Host-directed therapy for TB

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TB IS THE TOP INFECTIOUS KILLER IN THE WORLD

IN 2017

1.6 MILLION TB DEATHS

INCLUDING **0.3 MILLION DEATHS** AMONG **PEOPLE WITH HIV**

TB IS THE **LEADING KILLER** OF **PEOPLE WITH HIV**

AND **MAJOR CAUSE** OF **DEATH** DUE TO **ANTIMICROBIAL RESISTANCE**

10 MILLION PEOPLE FELL ILL WITH TB

5.8 MILLION MEN

3.2 MILLION WOMEN

1 MILLION CHILDREN

Standard TB treatment

2 months induction

- RIF, INH, PZA, EMB

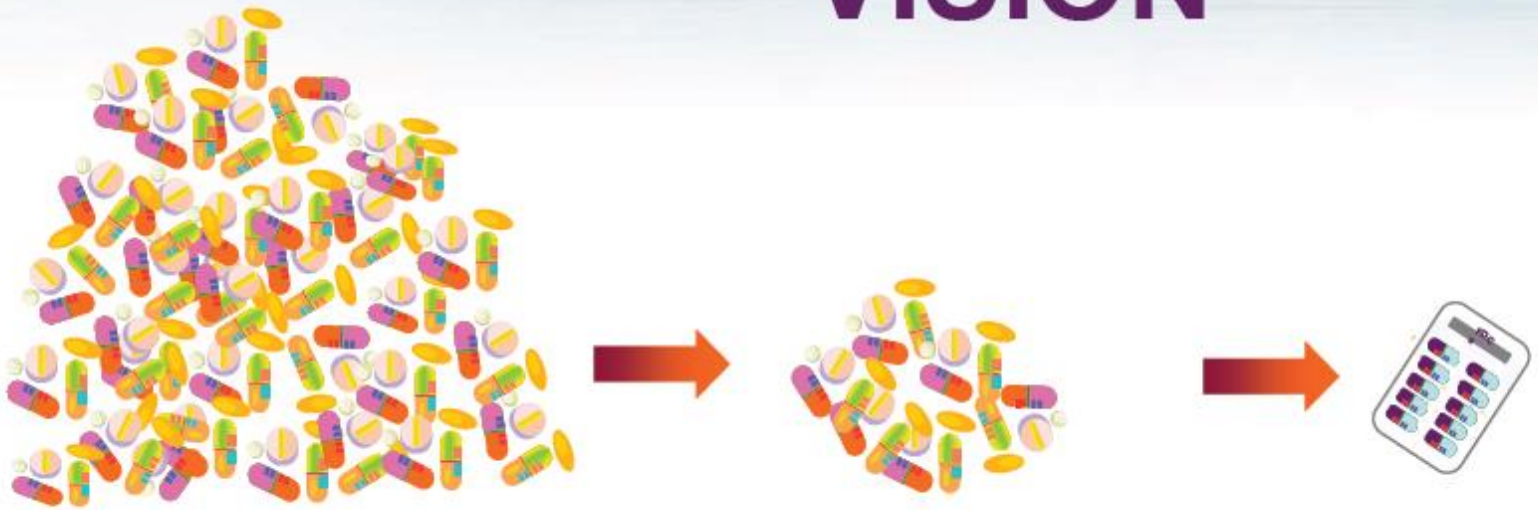
4 months continuation

- RIF & INH

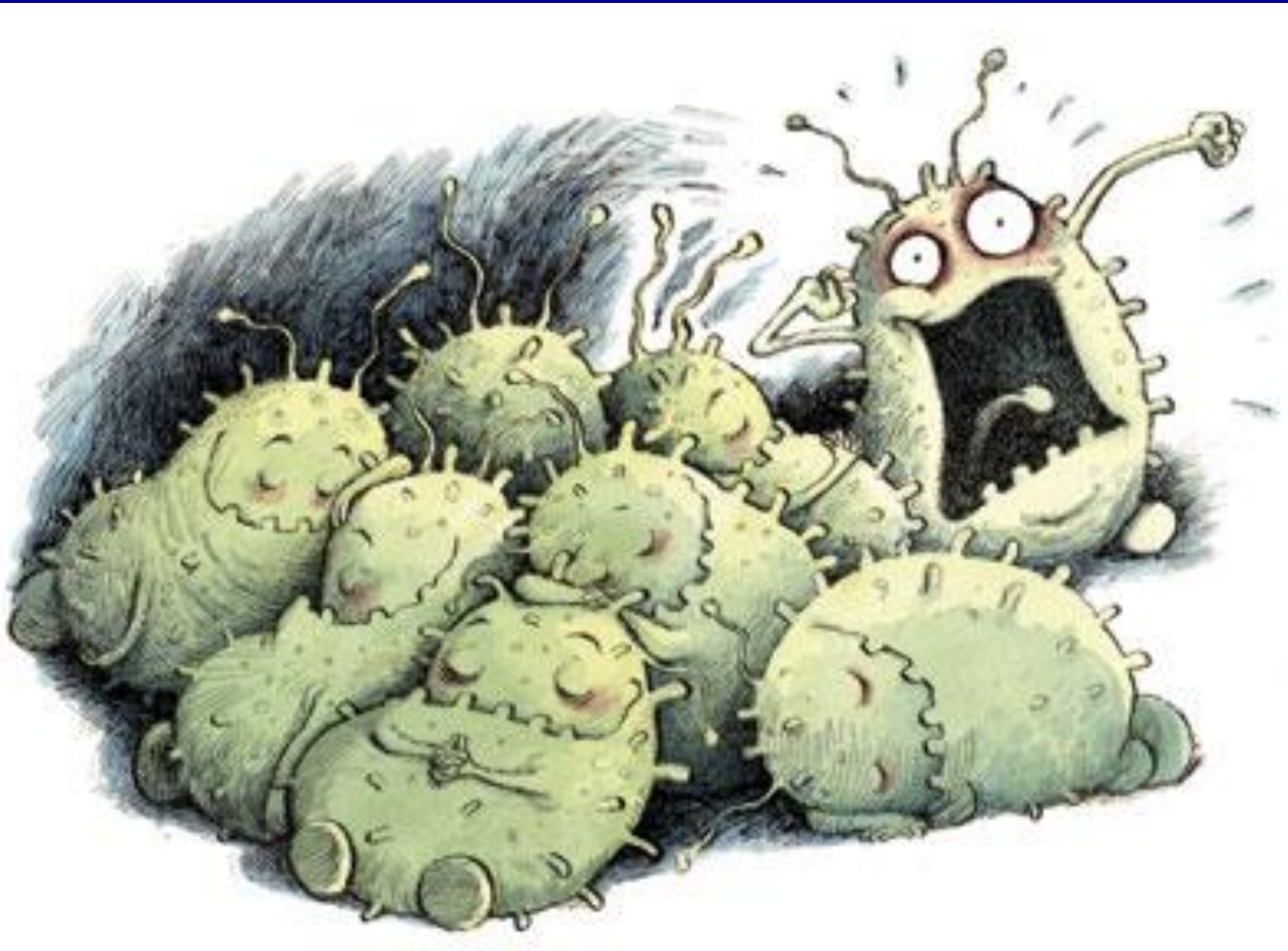
*

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

VISION



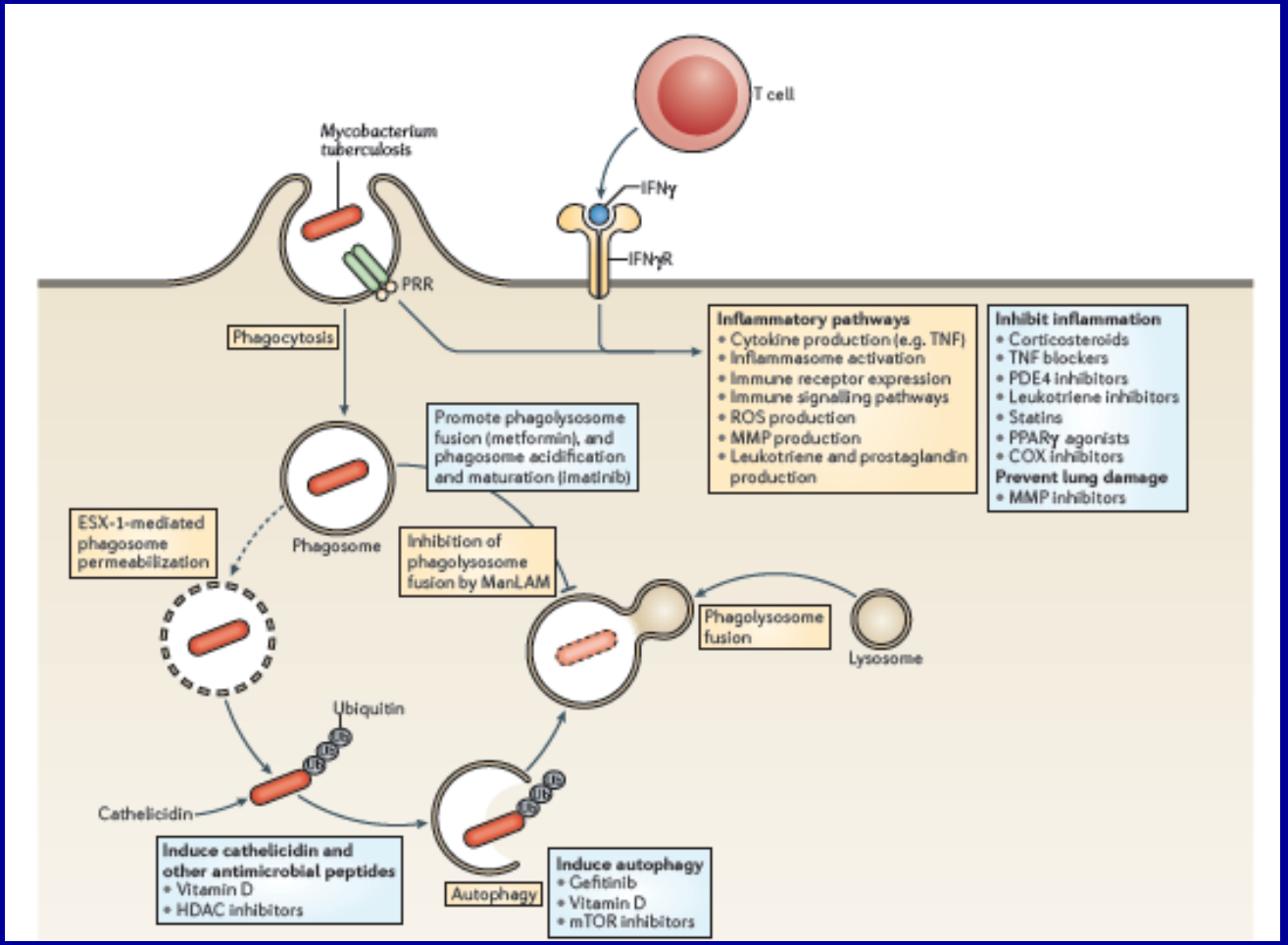
6 months *2 months* *10 days*



3 approaches to shorten treatment for TB

- New drug regimens with improved activity against dormant / persistent bacteria - “sterilising activity”
- Improve the immune response to clear persistent bacteria
- Innovative treatment strategies

Host-directed therapy for TB



Wallis & Hafner, Nature Rev Immunol 2015

Randomised controlled trial of Pascolizumab (anti-IL-4 monoclonal antibody) as an adjunct to standard TB treatment

NMRC National Medical Research Council Singapore

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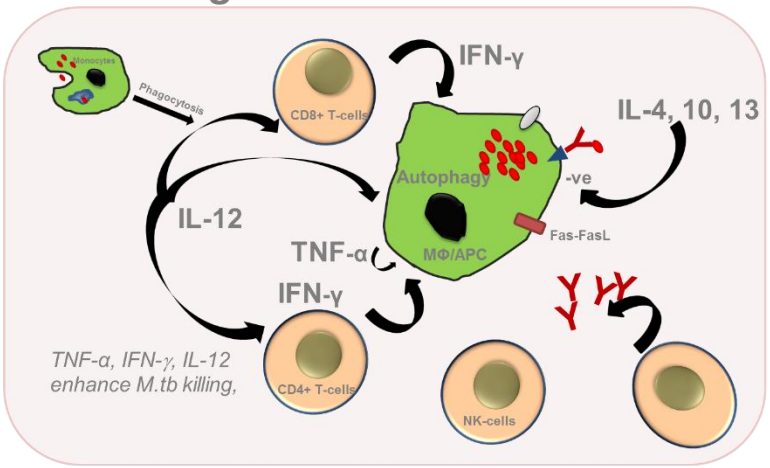
SINGAPORE PROGRAMME OF RESEARCH INVESTIGATING NEW APPROACHES TO TREATMENT OF TUBERCULOSIS

TRIAL RATIONALE

Immunological rationale



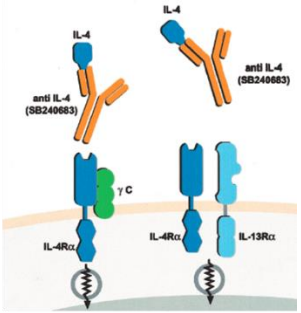
Availability of human anti-IL4 mAb

Clin Exp Immunol 2002; 130:93–100

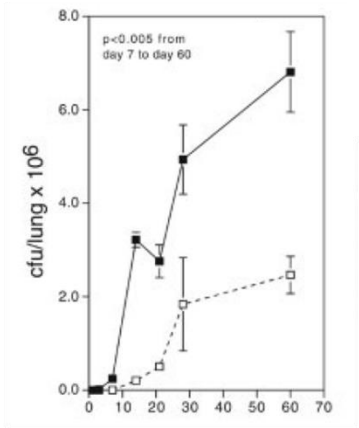
Preclinical efficacy and safety of pascolizumab (SB 240683): a humanized anti-interleukin-4 antibody with therapeutic potential in asthma

T. K. HART, M. N. BLACKBURN, M. BRIGHAM-BURKE, K. DEDE, N. AL-MAHDI, P. ZIA-AMIRHOSSEINI* & R. M. COOK† *GlaxoSmithKline, King of Prussia, PA, and Protein Design Laboratories, Inc., Fremont, CA, USA*

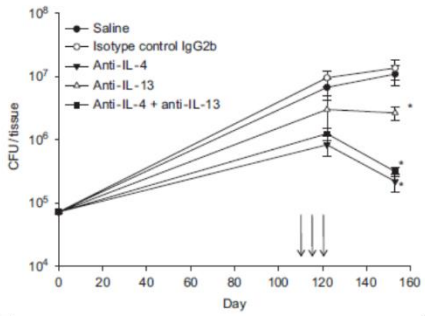
(Accepted for publication 25 July 2002)

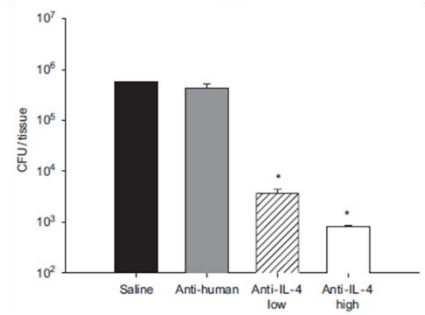


In vivo data



Hernandez-Pando et al
Eur J Immunol, 2004





Roy et al Tuberculosis, 2008

Study Number	Objective	No. and Type of Subjects Enrolled	N per protocol	Design	Delivery	Dose	Duration of Treatment	Age (range)
SB240683/ 001	Internal SB study	5 patients with mild to moderate asthma	5	Internal study reports	IV inf.	0.05 mg/kg	Single dose	26.8 (23-35)
PDL 683-801	Evaluate safety, tolerability and PK/PD	24 patients with mild to moderate persistent asthma	24	Single-blind, placebo-controlled, dose escalat'n	IV inf.	0.5, 1.5, 4.5, 10 mg/kg	Single dose	29.6 (19-45)
PDL 683-802	Evaluate safety, tolerability and PK/PD	14 patients with symptomatic mod-severe persistent asthma	13	Double-blind, placebo-controlled, dose escalat'n	IV inf.	1.5, 10 mg/kg	3 doses in total at monthly intervals	37.7 (21-49)
PDL 683-803	Exploratory Efficacy, safety and PK	121 patients with symptomatic, steroid-naïve asthma	103	Double-blind, placebo-controlled, parallel-group	IV inf.	1.5, 10 mg/kg	3 doses in total at monthly intervals	35.6 (18-62)
PDL 683-804	Evaluate safety, tolerability and PK	20 healthy adult volunteers	20	Double-blind, placebo-controlled, dose escalat'n	S.c. inj.	1.0, 2.0 mg/kg	3 doses in total (Days 0, 15 and 30)	39.1 (19-64)

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TRIAL AIMS

- Safety in DS-TB
- Efficacy: whether pascolizumab (with Rx for DS-TB) changes one or more parameters of bacterial / host response indicating potential for enhanced sterilization:
  - bacterial clearance
  - host clinical status
  - lung imaging
  - bacterial and host transcriptomics
  - immune response

ClinicalTrials.gov: NCT01638520

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PATIENTS: MAIN ELIGIBILITY CRITERIA

INCLUSIONS

- ✓ Aged 21 -75 years
- ✓ Male or female
- ✓ Confirmed pulmonary TB by (i) Gene Xpert™ or culture AND (ii) characteristic clinical features or +ve smear microscopy or both
- ✓ No rifampicin resistance (Gene Xpert)
- ✓ No history of anti-TB therapy for active disease (treatment for latent disease acceptable)

EXCLUSIONS

- X >28d of standard anti-TB Rx
- X Disseminated TB
- X Underlying serious chronic disease/ significant organ dysfunction
- X Currently pregnant/breastfeeding women
- X Autoimmune disease (current or previous)
- X Chronic use of an immunosuppressant
- X HIV infection; HBsAg +ve; HCV Ab +ve
- X Creatinine > 1.4 times ULN or ALT > 2.5 times ULN

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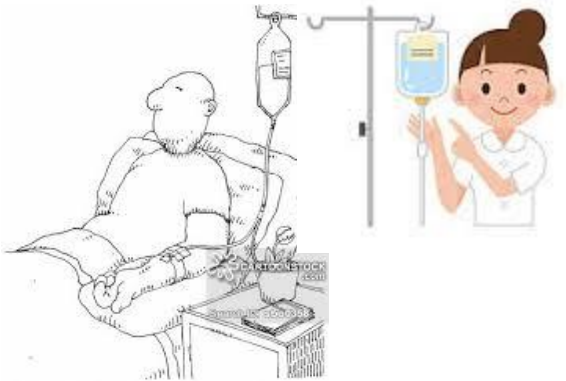
Pascolizumab Phase IIb trial

Patients randomized to pascolizumab / placebo (in addition to normal TB Rx).
Pascolizumab given by i.v. infusion

Dose increases with successive cohorts.

Cohort 1:	**0.05mg/kg** single dose; 4 active
Cohort 2:	**0.5mg/kg** single dose; 4 active
Cohort 3:	**2.5mg/kg** single dose; 9 active, 3 placebo
Cohort 4:	**10mg/kg** single dose; 9 active, 3 placebo

Safety review committee between each cohort



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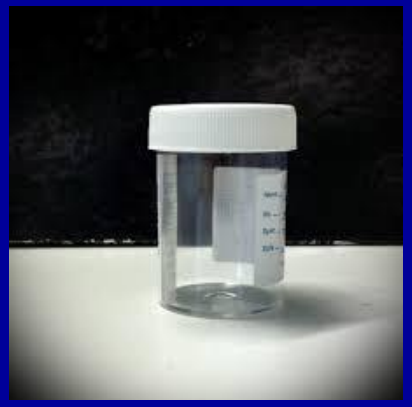
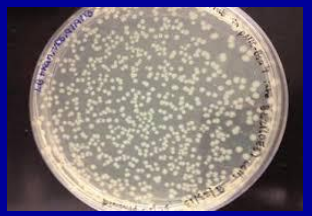
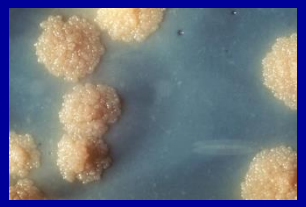
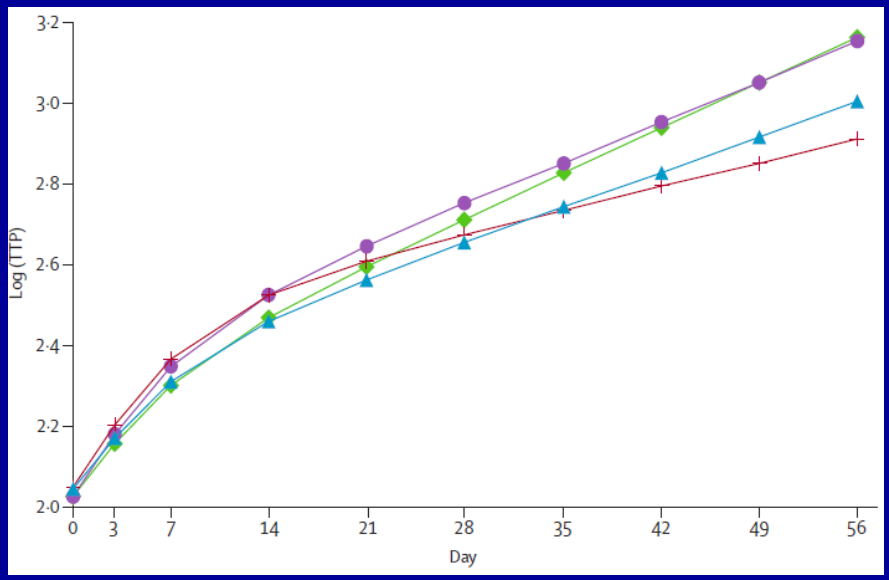
Phase IIb: Serial sputum colony count (SSCC) trial









TRIAL SCHEDULE

0-28 days from start of TB Rx ↓

Visit timing Phone assessment	Scr.	D0	D1	D2	D3	D4	D5	D6	W1	W2	W3	W4	W6	W8	W12	W16	W20	W24	W 36	W 48	W 96
Informed Consent	X																				
Entry criteria	X	X																			
Randomisation		X																			
Pascolizumab dose		X																			
Medical history	X	X																			
Symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X			
Urine Pregnancy test	X	X										X		X	X			X			
ECG	X	X	X									X									
CXR	X	X												X				X			
PET/MRI or PET/CT		X												X				X			
Spot sputum for Gene Xpert test	X																				
Overnight sputum collection		X	X		X		X		X	X	X	X	X	X	X	X	X	X			
Spot sputum collection		X			X				X	X		X		X							
Blood for standard laboratory tests	X	X							X	X		X		X		X		X			
Blood for HIV, HBV, HCV testing	X																				
Blood for Immune profile		X	X		X		X		X	X		X		X				X			
Blood for pascolizumab PK/PD profile		X	X		X		X		X	X		X		X				X			
Blood for anti-pascolizumab Ab levels										X				X				X			
Blood for host transcriptomics		X								X		X		X				X			
Blood for EPIMAX Ag stimulation		X										X									
Blood sample for storage		X										X		X				X			
Urine sample for storage		X										X		X				X			

ClinicalTrials.gov: NCT01638520

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METHODS: **SAFETY ASSESSMENTS**

- Follow-up visits to week 24 in person
  (by telephone until week 96 for relapse)
- Symptom review and physical examination each visit
- Safety blood tests at D0, W1, W2, W4, W8, W16, and W24 visits

Primary safety outcome definition

Adverse events:

Occurring between D0 to W24

AND

At least possibly related

AND

Serious and/or Grade 4 severity

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METHODS: **MICROBIOLOGY**

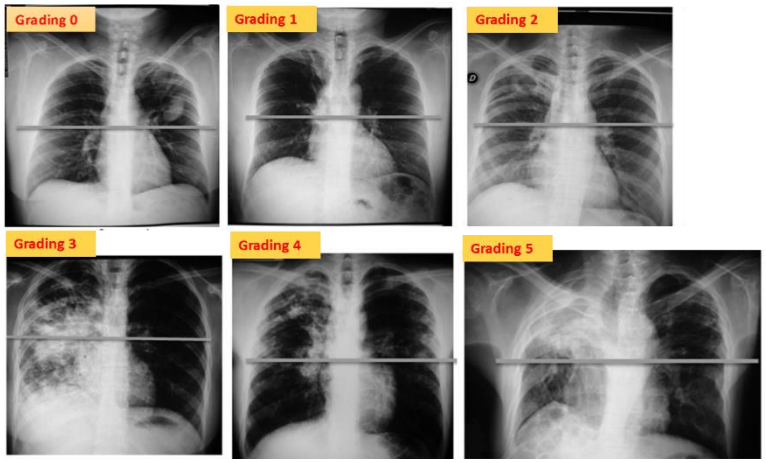
- Liquid cultures
  - MGIT
  - Positive cultures confirmed by Ag test and BAP culture
  - Time to detection (TTD) recorded (inversely related to bacterial load)

- Solid cultures
  - Serial dilution on 7H10 agar
  - Colony Forming Units (CFU)/ml counted visually

METHODS: IMAGING, CHEST X-RAY

- CXRs at D0, W8, and W24 visits
- Central review by 2 independent radiologists
- Calculation of % lung affected (standard approach based on quadrants)
- Cavitation: present / absent
- Overall combined score: % lung involvement and cavitation

Baez-Saldana (2013)



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METHODS: PET-BASED IMAGING

- Done at D0 and W8 visits (additional W24 if PET/MRI)
- PET/MRI in Singapore, PET/CT in other countries
- ^{18}F-FDG: ligand, detects increased glucose metabolism (increased macrophage and neutrophil activity)
- Standard protocol with central analysis at Clinical Imaging Research Centre (CIRC) in Singapore

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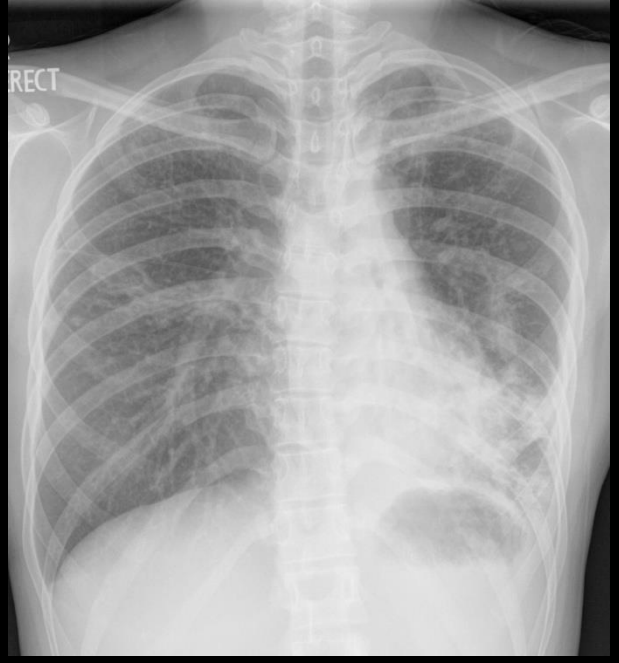
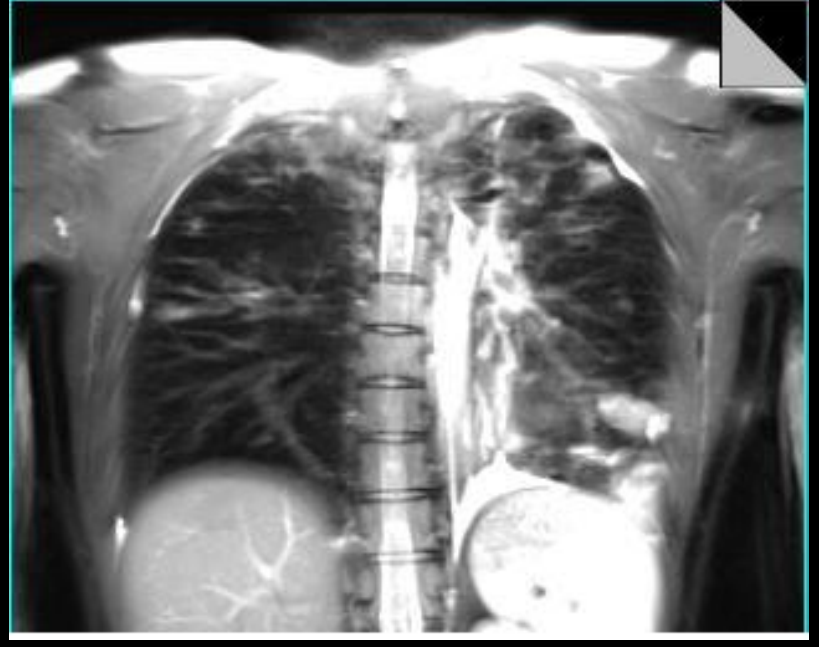
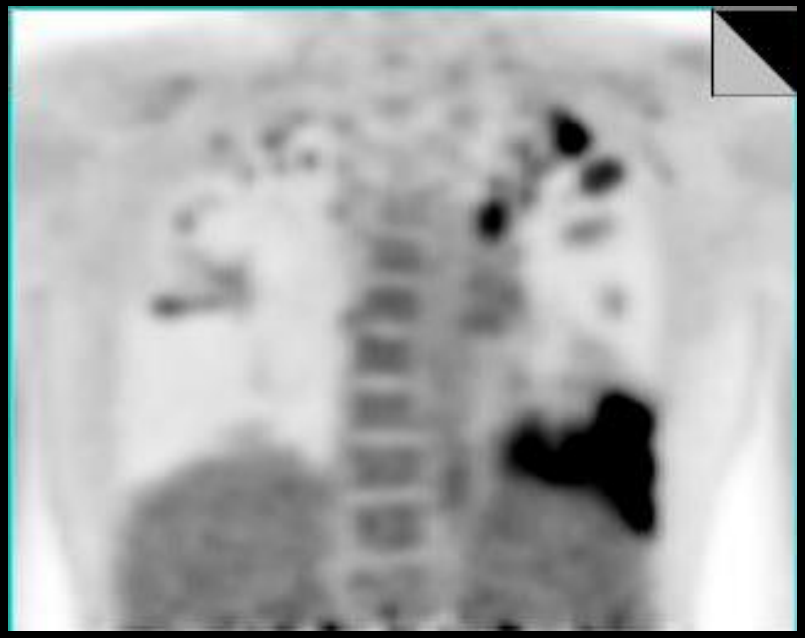
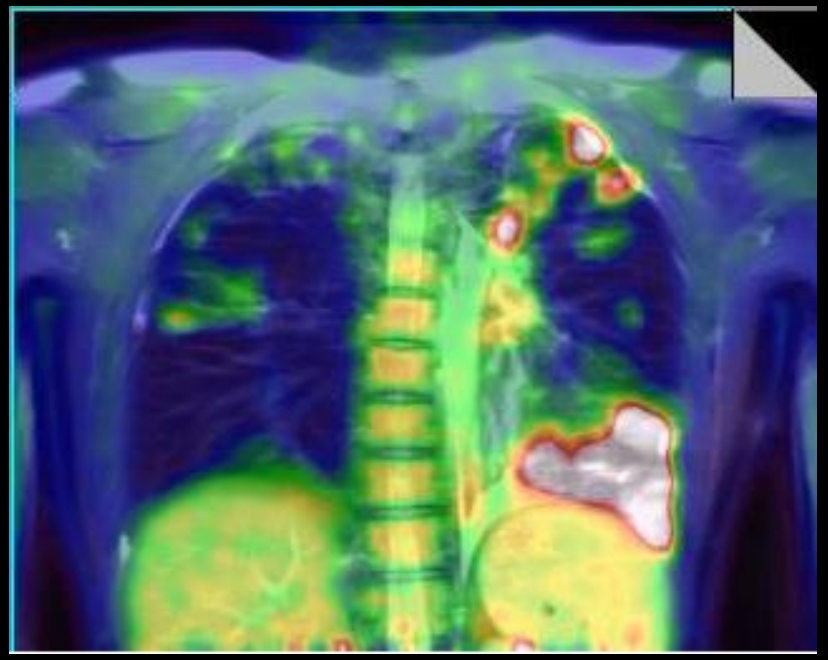
O-H101









TRIAL IMPLEMENTATION

Singapore:

- National University Hospital
- 4 other referring sites

Malaysia:

- Institut Perubatan Respiratori
- University Malaya Medical Centre

Philippines:

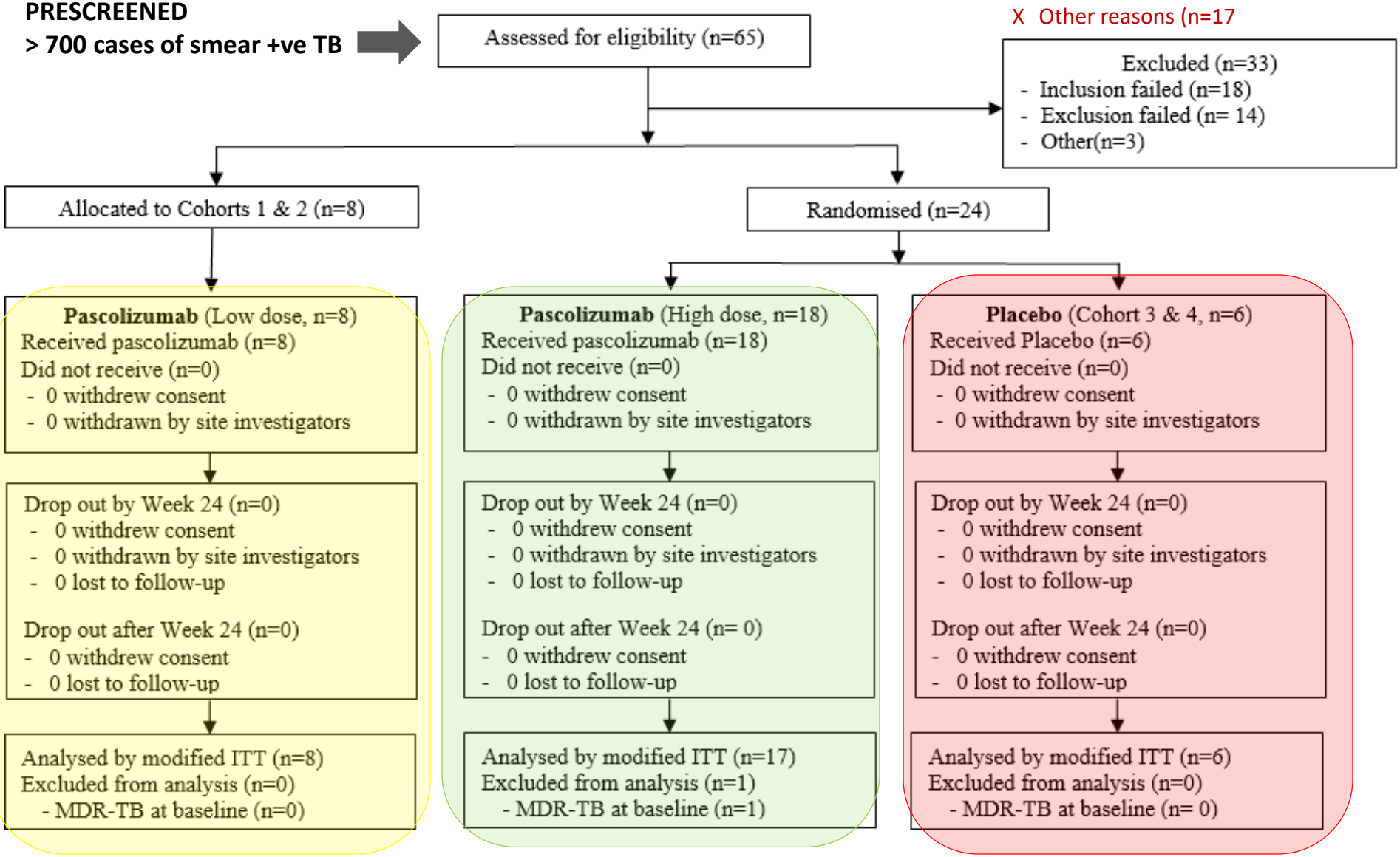
- Philippines Tuberculosis Society Inc.
- Lung Centre Philippines

Meera Gurumurthy

ENROLLMENT: CONSORT DIAGRAM

X GeneXpert negative (8)
X HIV/HBV/HCV positive (5)
X Cardiac problems (4)
X Withdrew consent (7)
X Other reasons (n=17

PRESCREENED
> 700 cases of smear +ve TB



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BASELINE CHARACTERISTICS

	Pascolizumab Low dose (N=8)	Pascolizumab High dose (N=17)	Placebo (N=6)
Demographic characteristics			
Male	7 (87.5)	12 (70.6)	4 (66.7)
Age, Median (IQR)	34 (18)	43 (28)	44 (14)
Diabetes, n (%)	2 (25.0)	3 (17.6)	1 (16.7)
TB characteristics			
Duration of TB treatment (days), median	3.3 (5.1)	8.5 (8.6)	7.0 (8.4)
Liquid culture			
TTD(days), Median (IQR)	11.1 (18.7)	13.2 (3.8)	14.2 (31.2)
Culture positive, n (%)	6 (75)	15 (88)	4 (67)
Solid culture			
Colony count (log_{10}CFU/ml), Median (IQR)	3.1 (2.8)	2.8 (2.4)	2.6 (3.2)
Culture positive, n(%)	6 (75)	12 (71)	4 (67)
Chest X-ray			
Proportion of Total Lung Affected (%), median (IQR)	25.0 (15.0)	25.0 (12.5)	42.5 (35.0)
Cavitation present, n (%)	3 (37.5)	9 (52.9)	4 (66.7)
PET-based imaging			
Total lesion glycolysis (UNIT), Median (IQR)	515.0 (300.1)	576.8 (578.9)	738.8 (840.0)

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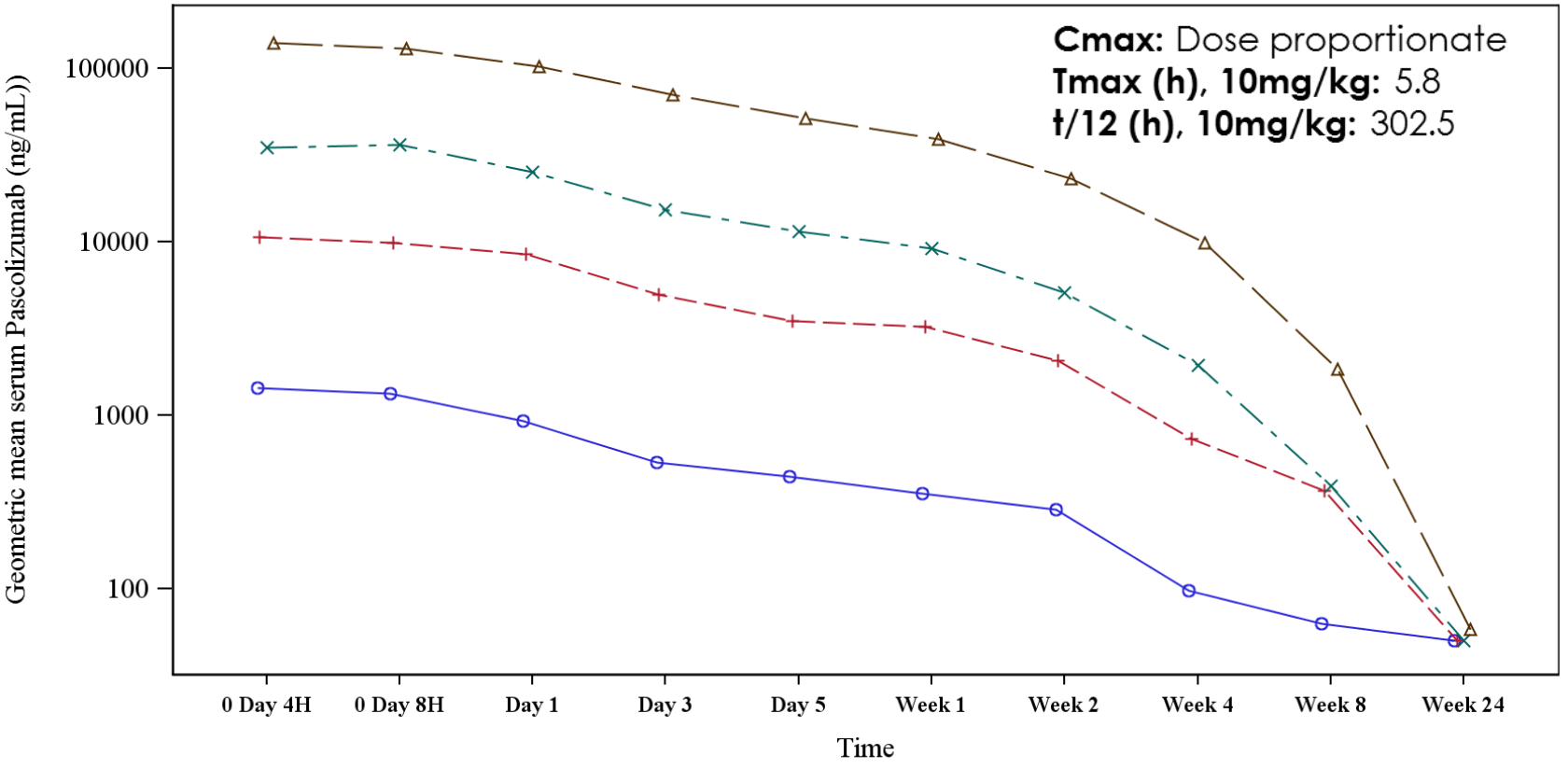
PHARMACOKINETICS: PASCOLIZUMAB DRUG LEVELS



C_{max} (ng/mL) Geometric Mean	1458	10697	35711	140873

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SAFETY ANALYSIS: PRIMARY OUTCOME MEASURE

Primary safety outcome definition

Adverse events:

Occurring between D0 to W24

AND

At least possibly related (site investigator classification)

AND

Serious and/or Grade 4 severity (DAIDS classification)

Result

Nil events meeting definition in either group

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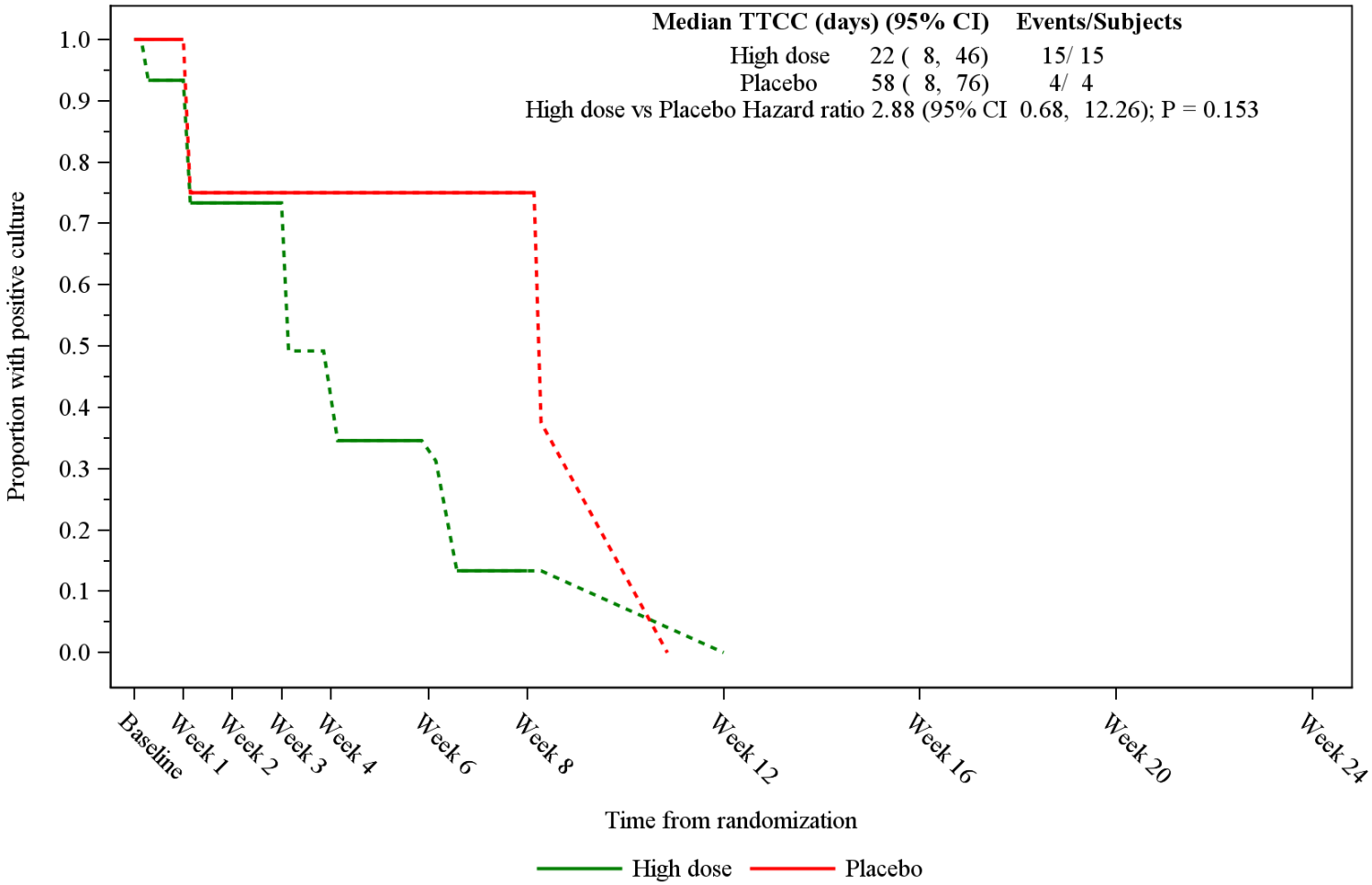
LIQUID CULTURE: TTCC



- Randomised efficacy analysis (pasco/placebo groups combined from 2.5 mg/kg and 10 mg/kg cohorts)
- TFR analysis; main imputation

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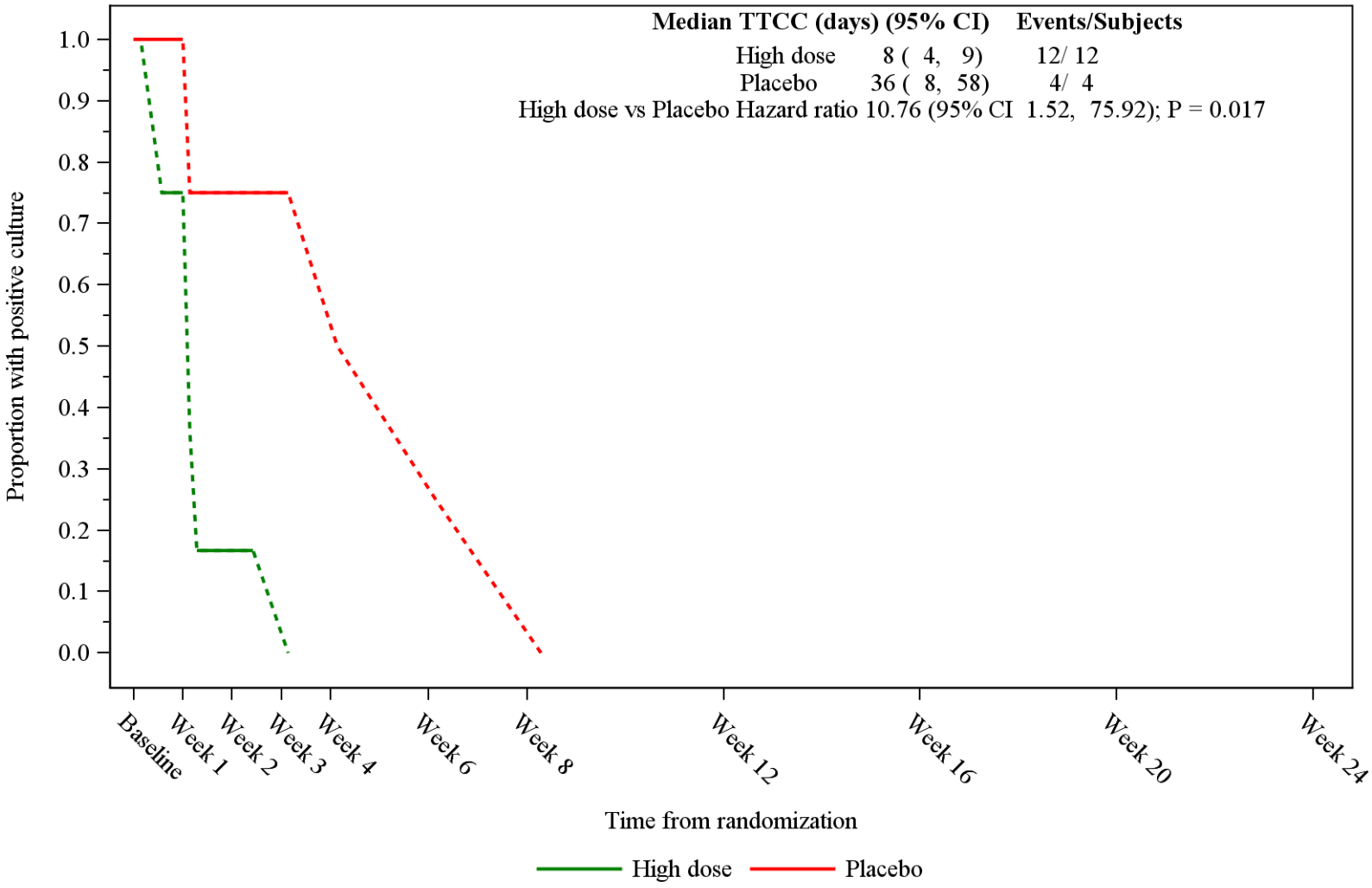
SOLID CULTURE: TTCC



- Randomised efficacy analysis (pasco/placebo groups combined from 2.5 mg/kg and 10 mg/kg cohorts)
- TFR analysis; main imputation

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EFFICACY ANALYSIS: IMAGING BASED OUTCOMES

PET-Imaging Median (IQR)	**Pascolizumab** **(N = 17)**	**Placebo** **(N = 6)**	**p-value**
Change in TLG from baseline to week 8	-296.0 (591.0)	-637.0 (498.2)	0.3166[1]
Change in SLV from baseline to week 8	-6.4 (85.3)	-35.1 (153.0)	0.4932[1]

1: Wilcoxon-Mann-Whitney test.

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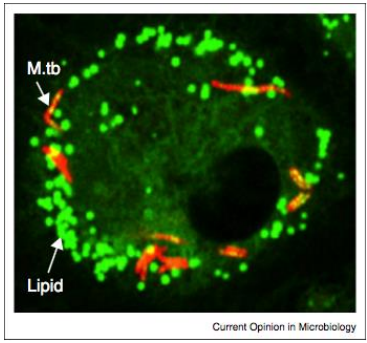
Clinical trial of rosuvastatin as an adjunct to standard treatment for DS-TB

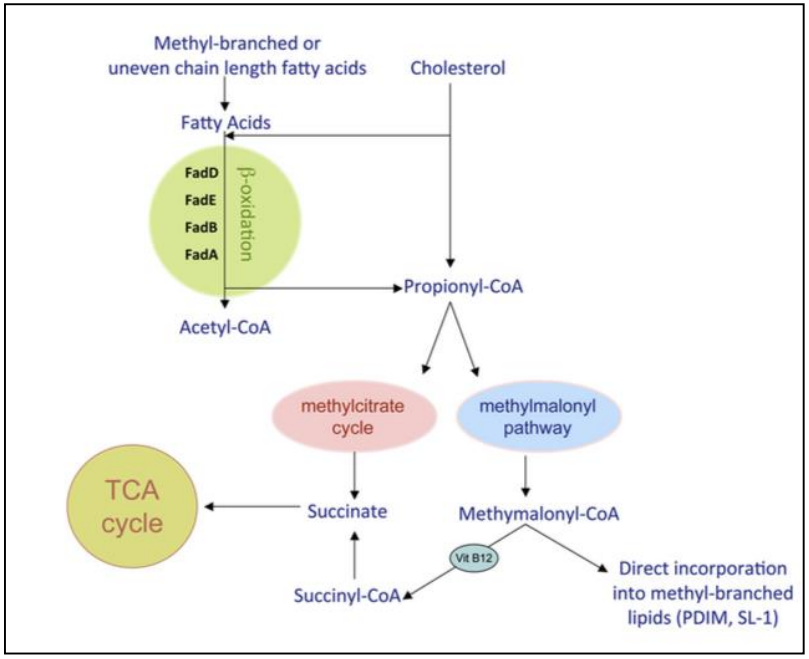
NMRC National Medical Research Council Singapore

Mtb needs cholesterol

- Mtb changes host cell metabolic pathways to drive excessive uptake of Cholesterol within macrophages **(forms Foamy cells)**
- Lipid/ Cholesterol within granulomas are a consequence of foamy cell necrosis
- Cholesterol is the primary carbon source for energy with 250 genes postulated to have role in cholesterol metabolism.
- Utilises cholesterol breakdown products for synthesis of cellular membrane lipids associated with virulence (PDIM)
- MTB scavenges **HOST** cholesterol through *mce4* transporter, no denovo production
- Cholesterol in macrophages limits phagolysosomal fusion, but +++ other

Close proximity of lipid bodies with MTB in macrophages





How do statins work?

Statins are pleiotropic

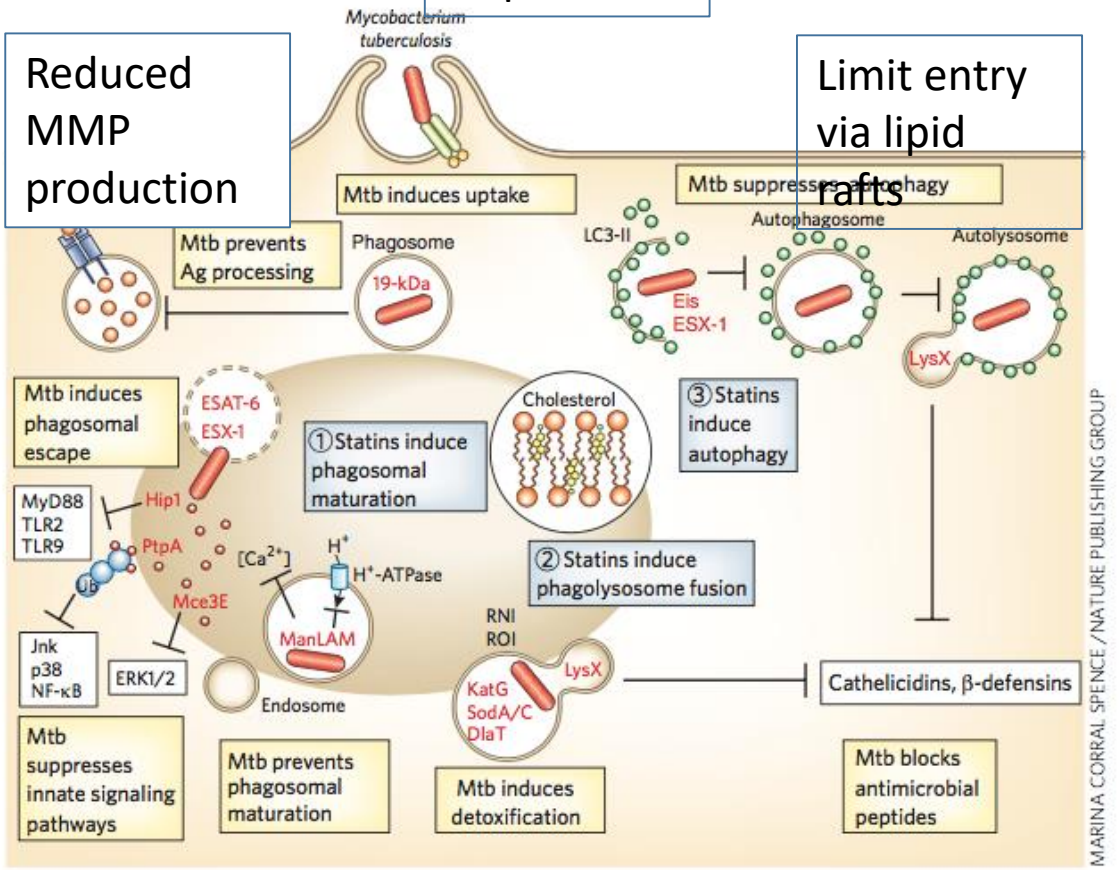
- Anti-cancer
- Anti-inflammatory
- Immunomodulatory activity
- Established in cardiovascular disease/ oncology/ transplant medicine
- Multiple meta-analyses of Statin trials in Sepsis and Pneumonia
- Statins limit development of foamy macrophages (atherosclerosis)

Boosts Th1 response

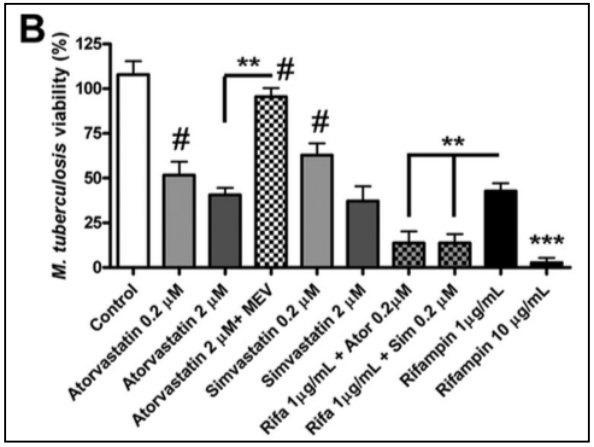
Plethora of others

Reduced MMP production

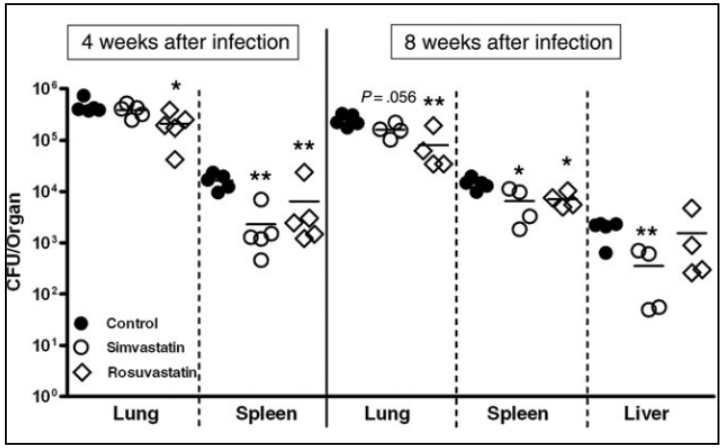
Limit entry via lipid rafts



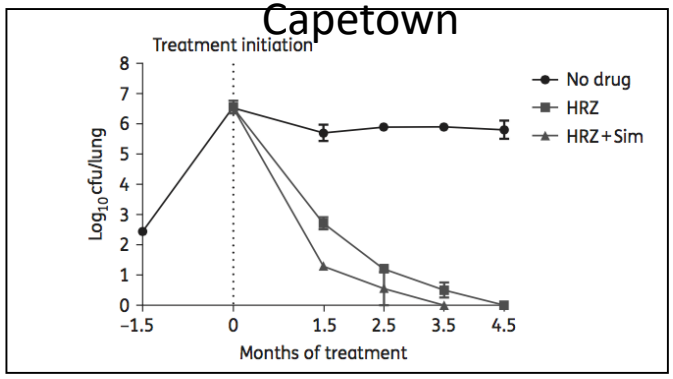
Statins



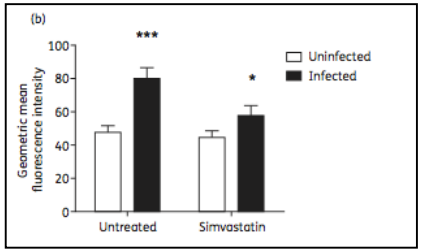
Lobato, Brazil

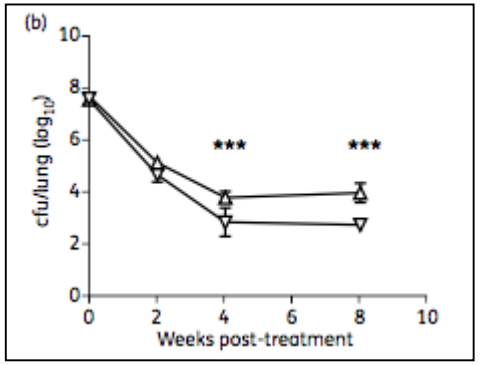


Parihar, Capetown



Johns Hopkins





Johns Hopkins

Dutta

1. Lobato, AAC 2014
2. Parihar, JID 2014
3. Skerry, JAC 2014
4. Dutta, AAC 2016

Trial Design and AIM

Randomised, controlled, double-blind, placebo controlled trial

- n= 110

- Rosuvastatin (10mg) for 8 weeks + HRZE

  OR

  Placebo for 8 weeks + HRZE

- 48 weeks follow-up

Trial Outcomes

Primary Outcome

Time to sputum culture conversion (liquid culture)

Secondary outcome

- Proportion of patients with positive culture at week 8
- Changes in molecular bacterial load at week 8
- Changes in SUVmax/ Total Lesion Glycolysis in TB lesions seen on Pet CT at week 8 vs. baseline
- Total Grade 3 or Grade 4 clinical adverse events
- All-cause mortality between randomization and week 24
- Relapse at week 48

Other markers to be measured

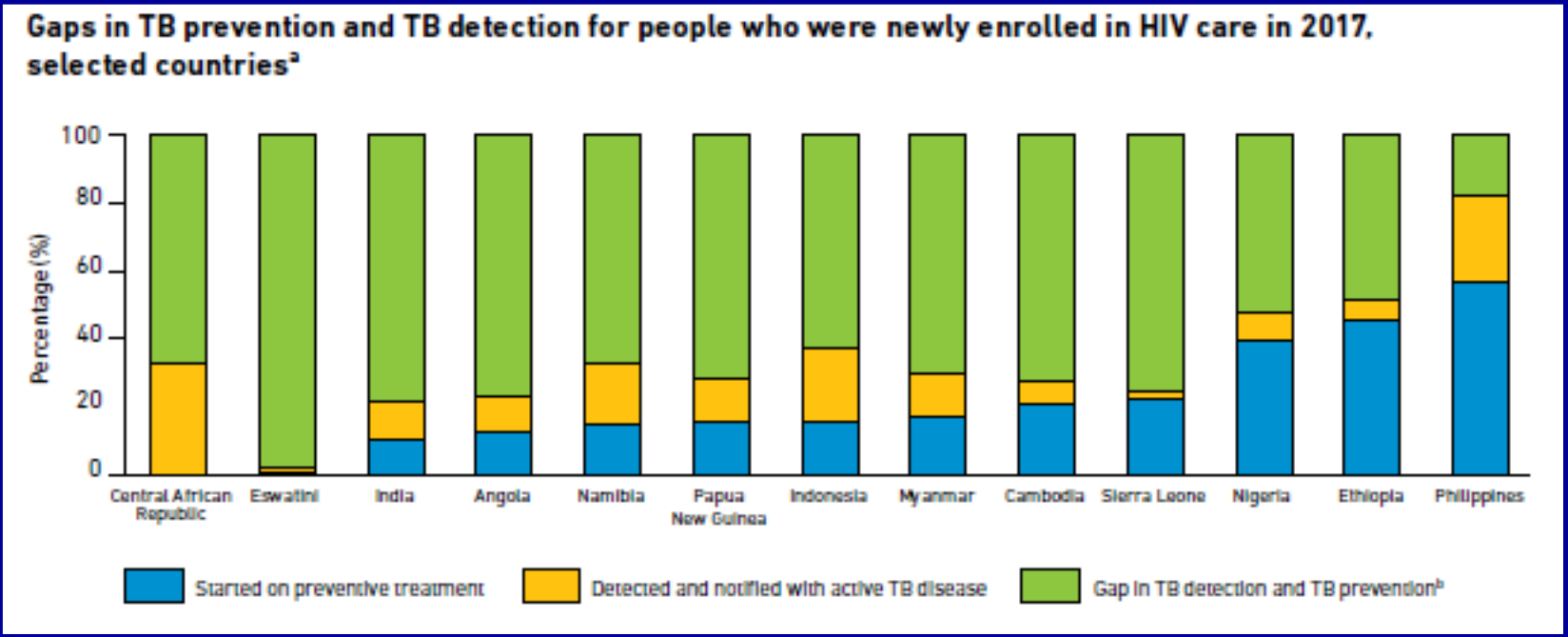
- Host cellular immune markers and cytokines
- Bacterial and host transcriptome

Trial Schedule

Assessments/ Visits[1]	Scr	D0	W1	W2	W3	W4	W5	W6	W7	W8	W10	W12	W13-W23	W24	W48
Informed Consent	X														
Eligibility criteria	X	X													
Randomisation		X													
CLINICAL EVALUATION															
Clinical Progress Assessment		X	X	X		X				X		X		X	X[2]
St George Respiratory Questionnaire		X								X				X	
PULMONARY INVESTIGATIONS															
CXR	X[3]	X								X				X	
PET CT		X								X					
SPIROMETRY		X								X				X	
URINE															
Pregnancy test[4]	X	X								X					
Dipstick for Proteinuria	X			X						X					
Sample for storage (20ml)		X				X				X				X	
SPUTUM[5]															
GeneXpert	X														
Smear, culture, DST[6], molecular bacterial load	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	X	
Sputum for storage[8]		X	X	X	X	X				X		X		X	
BLOOD															
Screening tests[9]	X														
Safety monitoring tests[10]				X						X		X			
Pharmacokinetic studies (rosuvastatin and rifampicin plasma concentration)		X	X	X						X					
Bloods for storage[11]		X	X	X		X				X		X		X	

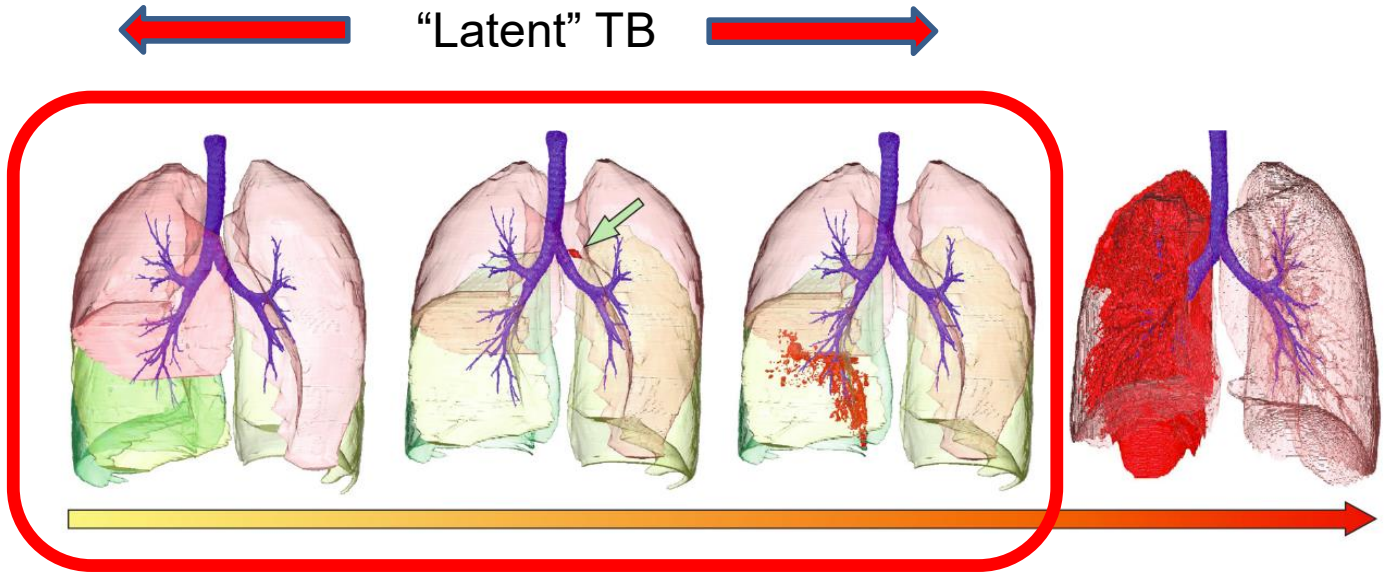
Latent TB

Implementation status



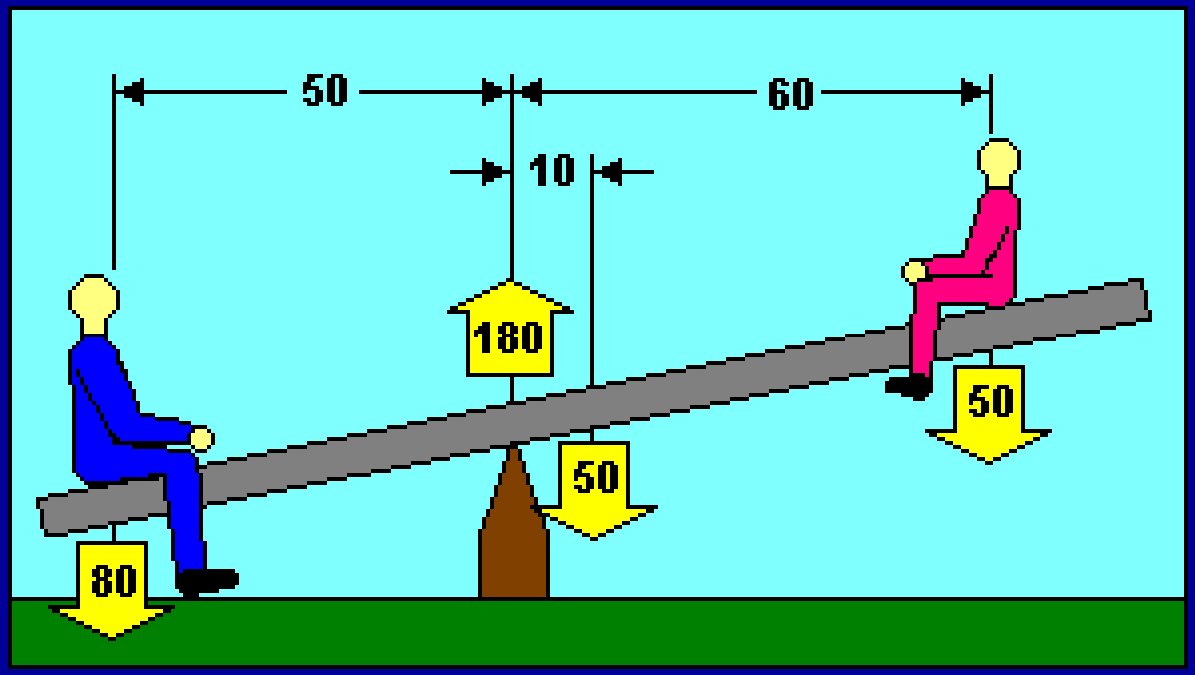
WHO TB Report 2018

HDT in latent TB



IGRA/TST: ≈ 30% of the world’s population have “latent” TB (unable to stage)

HDT for latent TB …



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

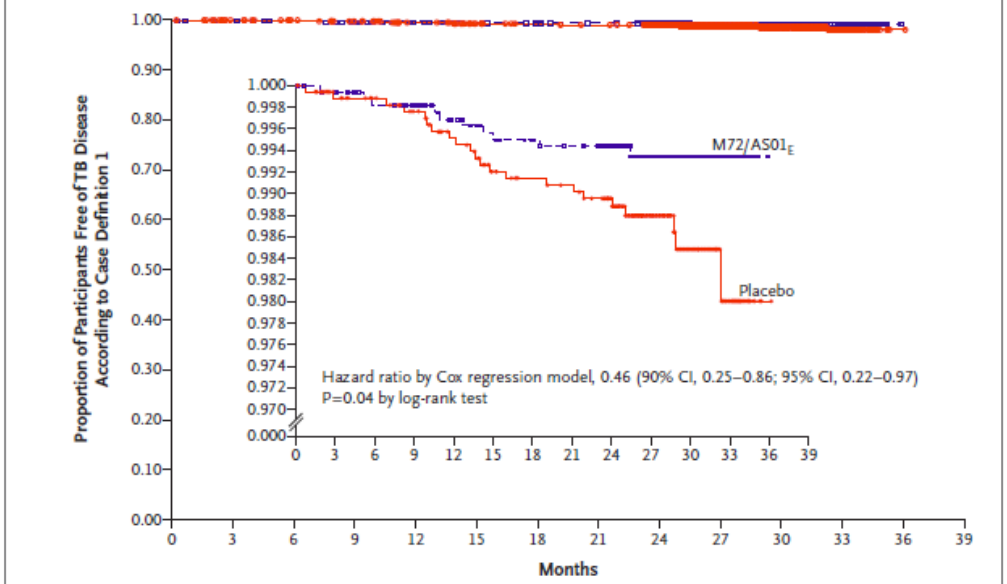


Figure 2. Kaplan–Meier Estimate of Definite Pulmonary Tuberculosis (TB) Disease Not Associated with HIV Infection (First Case Definition).

The analysis was conducted in the according-to-protocol efficacy cohort. The time shown is the time from the beginning of follow-up (i.e., 30 days after dose 2). The inset shows the same data on an enlarged y axis. The decreased number at risk after 24 months reflects the participants for whom follow-up after this time point had not occurred at the date of data lock.

NEJM 2018

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SPRINT TB

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Nick Paton

Thank you

SPRINT TB **S**INGAPORE **P**ROGRAMME OF **R**ESEARCH **I**NVESTIGATING **N**EW APPROACHES TO **T**REATMENT OF TUBERCULOSIS