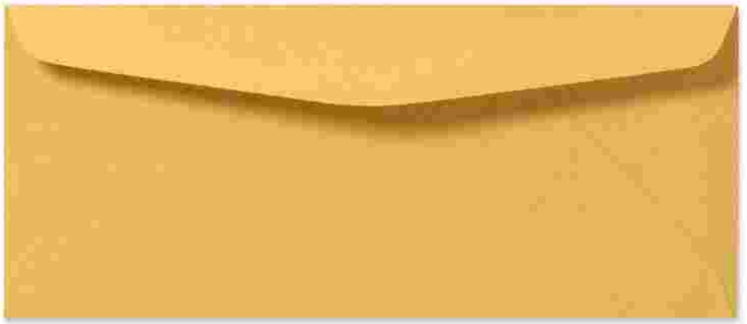
New TB Drugs Now

From Phase II to Phase III trials



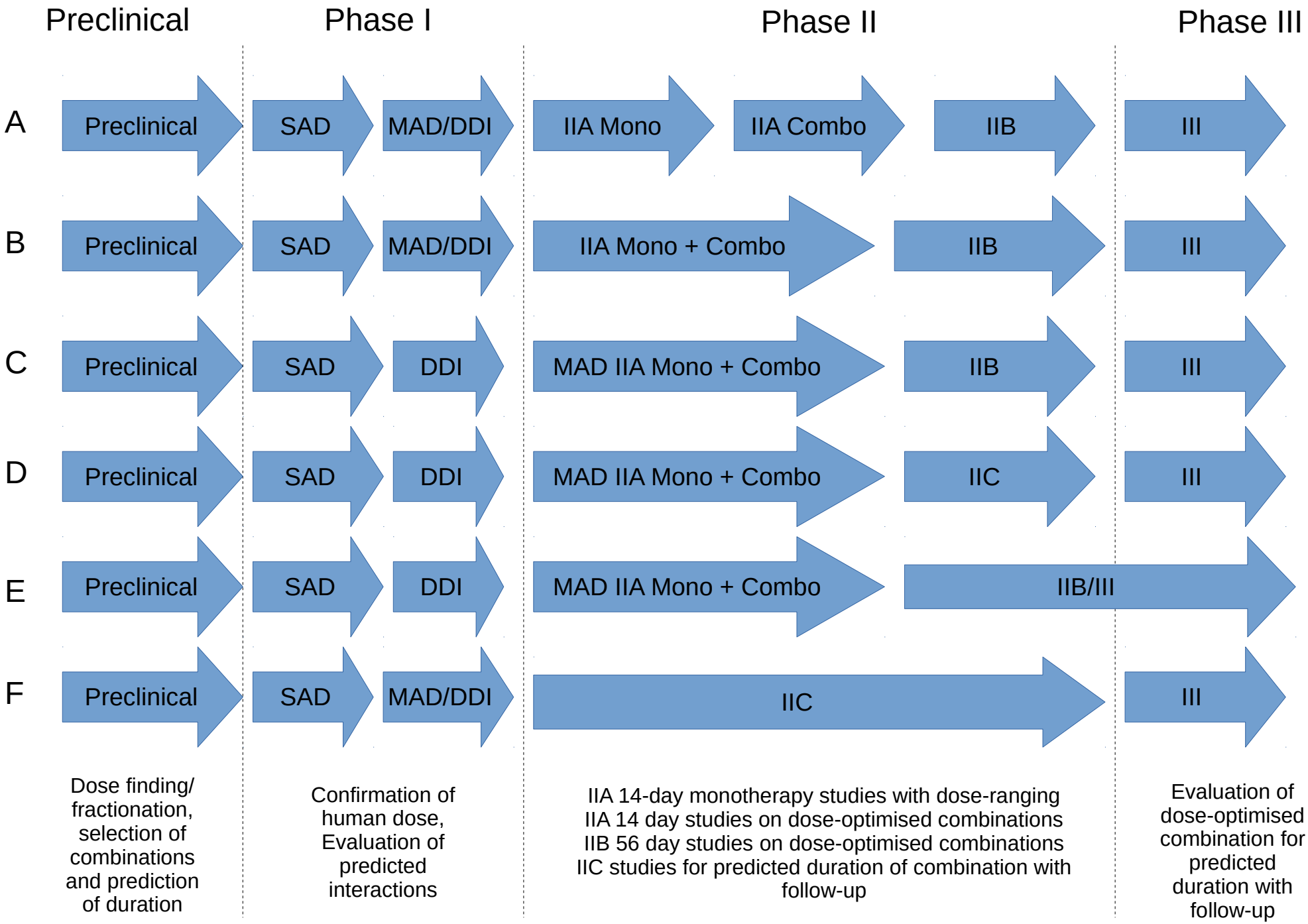
Gerry Davies

Professor of Infection Pharmacology,
University of Liverpool, UK

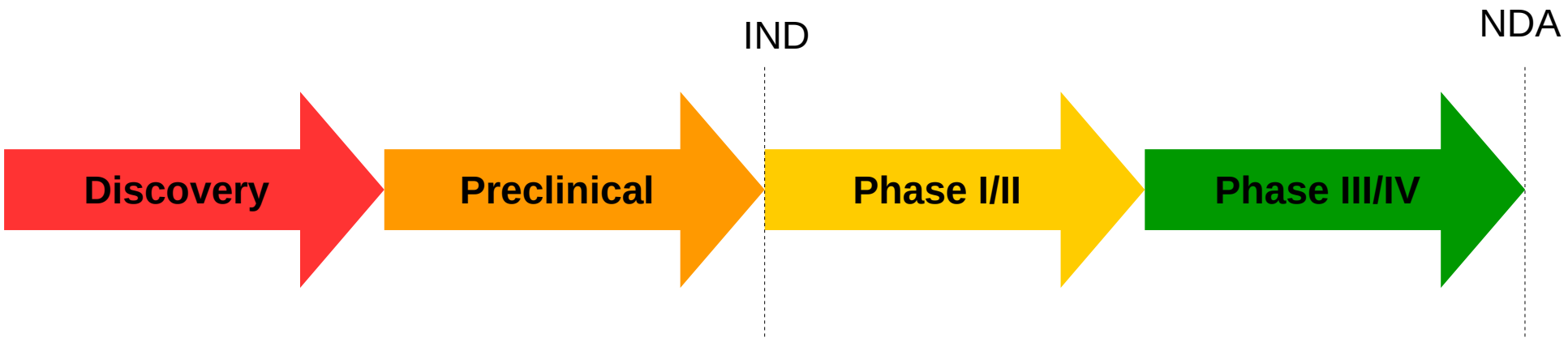
UNIVERSITY OF LIVERPOOL

Overview

- Demonstrating efficacy is the constraint, not safety
- Biomarkers are not the problem
- Dose-ranging in Phase IIA is dispensable
- Duration is an estimation not a hypothesis testing problem
- Our audience is not always or only regulatory
- A two trial development pathway is feasible
- A new decision-making framework is needed


Preclinical
Phase I
Phase II
Phase III
A
Preclinical
SAD
MAD/DDI
IIA Mono
IIA Combo
IIB
III
B
Preclinical
SAD
MAD/DDI
IIA Mono + Combo
IIB
III
C
Preclinical
SAD
DDI
MAD IIA Mono + Combo
IIB
III
D
Preclinical
SAD
DDI
MAD IIA Mono + Combo
IIC
III
E
Preclinical
SAD
DDI
MAD IIA Mono + Combo
IIB/III
F
Preclinical
SAD
MAD/DDI
IIC
III
Dose finding/ fractionation, selection of combinations and prediction of duration
Confirmation of human dose, Evaluation of predicted interactions
IIA 14-day monotherapy studies with dose-ranging
IIA 14 day studies on dose-optimised combinations
IIB 56 day studies on dose-optimised combinations
IIC studies for predicted duration of combination with follow-up
Evaluation of dose-optimised combination for predicted duration with follow-up

Safety in drug development



Non-GLP Toxicology			
In silico screens Mutagenicity Cytotoxicity Immunotoxicity Heptatotoxicity Embryotoxicity	Single and repeat dose-range finding studies in 2 species		
GLP Toxicology			
	Safety Pharmacology Genotoxicity (*in vitro & in vivo*) 28d repeat dose toxicity and recovery in 2 species	3-12m chronic toxicity in 2 species Reproductive toxicity in 1 species : Fertility & implantation Fetal development Pre/post-natal effects	24m carcinogenicity in 2 species
Clinical safety			
		FDIM/SAD (6) MAD (12) DDI/Thorough QT* Phase IIA/B (50-100 per arm)	Phase III (400 per arm)

From ICH M3(R2) Non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

- For combinations of two early stage entities, nonclinical combination toxicity studies are recommended to support clinical trials

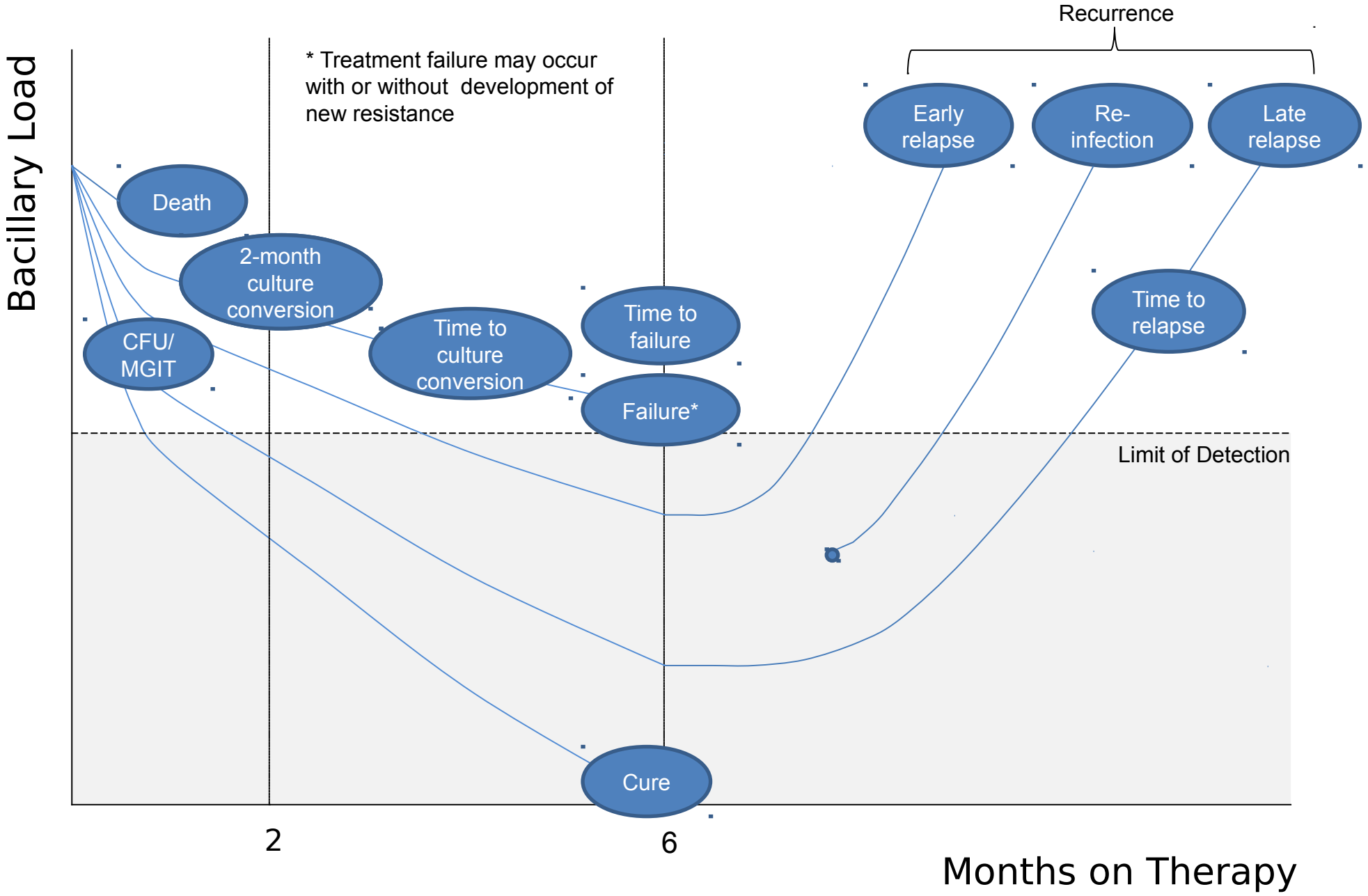
- Provided complete nonclinical development programs are being conducted on the individual entities and a nonclinical combination toxicity study is warranted to support combination clinical trials, the **duration of the combination study should be equivalent to that of the clinical trial**, up to a maximum duration of 90 days.

- A 90-day combination toxicity study would also support marketing. A combination toxicity study of shorter duration can also support marketing, depending on the duration of the intended clinical use.

- The design of the nonclinical studies recommended to characterize the combination will depend on the pharmacological, toxicological and PK profiles of the individual entities, the treatment indication(s), the intended patient population, and the available clinical data.

- Combination nonclinical studies should generally be limited to a **single relevant species**. If unexpected toxicity is identified, additional testing can be appropriate.

Biomarkers & Intermediate Endpoints



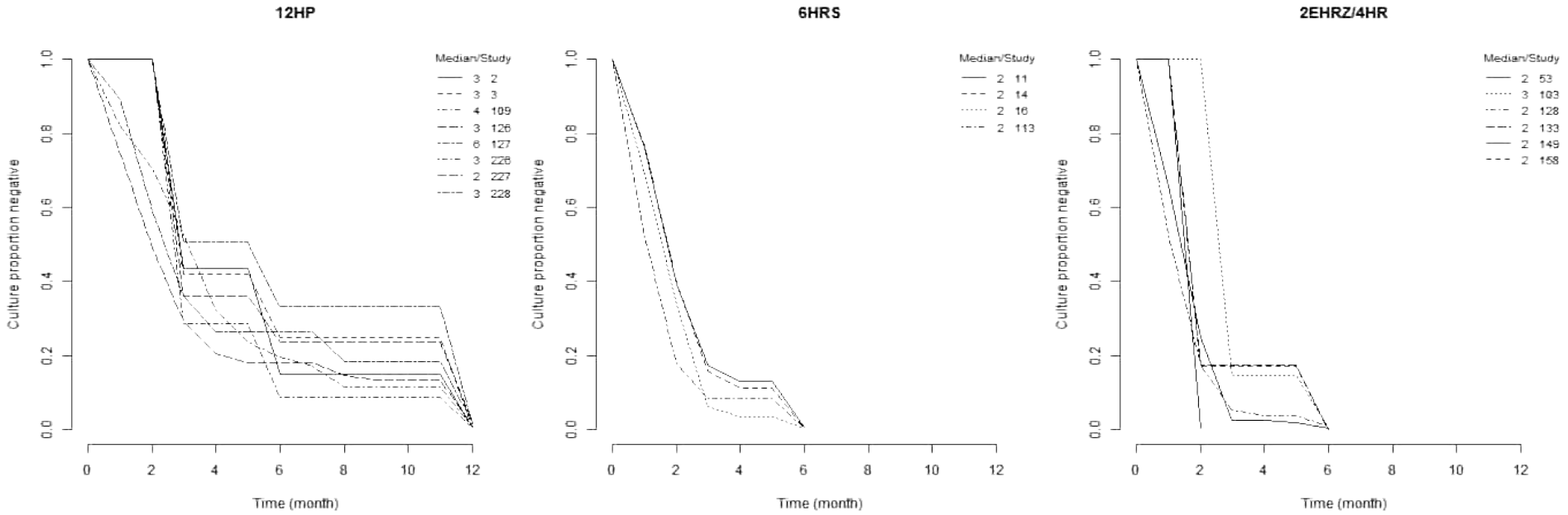
Metagression of Phase III Endpoints

$R^2 = 35.13\%$

Parameter	Estimate	SE	P
End of treatment			
Intercept	-1.6096	0.2059	<.0001
Logit month 2 culture positive rate	1.0817	0.1765	<.0001
Natural log treatment duration	-0.7503	0.2347	0.0014
Natural log treatment	-1.4682	0.3105	<.0001
Logit month 2 culture positive rate × Natural log treatment	-0.8954	0.2157	<.0001
Follow-up			
Intercept	-0.2900	0.3657	0.4277
Logit month 2 culture positive rate	0.3557	0.1007	0.0004
Natural log treatment duration	-1.3467	0.2885	<.0001
Natural log treatment	-0.7314	0.3313	0.0273
End of treatment + Follow-up			
Intercept	-0.4732	0.3647	0.1945
Logit month 2 culture positive rate	0.4954	0.1184	<.0001
Natural log treatment duration	-1.1984	0.2895	<.0001
Natural log treatment	0.0267	0.3397	0.9373

Ken-Dror G Lancet ID (Submitted)

Reconstruction of Time-to-event endpoints



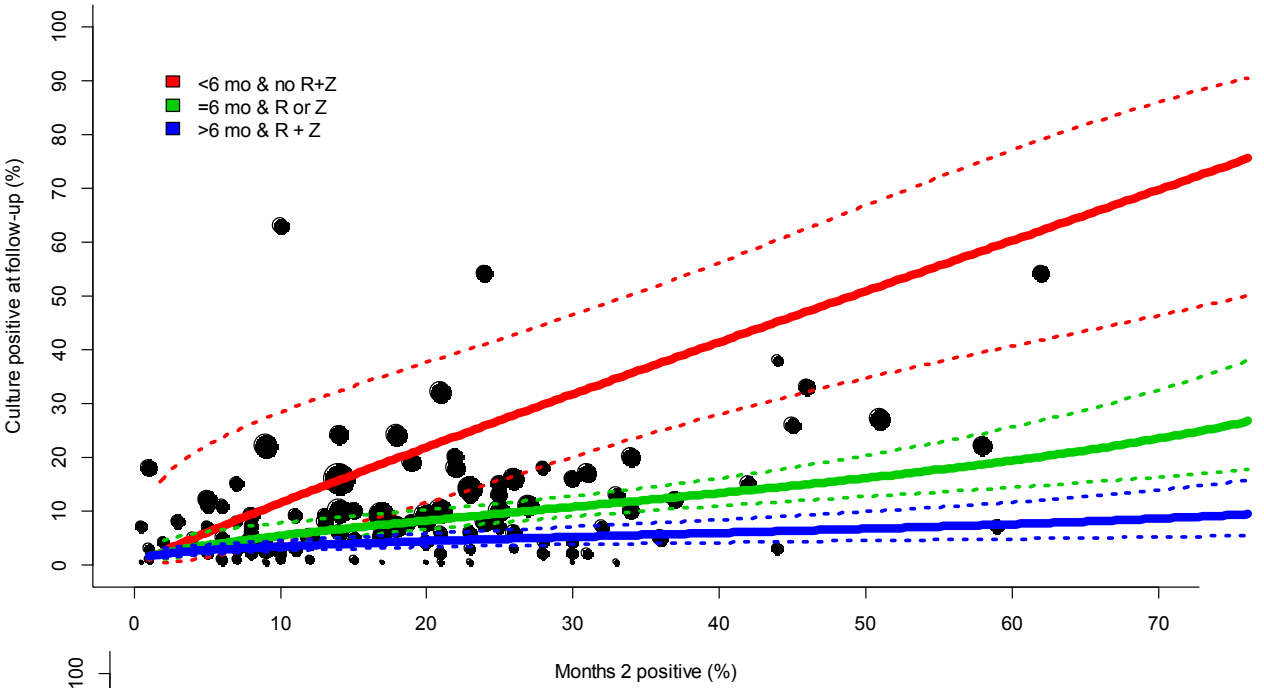
Metagression : Median time to CC

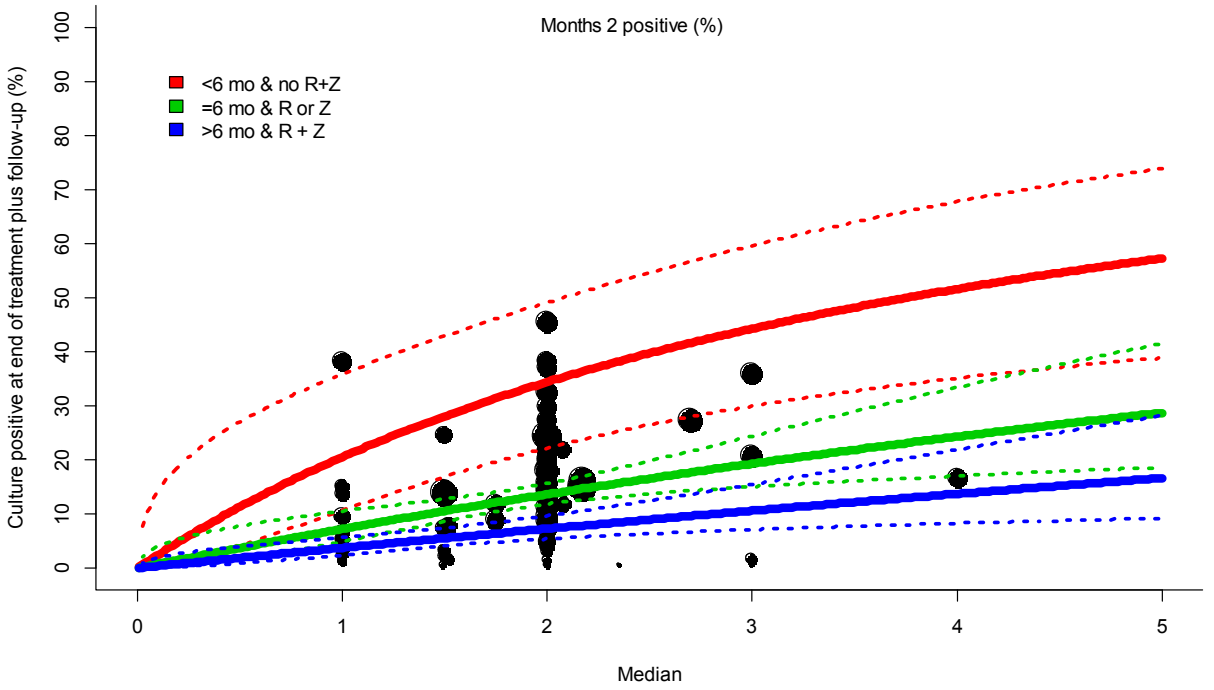
Combined outcome of treatment failure/relapse
(28 trials, 4,400 participants, 85 treatment arms, 73 regimens)

Parameter	Estimate	SE	P	R^2 x100 (%)
Intercept	-2.6589	0.2307	<.0001	
Log median	1.0664	0.3436	0.0019	20.45
Intercept	-2.0960	0.2687	<.0001	
Log median	1.2496	0.3303	0.0002	
Natural log treatment duration	-0.9928	0.2791	0.0004	35.13
Intercept	-1.3552	0.4704	0.0040	
Log median	1.0237	0.3492	0.0034	
Natural log treatment duration	-1.1471	0.2893	<.0001	
Natural log treatment	-0.5871	0.3066	0.0555	36.52
Intercept	-2.0822	0.8862	0.0188	
Log median	1.9761	1.0399	0.0574	
Natural log treatment duration	-1.1865	0.2934	<.0001	
Natural log treatment	0.2255	0.8915	0.80	
Log median × Natural log treatment	-1.0699	1.0984	0.33	35.08

* Treatment: No R or Z, R or Z and R + Z; Treatment duration: <6, =6, and >6

Predicting duration : meta-regression





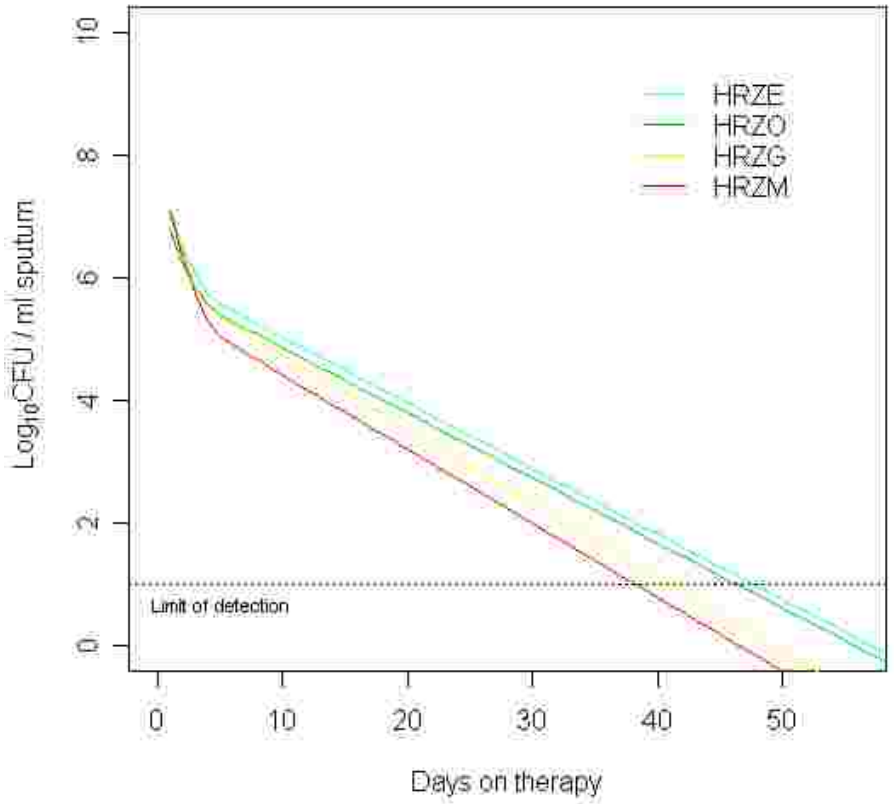
From FDA Guidance for Industry Codevelopment of Two or More New Investigational Drugs for Use in Combination

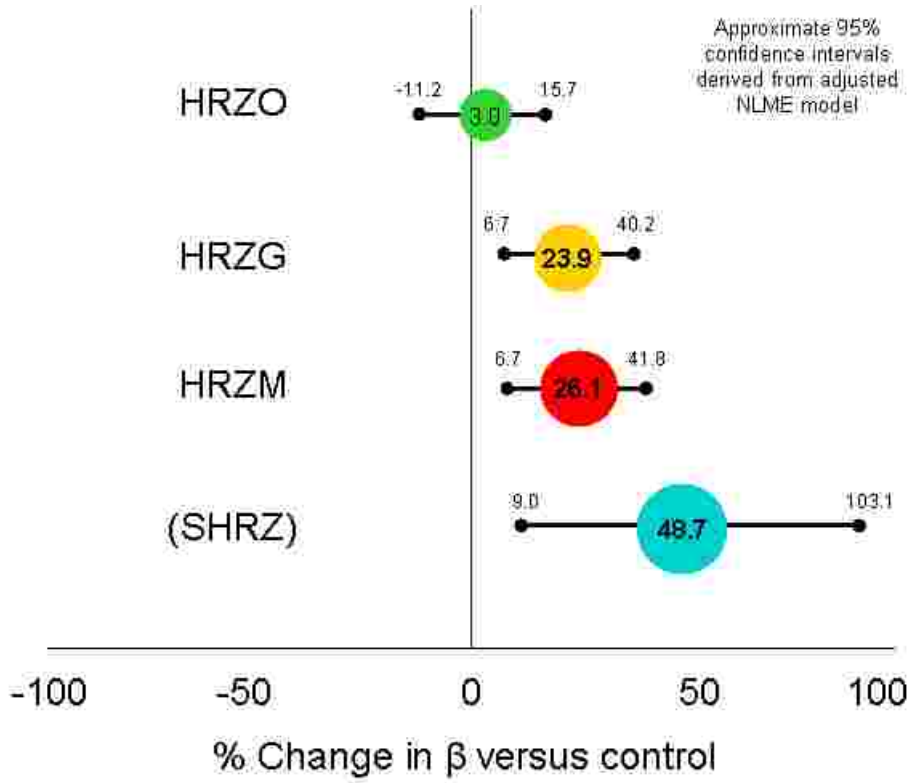
FDA believes that codevelopment should ordinarily be reserved for situations that meet all of the following criteria:

1) The combination is intended to treat a serious disease or condition.
2) There is a strong biological rationale for use of the combination (e.g., multidrug-resistant tuberculosis)
3) A **full nonclinical characterization** of the activity of both the combination and the individual new investigational drugs, or **a short-term clinical study on an established biomarker**, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents. A nonclinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents.
4) There is a compelling reason why the new investigational drugs cannot be developed independently (e.g., monotherapy for the disease of interest leads to resistance, one or both of the agents would be expected to have very limited activity when used as monotherapy)

Phase IIB : Selecting combinations

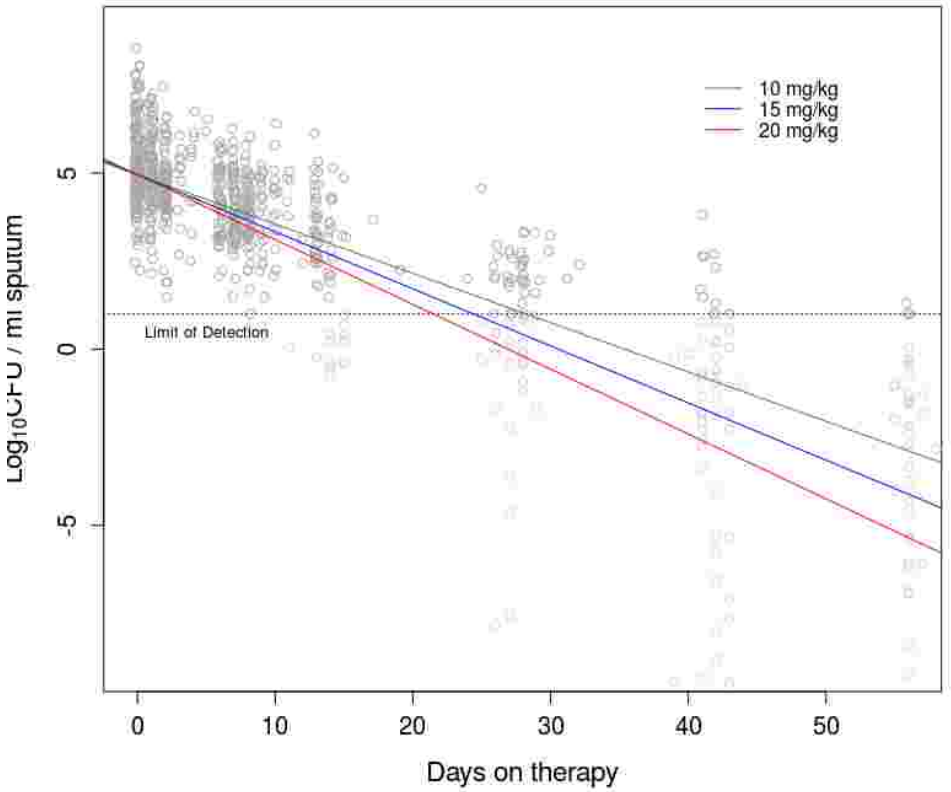
Predictions from unadjusted model





Rustomjee R. *Int J Tuberc Lung Dis.* (2008) 12(2):128-38

Phase IIB : Dose-ranging

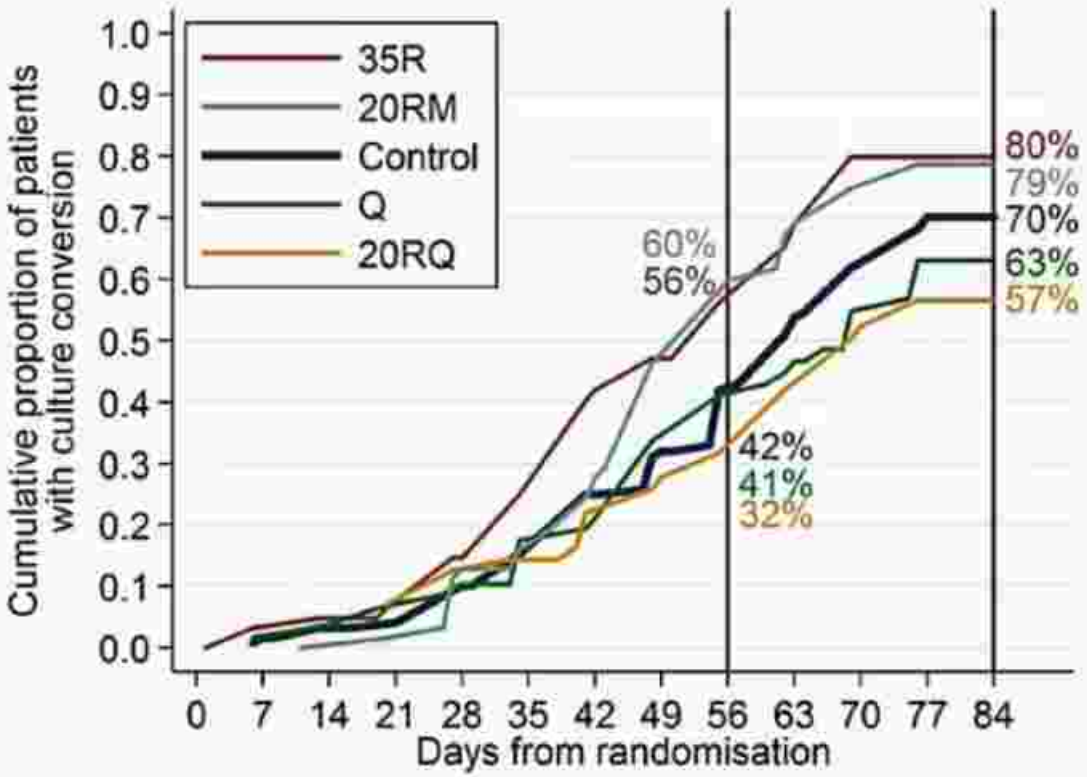


	Estimate (logCFU/mL/day)	95% CI	p-value
Treatment arm mITT (N=174)	-0.011	0.002/ -0.025	0.23
Treatment arm mPP (n=132)	-0.022	-0.002/ -0.046	0.022
Rifampicin $AUC_{0\text{-}6P}$ mPP (N=126)	-0.017	-0.007/-0.029	0.011
Rifampicin $AUC_{0\text{-}6}/MIC_{99.9}$ mPP (N=126)	-0.010	0.000/-0.021	0.053

Velazquez G CROI 2018

Phase IIB : Adaptation

Time to stable culture conversion on MGIT liquid media



HR

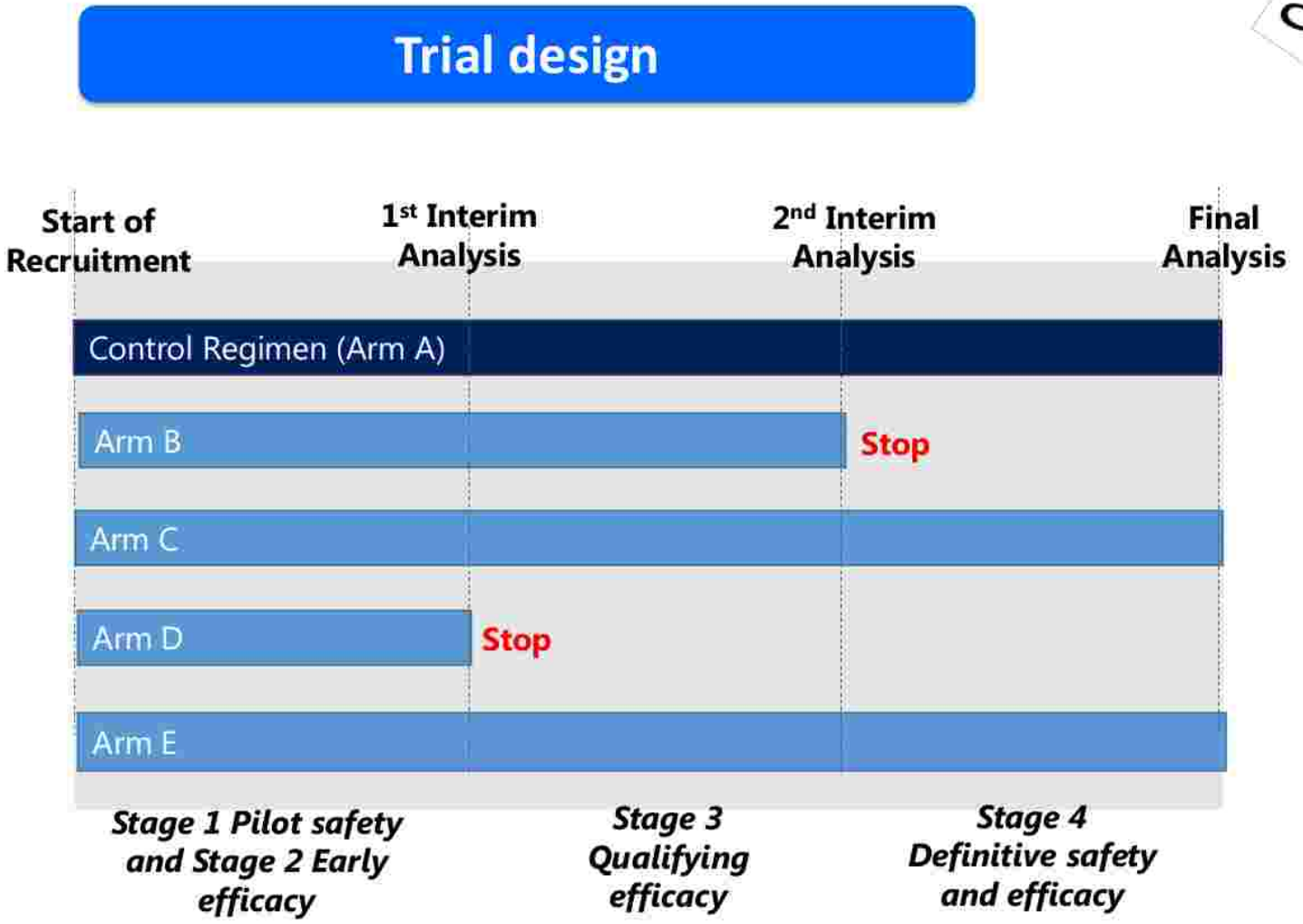
1.75 (1.21-2.55)
1.42 (0.98-2.05)

0.82 (0.55-1.24)
0.73 (0.48-1.13)

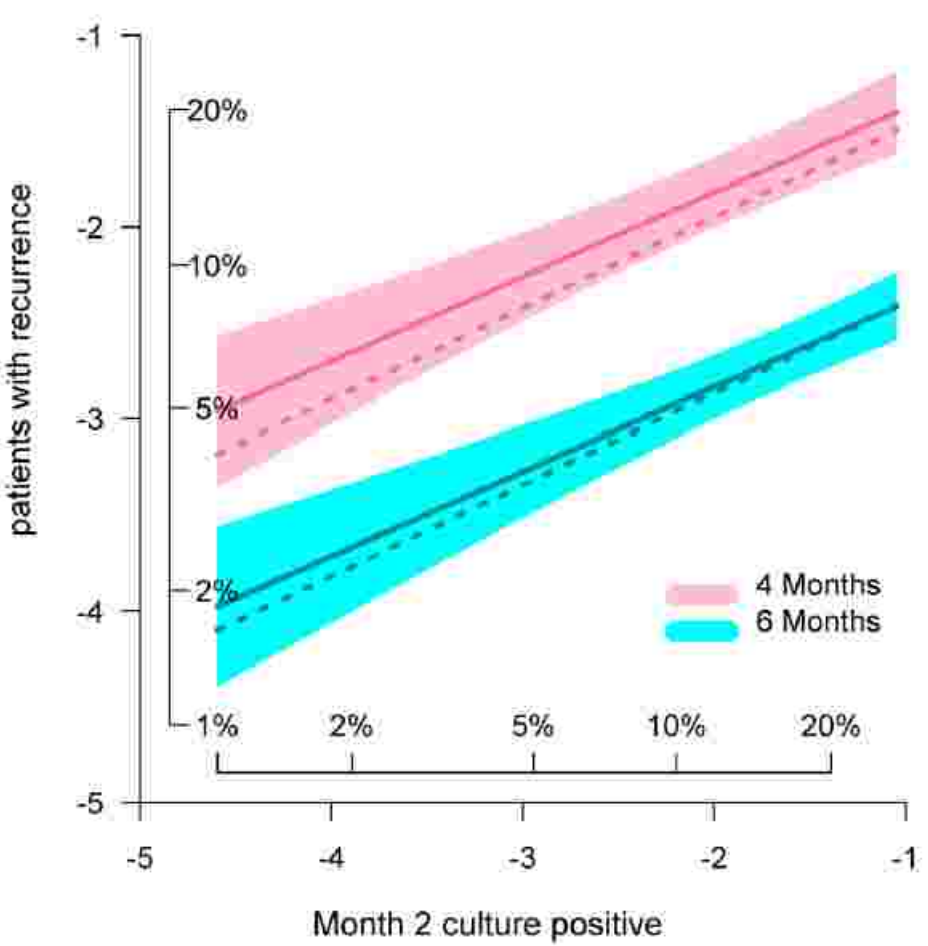
N=365

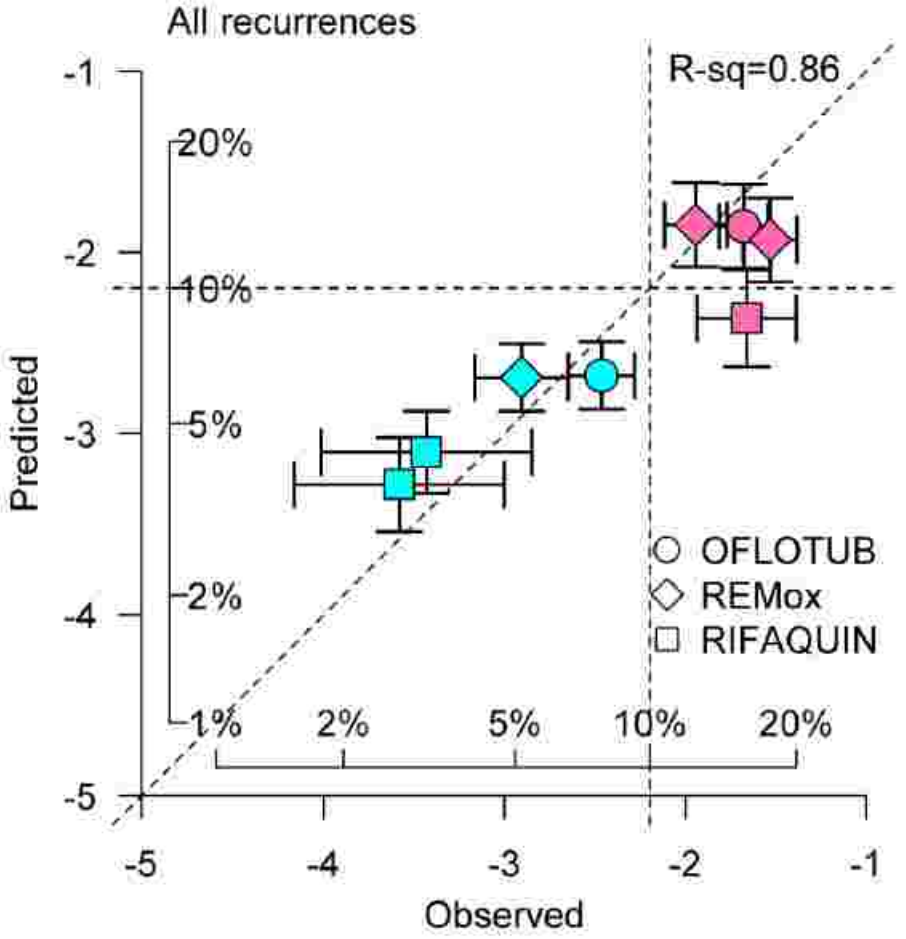
Boeree MJ CROI 2015 Abstract 95LB

Predicting duration: TRUNCATE-TB



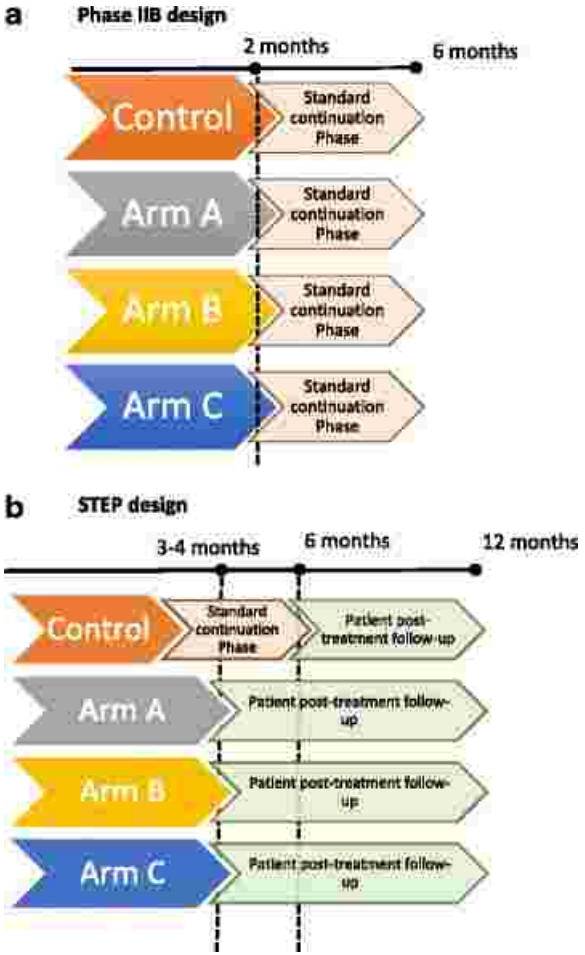
Predicting duration : meta-regression

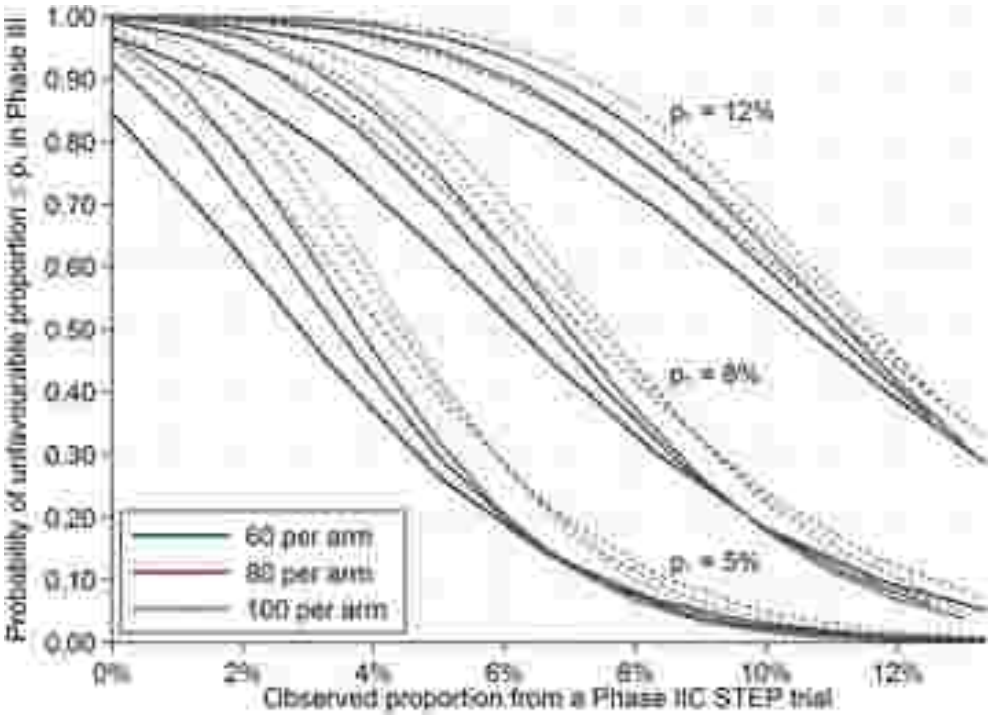




Wallis RS PloS ONE 2013 8(8) : e71116 & 2015 10(4): :e0125403

Prediction of Duration : Phase IIC designs

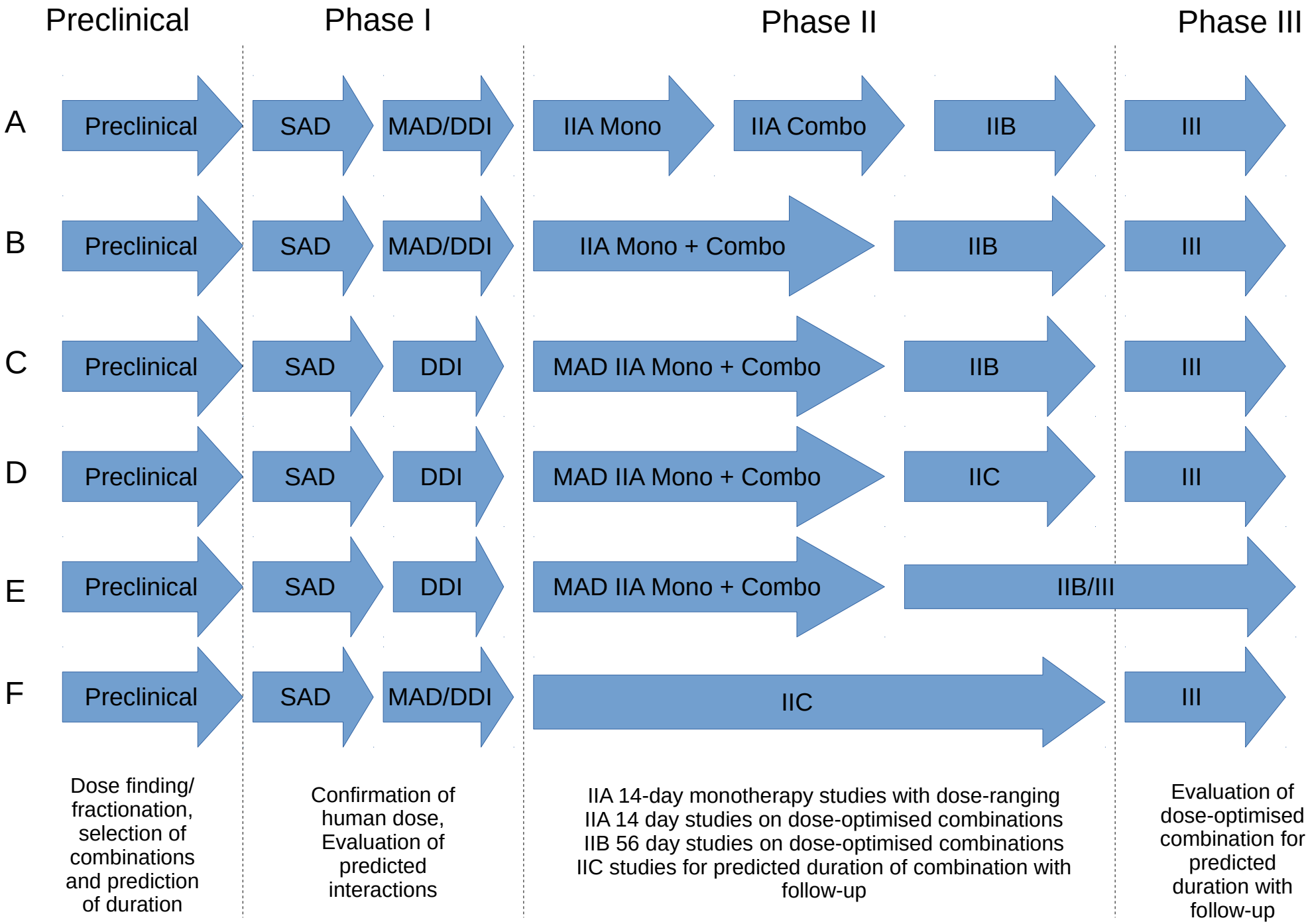




Phillips PJ BMC Med 2016 14 : 51

Future of Phase III trials

- Equipoise of designs for ultra-short regimens presupposes an implicitly acceptable prior for relapse
- The best justified priors are derived from predictive modelling of duration using intermediate endpoints
- Trials should aim to establish the minimum duration of therapy that a given regimen can achieve
- The minimum duration will be different within strata defined by prognostic factors
- Predictive power of intermediate endpoints within the trial could be better exploited
- A frequentist framework is not adequate for complex decisions of this nature


Preclinical
Phase I
Phase II
Phase III
A
Preclinical
SAD
MAD/DDI
IIA Mono
IIA Combo
IIB
III
B
Preclinical
SAD
MAD/DDI
IIA Mono + Combo
IIB
III
C
Preclinical
SAD
DDI
MAD IIA Mono + Combo
IIB
III
D
Preclinical
SAD
DDI
MAD IIA Mono + Combo
IIC
III
E
Preclinical
SAD
DDI
MAD IIA Mono + Combo
IIB/III
F
Preclinical
SAD
MAD/DDI
IIC
III
Dose finding/ fractionation, selection of combinations and prediction of duration
Confirmation of human dose, Evaluation of predicted interactions
IIA 14-day monotherapy studies with dose-ranging
IIA 14 day studies on dose-optimised combinations
IIB 56 day studies on dose-optimised combinations
IIC studies for predicted duration of combination with follow-up
Evaluation of dose-optimised combination for predicted duration with follow-up

Summary

- Demonstrating efficacy is the constraint, not safety
- Biomarkers are not the problem
- Dose-ranging in Phase IIA is dispensable
- Duration is an estimation not a hypothesis testing problem
- Our audience is not always or only regulatory
- A two trial development pathway is feasible
- A new decision-making framework is needed