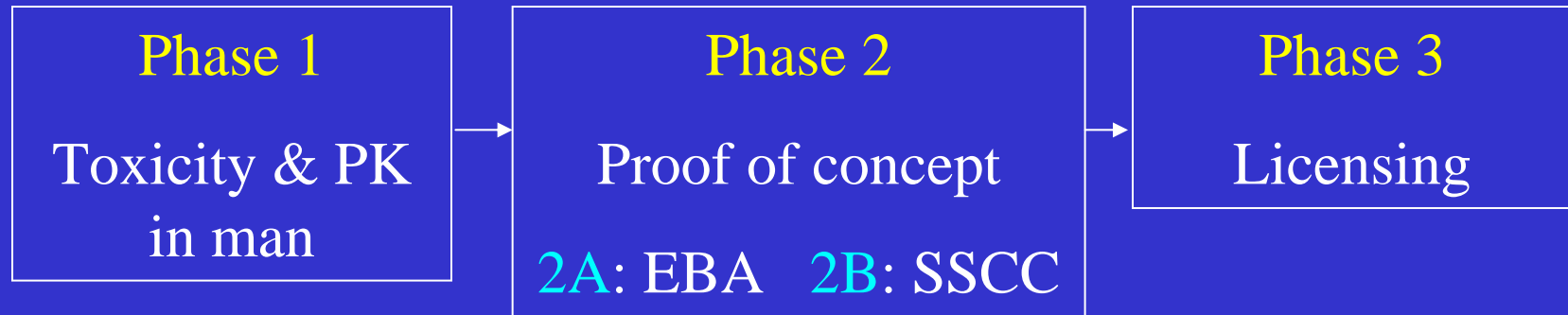


Phase 2 development
EBA and SSCC studies

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Safety

5-12 volunteers

EBA 15-60 patients

500-1500 patients

SSCC 50-100 patients

Efficacy

-

Bactericidal. ?Sterilizing
Dose size

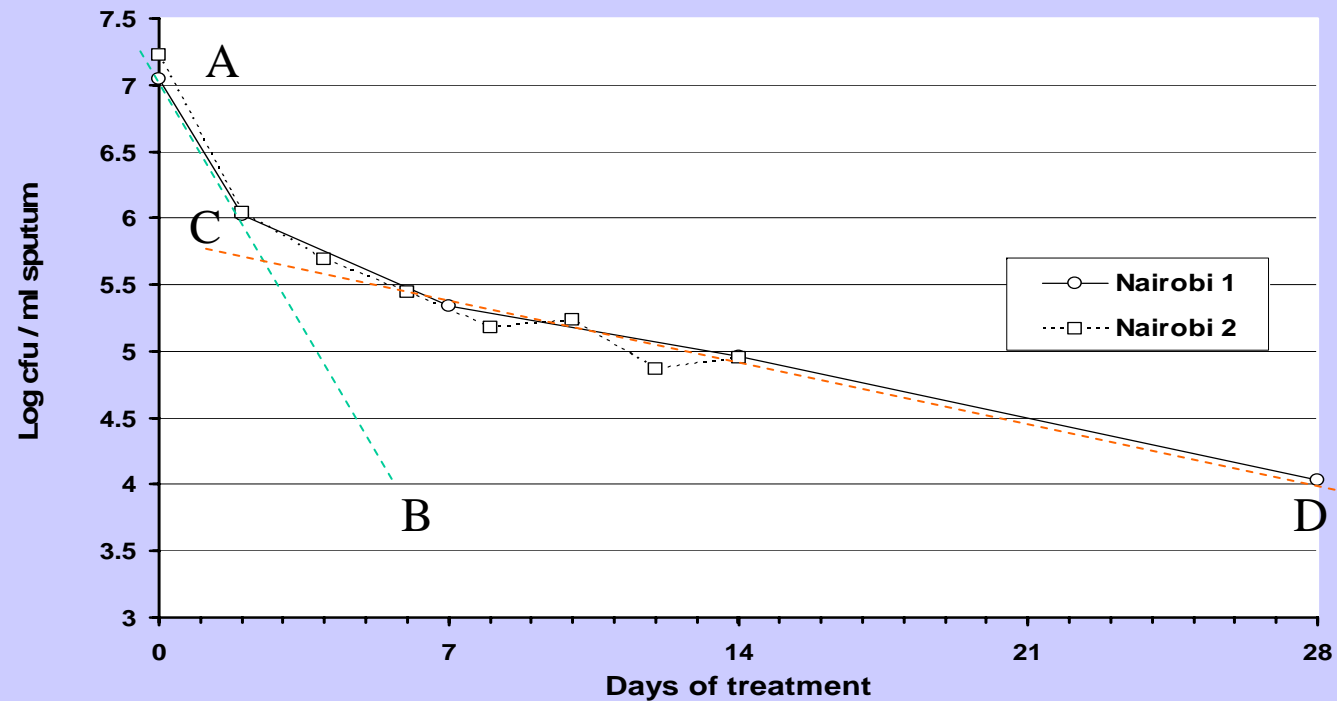
Drug in usable
regimen

Selective 7H11 culture medium

(Mitchison DA, Allen BW, Carrol L et al.
J Med Microbiol 1972, 5, 165)

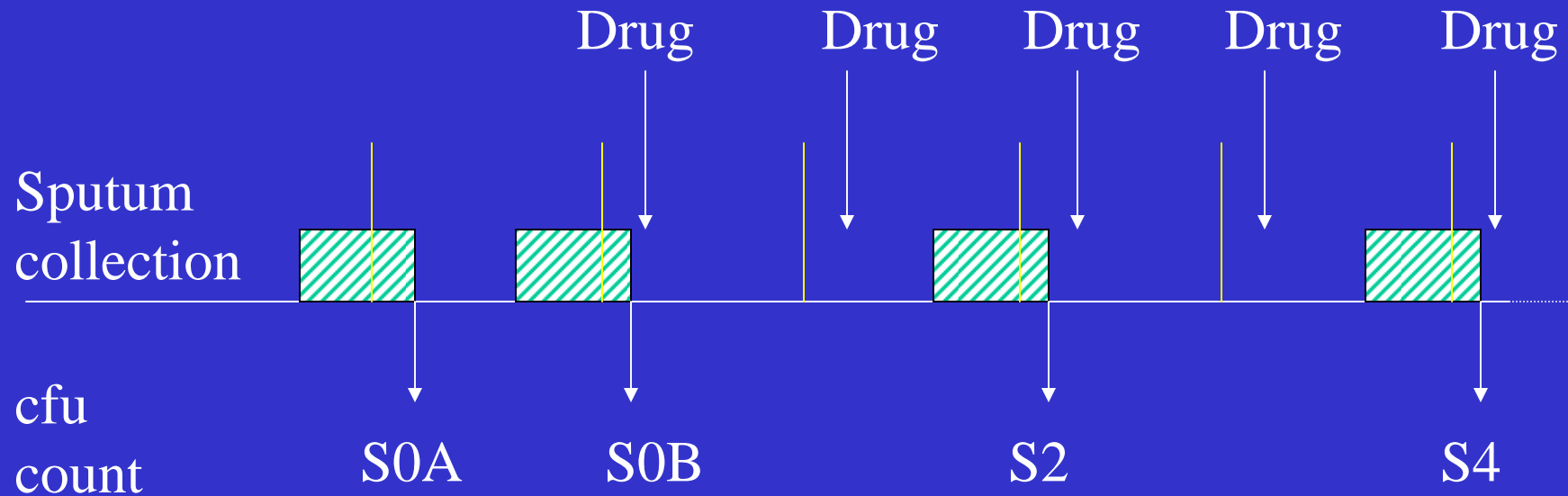
Antibacterials added

Polymyxin B		200 U/ml
Carbenicillin or Ticarcillin	}	100 µg/ml
Trimethoprin		20 µg/ml
Amphotericin B		10-20 µg/ml



- Measures viable TB in sputum and therefore in cavities.
- 2 phases of killing (bi-exponential). First rapid phase (? On dividing TB) usually lasts about 7 days. Replaced by slow sterilizing phase throughout initial 8 weeks at least.

Time-table for Standard & Extended EBA study



EBA 0-2 day = $[\text{Log } S2 - \text{Mean } (S0A, S0B)]/2 = \text{fall/day}$

Extended EBA = Regression of S2, S4, S6... on time for each patient. Analyse regression coefficients.

EBA 0-2 day estimates

(Nairobi & Stellenbosch University)

<u>Drug</u>	<u>Daily dose</u>	<u>Mean EBA</u>
INH	300 mg	0.58
OFLO	800 mg	0.39
EMB	25 mg/kg	0.28
PAS	15 g	0.26
RMP	600 mg	0.21
CIPRO	500 mg	0.09
PAROM*	15 mg/kg	0.09
SM	15 mg/kg	0.07
AMI [†]	15 mg/kg	0.05
TBI	150 mg	0.04
PZA	2 g	0.02
Nil		0.0004

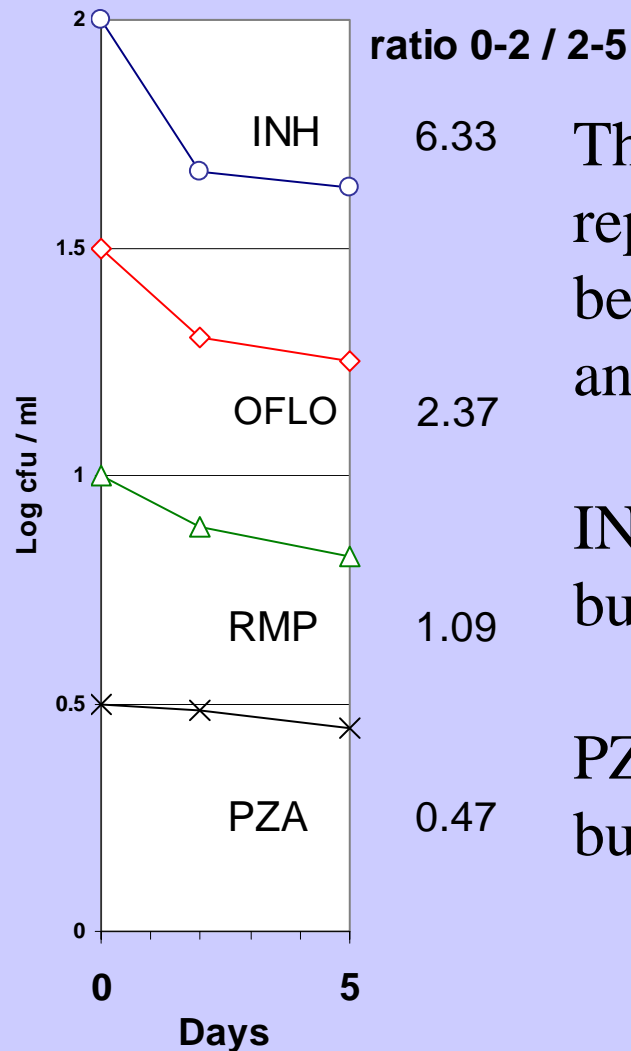
* Paromomycin (aminosidine)

[†] Amikacin

Points in EBA studies

- Drugs in monotherapy. Large difference between drugs and dose sizes.
- Greatest differences during first 2 days
- No previous Rx. Urine tests for INH.
- Controls: Positive, INH 300 mg daily.
Negative, EBA = 0.
- DSTs at start and end.

Curvature method for indicating sterilizing activity

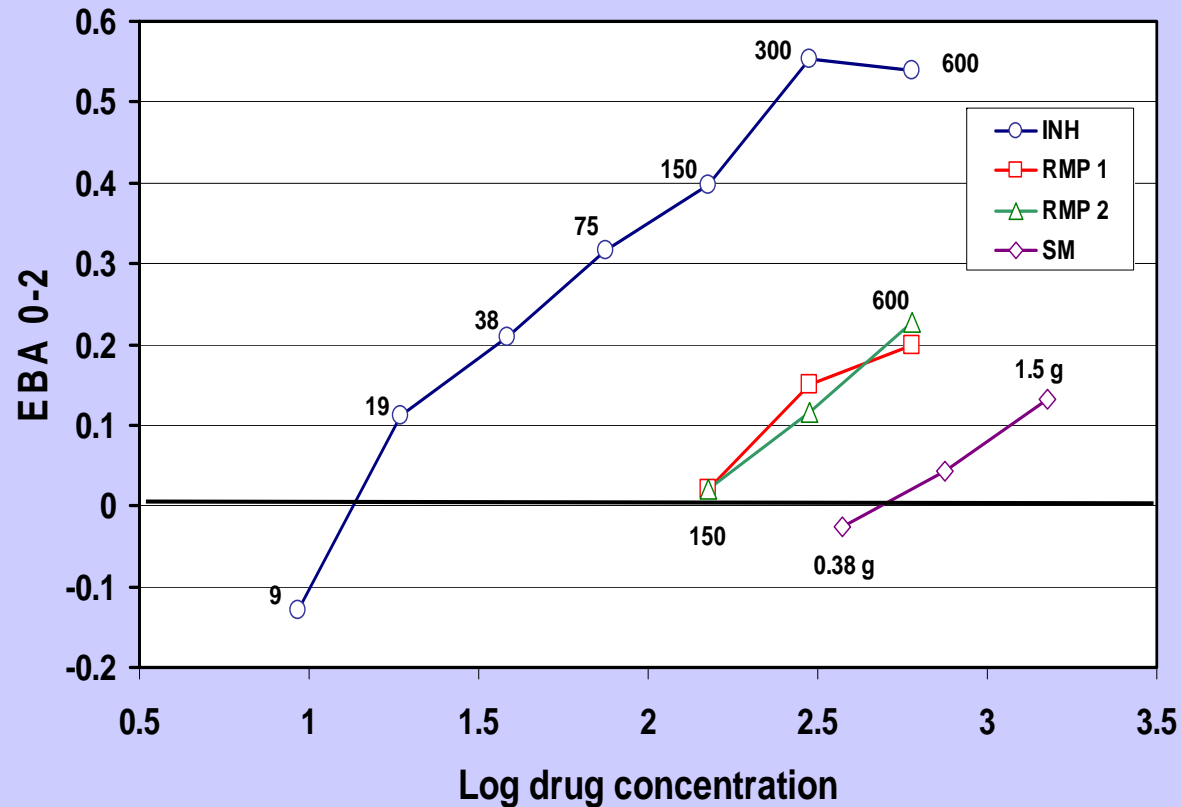


The extent of curvature represents the balance between early bactericidal and sterilizing activities.

INH has most early bactericidal but little sterilizing activity.

PZA has little early bactericidal but considerable sterilizing activity.

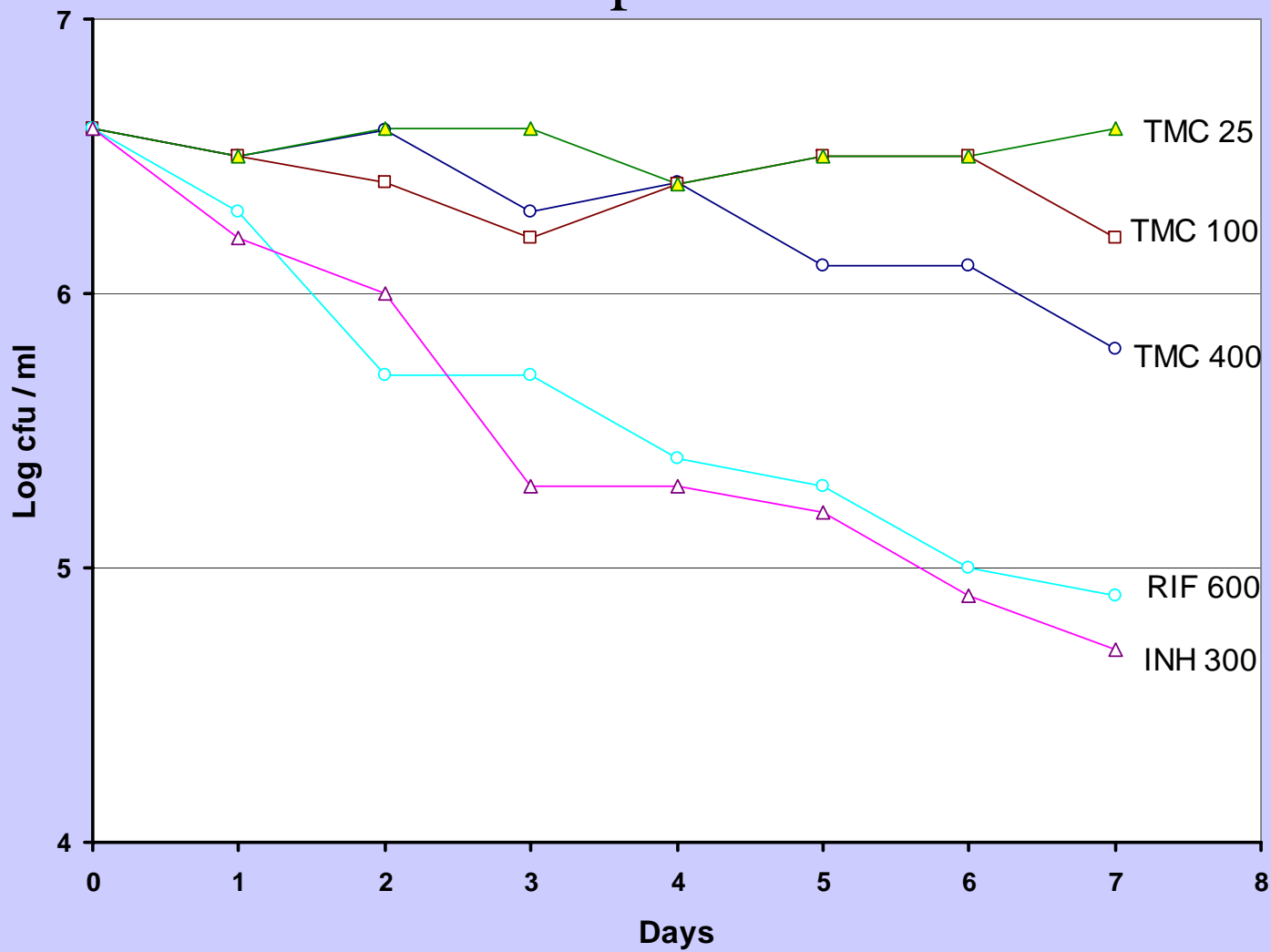
EBA titrations of INH, RMP & SM



- For most drugs, the effect of different dose sizes is measured most accurately over first 2 days
- Can measure the minimal effective dose (MED) and therapeutic margin (ratio of dose used: MED)

EBA study on TMC 207 (J)

Durban and Cape Town: Tibotec



Optimal plan for EBA studies

1. Single high dose study for 14 days.

- Ethics: new drug will not be used further in treatment.
- Look for immediate or delayed kill and for shape of curve to give idea of sterilizing activity.

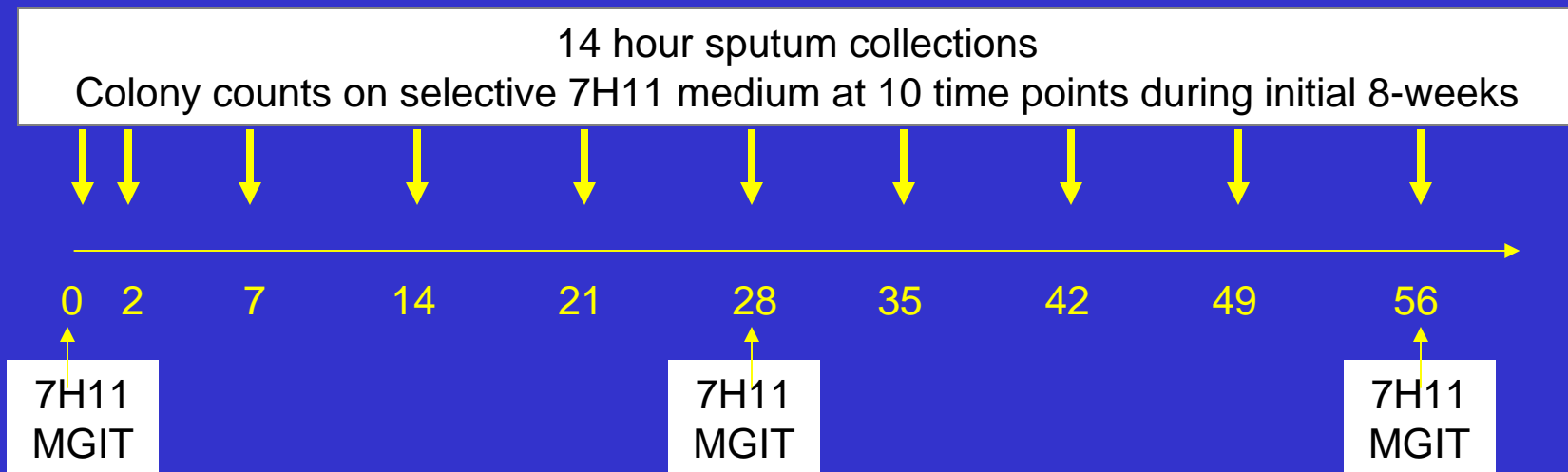
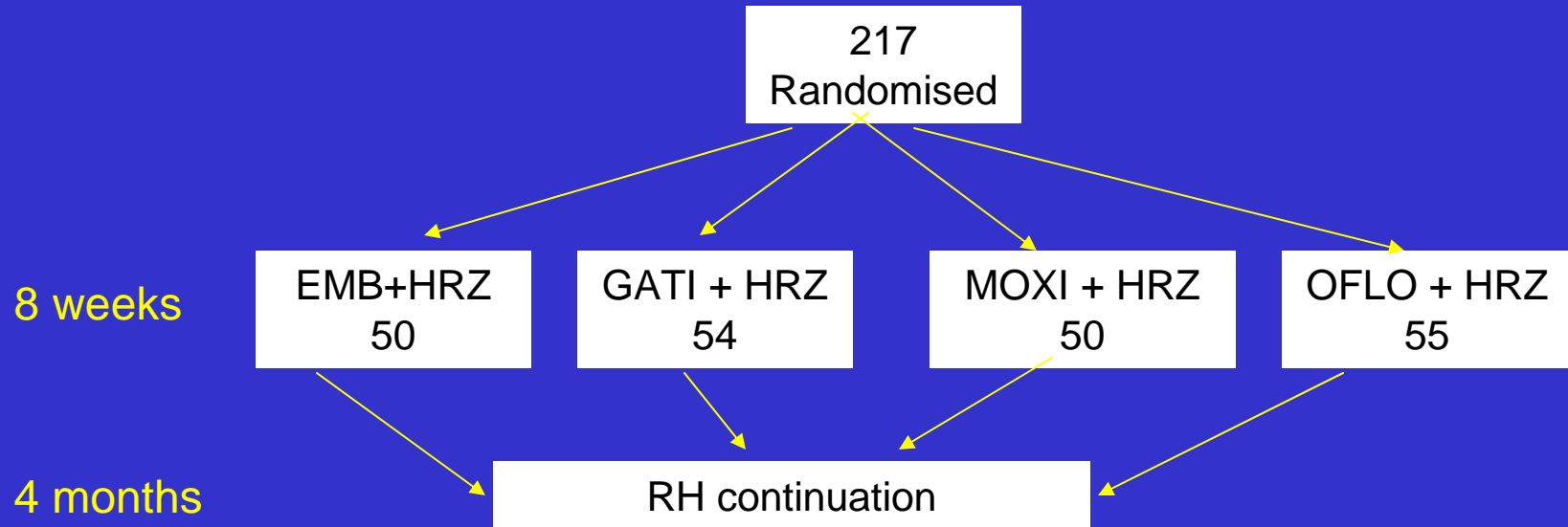
2. Titration of dose size.

- Dependent on single dose 14-day study, choose 0-2 days, 0-5(7) days or 0-14 days.
- Choose dose sizes in descending logarithmic steps, e.g. 200 mg, 100 mg, 50 mg, 25 mg.
- Calculate minimal effective dose (MED) and choose dose with a therapeutic margin (ratio of dose:MED) of at least 8, to get penetration into lesions.

Measuring sterilizing activity of drug combinations

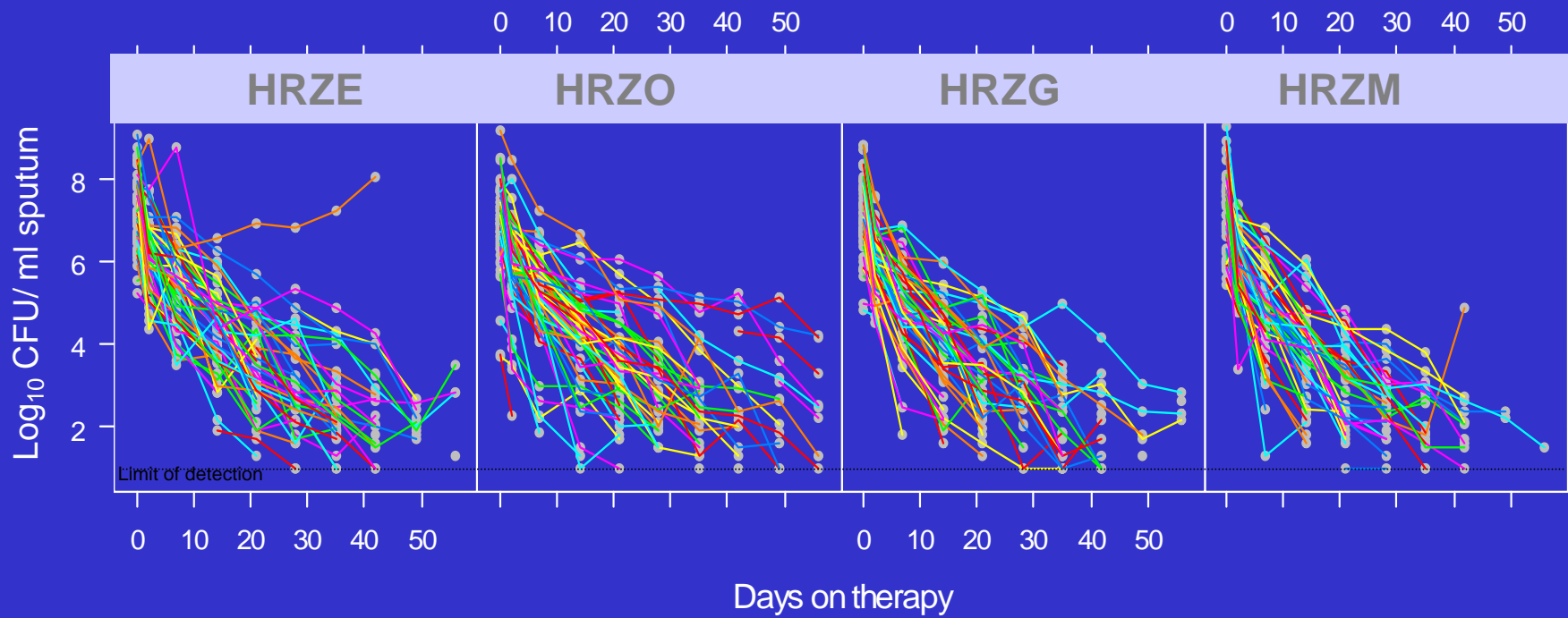
- Differences between combination regimens will be small
- Must have efficient design
- Need sputum samples during full 8 weeks for greatest efficiency

Oflotub SSCC study (S African MRC, Durban)

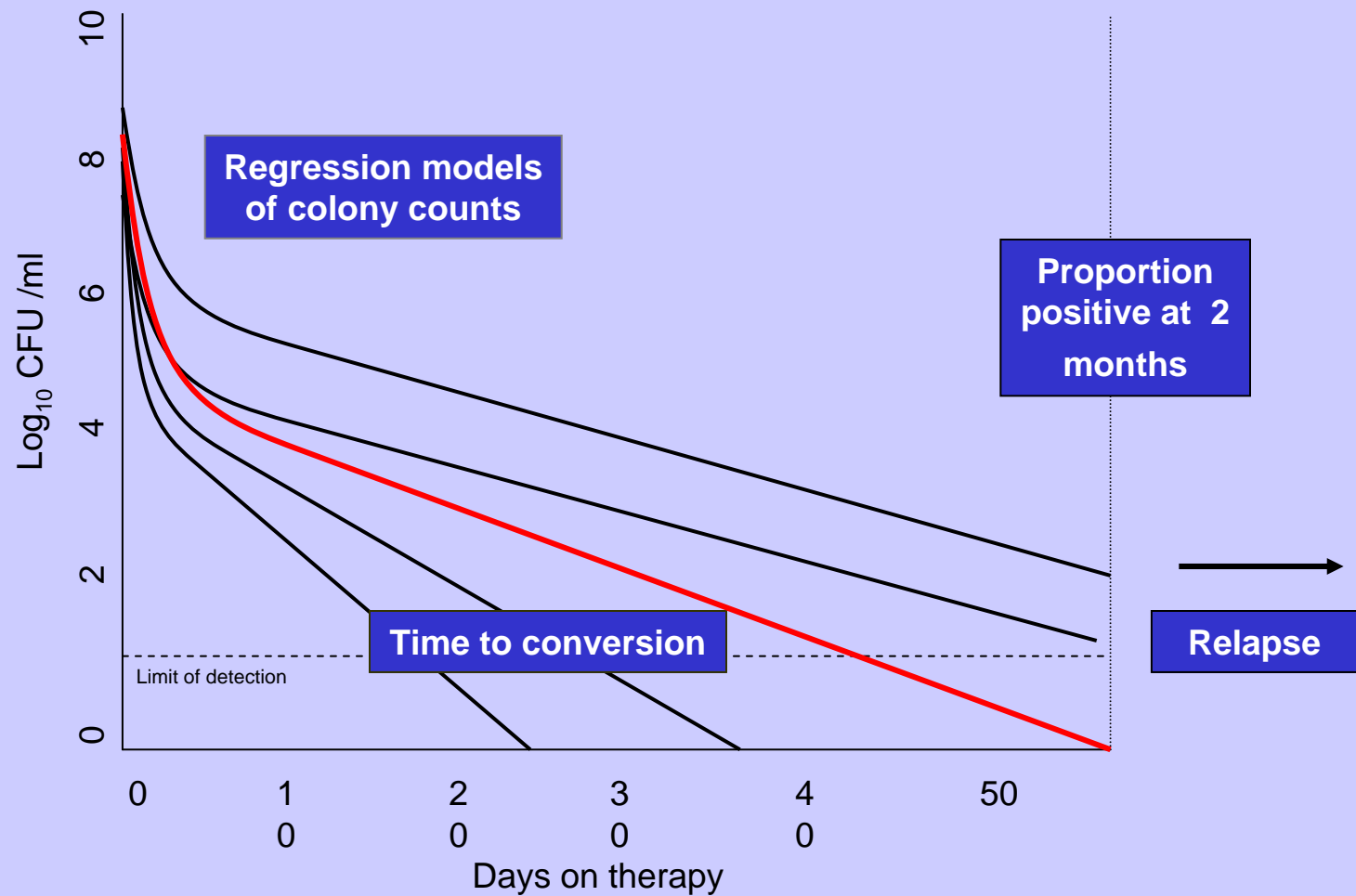


Oflotub

Summary of SSCC data

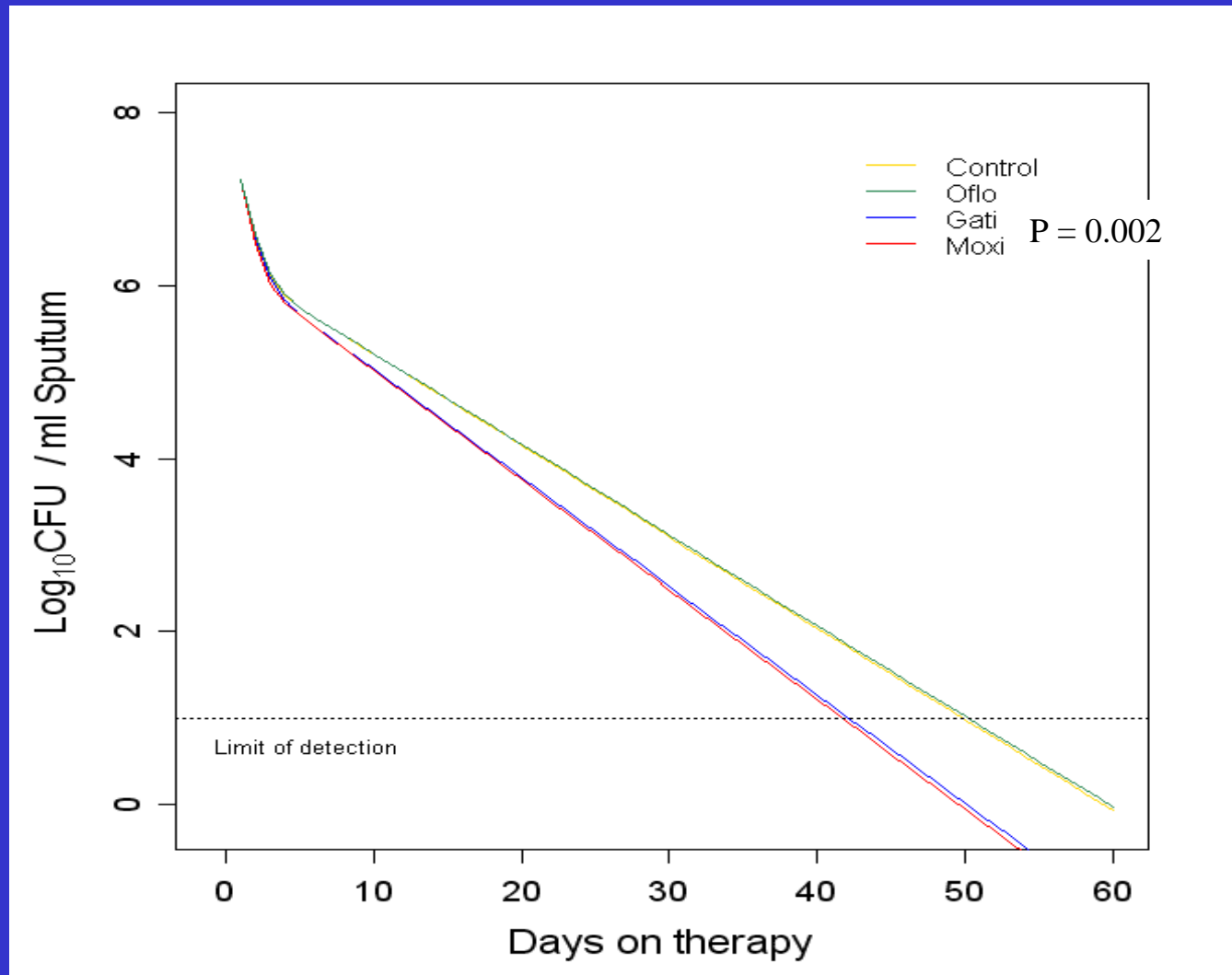


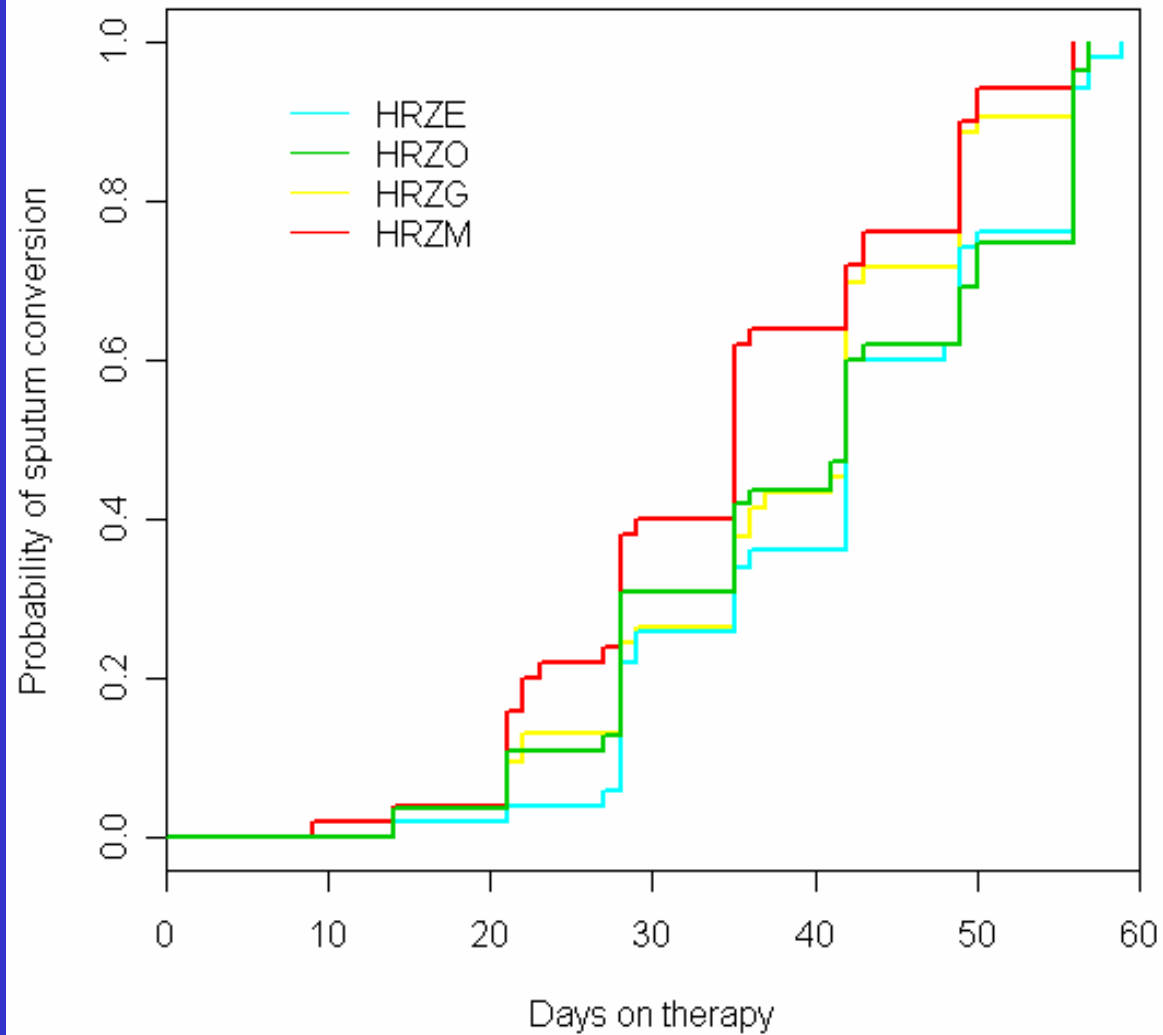
Phase II surrogate endpoints



Mean fall in sputum colony counts

Bi-exponential fits

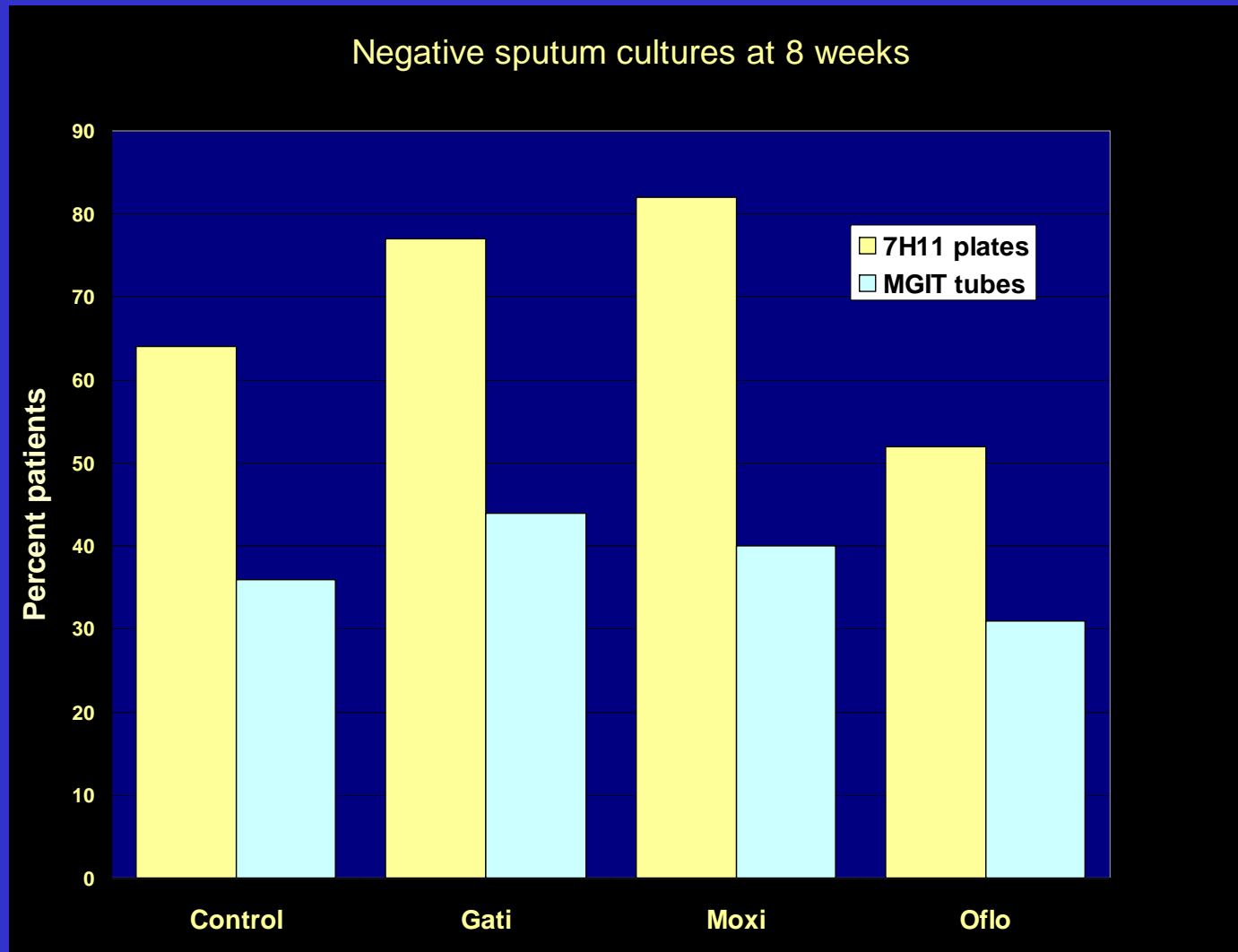




Hazard ratios

p v control

Gati	0.054
Moxi	0.017
Oflo	0.4



7H11 $\chi_{[3]}^2 = 7.3, p = 0.062$: MGIT $\chi_{[3]}^2 = 1.7, p = 0.6$

Efficiencies of 3 assessment methods Gati or Moxi v. control

Mean regressions	Highly significant	$p = 0.002$
Speed of conversion	Just significant	$p = 0.054,$ 0.017
Proportion neg at 8 wk	Not significant	

SSCC Phase IIB Factorial Design

4 New drugs A, B, C, D + Pyrazinamide (Z)

Drugs	A	A	A	B	B	C	Control
	B	C	D	C	D	D	(2HRZE/4HR)
	Z	Z	Z	Z	Z	Z	

No. of patients	25	25	25	25	25	25	100
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Total 250

Main effects A v. B v. C. v D. v Control, each based on 75 patients. Interactions between drugs estimated.

Measuring duration of treatment

BMRC East African Studies

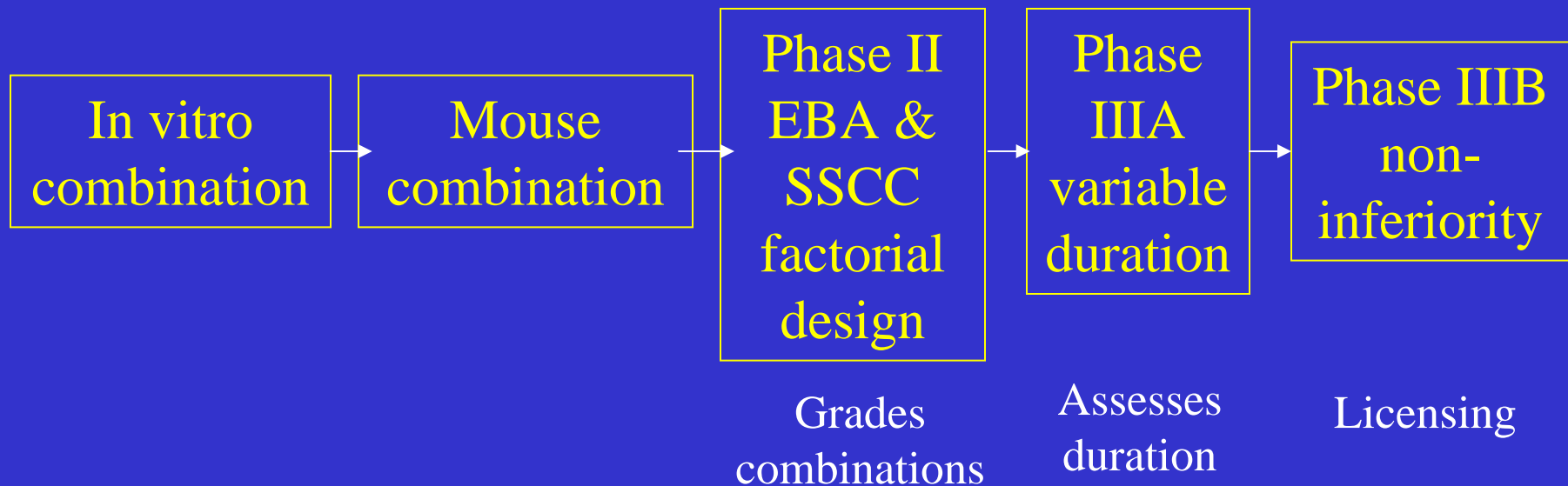
Study	Regimen	No. of patients	Duration (months)	Relapse rate (%)
1	2SHRZ/TH	75	6	13
		81	8	0
	1SHRZ/TH	79	6	18
		58	8	7
	1SHRZ/(SHZ)	75	6	9
3		86	8	2
2	2SHRZ/H	156	6	10
		123	8	3

New Phase IIIA study design

	Duration (months)	No. of patients
New drug combinations	3	150
	4	150
	5	150
Control (2HRZE/4HR)	6	200
	Total	650

Then go on to non-inferiority design Phase IIIB
for final assessment

Possible progression of drug assessments



Conclusions

2-stage EBA study shows

- Bactericidal activity
- Choice of drug dose size
- ? Sterilizing activity

8-week sputum study

- SSCC > speed of conversion > proportion neg at 8 wk
- Ranked in order:
 1. Efficiency
 2. Bacteriology required
 3. Depth of analysis