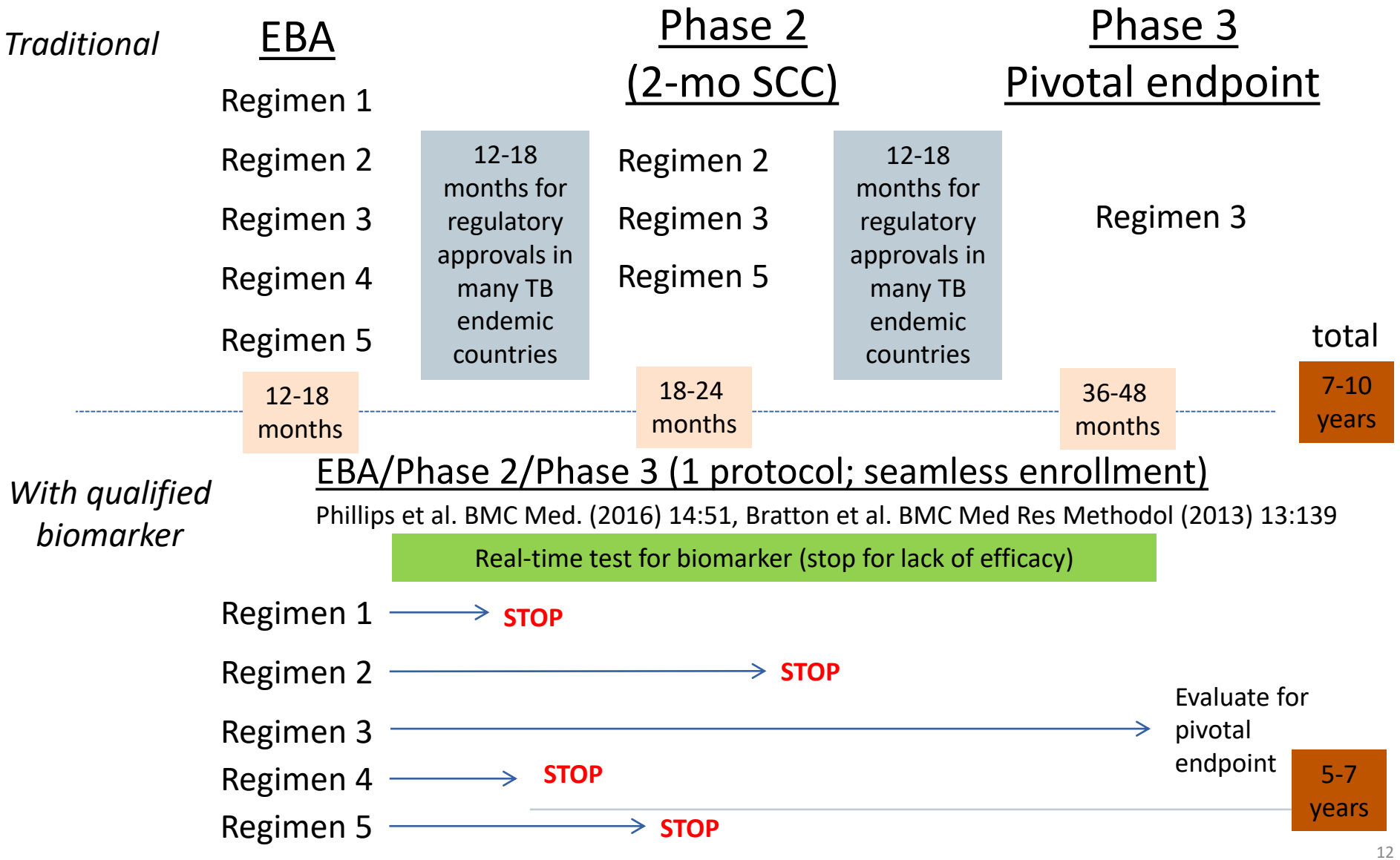
MGIT = Mycobacteria Growth Indicator Tube; BACTEC MGIT 960 System (Becton Dickinson)

Sputum Culture Conversion is a Delayed Efficacy Measurement

- SCC determination requires up to 2 months

- Technical challenges
  - Contamination
  - Drug carry-over (over-estimate of efficacy)

The Envisioned Impact:
Potentially Shortens Development Time by 2-3 Years



The Opportunity: LAM as a Real-Time Evaluation of Treatment Response

- LAM: Lipoarabinomannan; a major cell wall component

- A new immunoassay was developed (LAM-ELISA) that measures sputum LAM
  - Specific for LAM from MTB and a few slow growing mycobacterium strains
  - No cross-reactivity with oral bacteria
  - Strong correlation between sputum LAM and cfu counts/TTD

- Not affected by contamination or drug carry-over
- LAM-ELISA: 20 min LAM extraction; 5 hours ELISA
- Quicker tests being developed (results in <1 hour)

Basic LAM-ELISA Characteristics

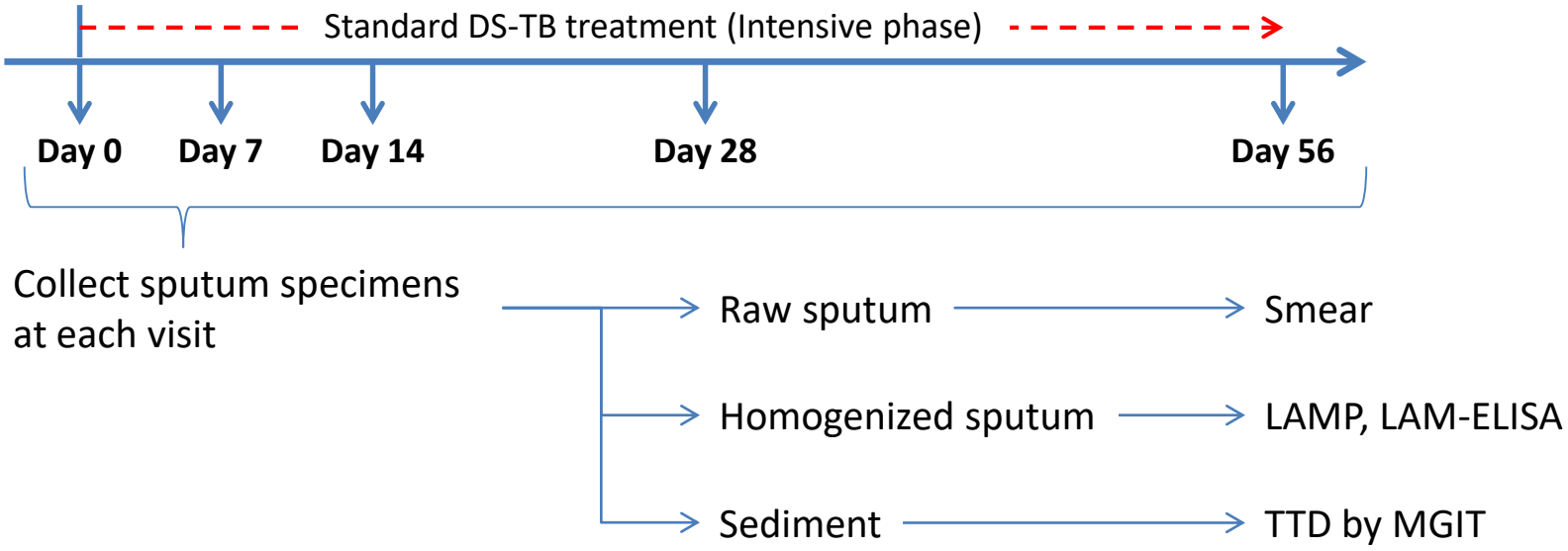
- Laboratory strains
  - 1 pg of LAM = 8.06 cfu (H37Rv)
  - LLoD: 8.5 pg/mL (~69 cfu/mL); LLoQ: 15 pg/mL (~121 cfu/mL)
  - Specific for LAM from *Mycobacteria tuberculosis* and with lower sensitivity to slow growing non-tuberculosis mycobacteria [NTM]; not reacting with fast growing NTMs

Results from 4 Studies Submitted as Part of CPIM Request

- **Summary of 3 studies evaluating sensitivity and specificity**
  - In smear+/culture+ sputum specimens, sensitivity is 100% in two studies: one with n=70 and another with n=100 (bio-bank)
  - In smear-/MGIT+ sputum specimens, sensitivity is 51% (n=57) (vs. 79% by Xpert) in one study and 74% (n=20; bio-bank) in another
  - Specificity is 100% in non-TB subjects (n=56)
  - NTM detection is low (7%; 2/28)

The 4th Study Evaluated LAM Changes During Treatment

- Enrolled acid-fast bacilli (AFB) smear positive patients in Manila, Philippines
- Purpose: Evaluated LAM concentration changes during HRZE standard drug susceptible pulmonary TB treatment in relationship with MGIT-TTD



[Sponsored by Otsuka]
LAMP: loop-mediated isothermal amplification (Eiken, Japan); a nucleic acid amplification test

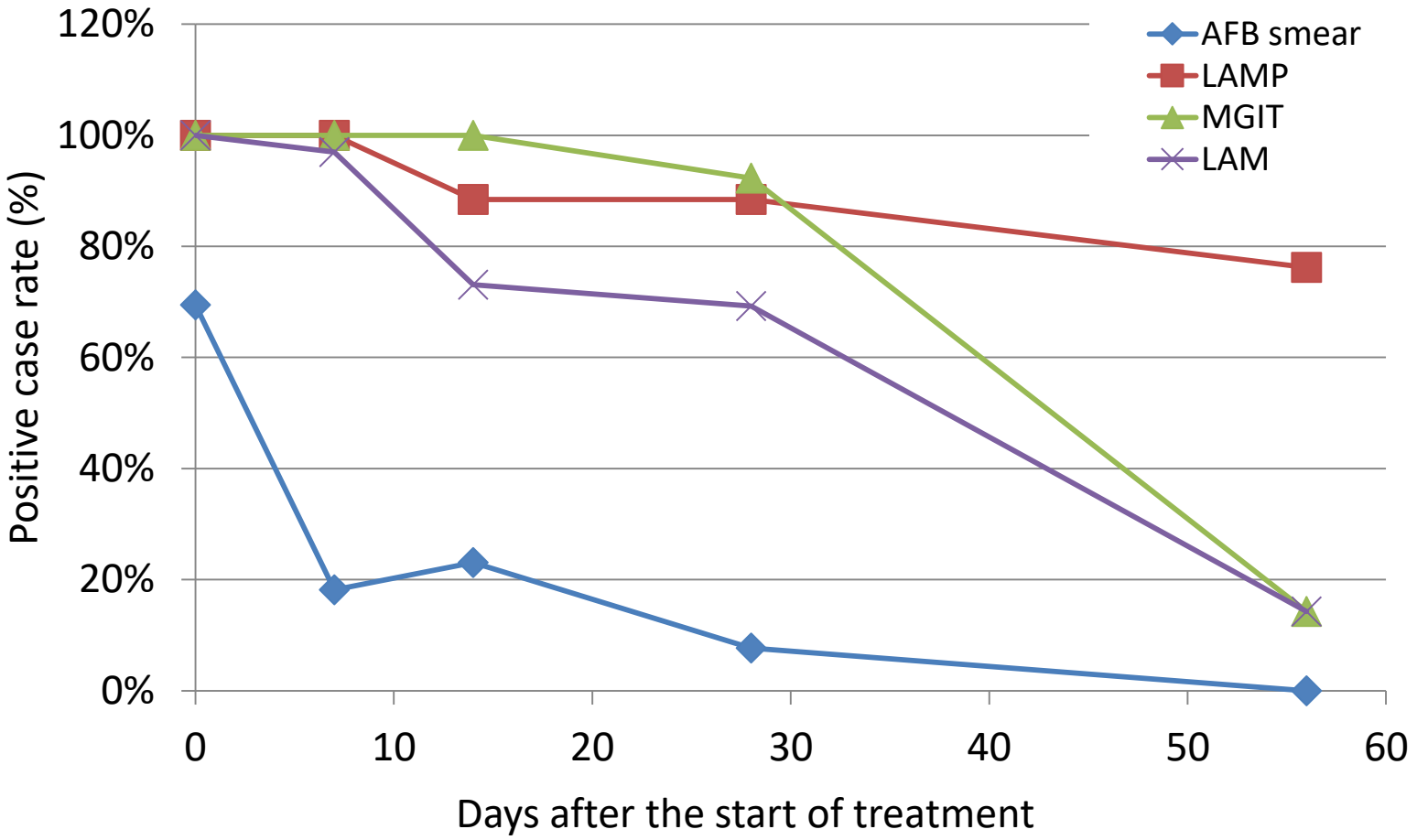
H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol

Sputum LAM Concentration Significantly Decreased During 14 Day Treatment

	LAM (Log pg/mL) (n=24)		*colony counts on solid media (Log cfu/mL) (n=6)		MGIT TTD (hr) (n=24)	
	Average	SD	Average	SD	Average	SD
Day 0	3.97	0.97	6.36	0.61	130.9	31.3
Day 14	2.73	1.04	4.78	1.58	351.7	88.3
delta	**-1.24**		**-1.58**		**+227.8**	

SD: standard deviation
n: number of patients
*: Diacon, Int J Tuberc Lung Dis 2011

Sputum LAM Conversion and MGIT Culture Conversion Trended Similarly in 4th LAM Study



Additional Studies: NexGen EBA Study

Study Design*

a prospective, randomized study of drug-naïve subjects with smear-positive, drug-susceptible pulmonary TB, comparing microbiological and immunological parameters, and imaging during the first 14 day drug therapy

8 arms (n=20 in each arm)

Isoniazid (H)	Rifampin (R)	Pyrazinamide (Z)	Moxifloxacin (M)	HZ	RZ	MRZE E: ethambutol	HRZE

*: Sponsored by NIAID and being conducted in Cape Town, South Africa (NCT02371681)

Next Steps

- Obtain Data from the NexGen study
- Studies of the degradation of LAM during treatment so that dead bacilli are not detected by the antibodies
- Identification of LAM epitopes that are the antibody binding side(s)

Proposed “Context of Use”

- LAM is a pharmacodynamic biomarker for quantitative measurement of bacterial load in sputum. A decrease of LAM in sputum likely reflects the reduction of bacterial load in the lung.
- This pharmacodynamic biomarker should be considered with other microbiological measurements, such as culture, as a real-time evaluation of treatment response in clinical trials of patients with pulmonary TB and positive smears and cultures, such as:
  - 14-day early bactericidal activity (EBA) trials,
  - In clinical trials of pulmonary TB up to 56 days, or
  - In clinical trials to provide evidence for early decision making in adaptive trial designs.

Summary

- Sputum LAM concentration measured by LAM-ELISA is a promising biomarker of viable tubercle bacillus load in sputum
  - Change in sputum LAM concentration likely correlates with change in sputum cfu and MGIT TTD, thus a useful test in EBA studies
  - Sputum LAM conversion is closely associated with MGIT conversion after 56-day treatment in DS-TB patients
  - Not affected by contamination

Thank you!