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Key Issues in TB Drug Development

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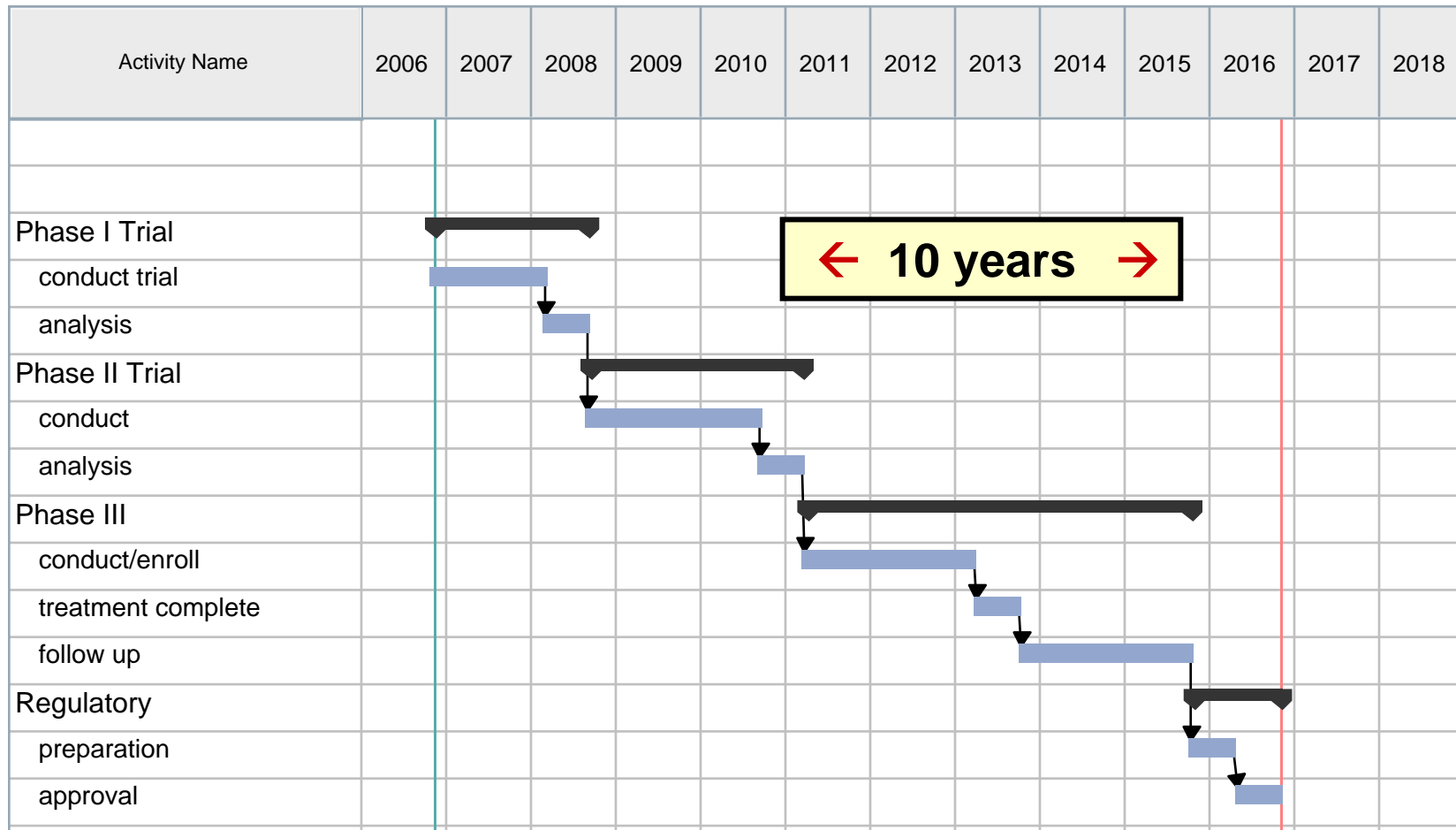
**A non-EBA approach for proof-of-concept
safety and efficacy of a new TB drug**

plus

A 'new' clinical trial concept



Classic drug development clinical timeline



The Economics of TB Drug Development, The Global Alliance for TB Drug Development, 2001

Critical Path for new TB Drug

- **Determine safety range in “normal” human volunteers**
 - Phase 1a: safety of escalating single doses of drug
 - Phase 1b: safety of escalating multiple doses of drug

- **Determine safety and preliminary efficacy in TB patients**
 - Dose escalation (based on Phase 1) to determine safety
 - Finalize safe dose that achieves an important clinical endpoint(s) [therapeutic window]

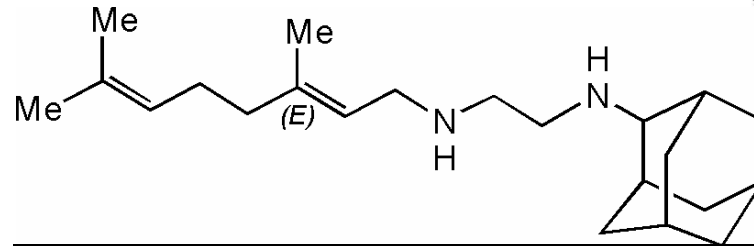
- **Determine safety and efficacy of Phase 2 dose in a larger, statistically evaluable and broader TB patient population**
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Our premise: each drug is unique and requires an individualized clinical approach based on specific **drug attributes** and **proposed indication**

(SQ109 as example)

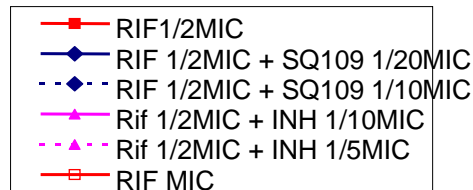
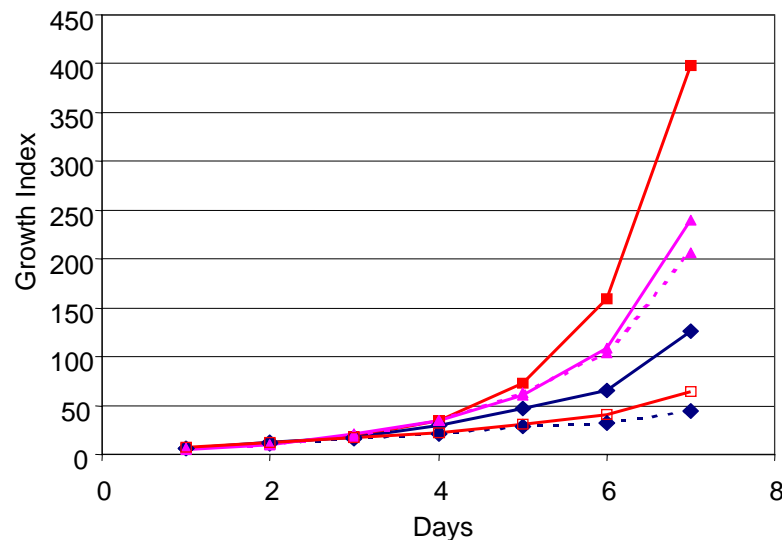


SQ109 *in vitro*

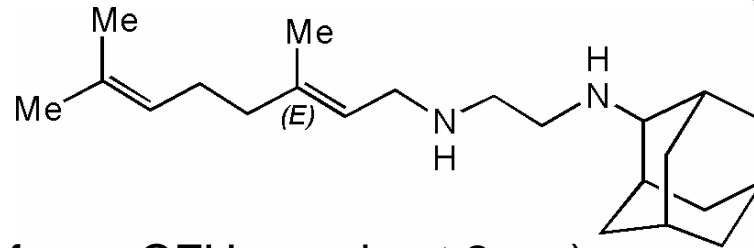


- SQ109 acts synergistically with RIF
- SQ109 also has synergistic or additive activities with INH and SM

| Drugs | Folds of MIC | INH | SM | RIF | | | |
|-------------------------|--------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | | 1/2 | 1/2 | 1/20 | 1/10 | 1/4 | 1/2 |
| SQ109 (folds of MIC) | 1/20 | 1 | 1 | 1 | 1 | 1 | 0.32 |
| | 1/10 | 1 | 0.98 | 1 | 1 | 1 | 0.16 |
| | 1/5 | 0.83 | 0.74 | 1 | 1 | 1 | 0.4 |
| | 1/2 | 0.45 | 0.57 | 0.61 | 0.29 | 0.23 | 0.12 |



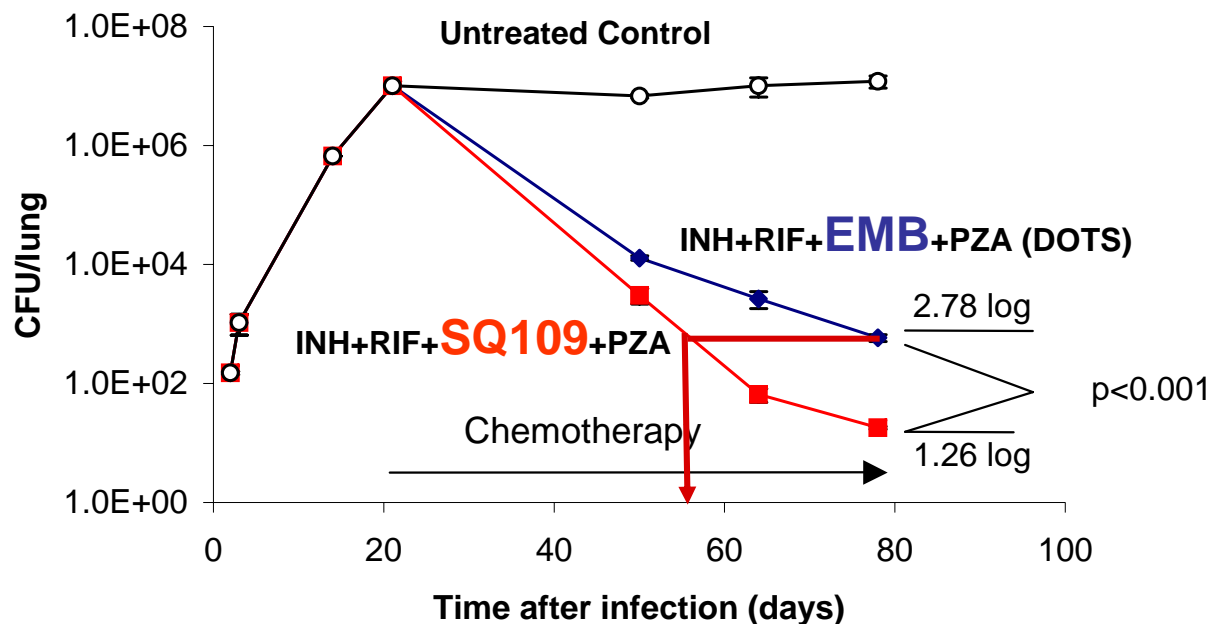
Strain: *M. tuberculosis* H37Rv
 Drugs tested (MIC in µg/ml by BACTEC):
 INH (0.05); RIF (0.20); SM (0.25);
 EMB (3.50); SQ109 (0.32)



SQ109 *in vivo*

SQ109-containing regimen:

- is more efficacious (1-2 log₁₀ fewer CFU remain at 2 mo)
- reduces treatment time >30% (achieves same CFU as DOTS at earlier time)



Individual mouse data at the end of treatment, CFU/mouse (undiluted lung homogenate samples):

DOTS:

640, 820, 493, 300, 833, 400

INH+RIF+SQ109+PZA:

0, 40, 33, 0, 20, 27

Possible SQ109 indications:

Same MIC on DS/DR/MDR/XDR Mtb: *Treatment of MDR-TB?*

Works on non-replicating Mtb: *Treatment of latent TB?*


Better efficacy and shorter timeline for lung CFU clearance: *Pulmonary TB?*

Preferred Indication:

**Combine with one or more existing
anti-TB drugs for treatment of adult pulmonary TB**


Obvious drug for replacement in standard regimen: EMB
(not very active; role is to protect RIF and INH; not synergistic with SQ109)

Obvious drugs for inclusion in SQ109-containing regimen: RIF and INH
(SQ109 is synergistic with both)




Phase 2 clinical trial design

Issues:

- How to establish safety when drug will always be dosed with other drugs
 - How to define the efficacious dose for a pivotal trial that will use combination therapy
 - What is an appropriate clinical endpoint for proof of efficacy
- 

Things to consider in Phase 2 design:

- SQ109 Indication: intensive-phase treatment of pulmonary TB with one or more existing TB drugs
 - SQ109 will always be used in combination with other drugs
 - SQ109 has known synergistic (positive) drug interactions with 2 of standard TB drugs
 - Dose of SQ109 that is safe and efficacious for pivotal clinical trials must be determined in the presence of the selected partner drugs
 - Must achieve a clinical endpoint to demonstrate efficacy and design pivotal trial
 - What SQ109 preclinical data supports a clinical endpoint?
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Possible clinical endpoints:

Treatment of Pulmonary TB in intensive phase:

1. reduce time to negative sputum culture
2. reduce CFU from sputum culture at 2 mo compared to standard of care
3. Increase % patients with sterile sputum cultures at 2 mo
4. prevent development of INH & RIF resistance
5. decrease TB relapse rate
6. improve safety profile (eliminate one or more toxic issues in regimen)

Preclinical data on SQ109 supports #2 or #3 for primary clinical endpoint



Critical Path for SQ109

Safety and efficacy of SQ109
will be established in the presence
of the drugs that will also be used in the pivotal trial

We propose to use a “new” clinical trial design to
establish the safe and efficacious dose
and shorten the development timeline...



Adaptive Clinical Trial Design

- A “**Learn and Confirm**” trial design
- Data from ongoing study is used to modify conduct of the study:
 - Not a substitute for poor planning
 - Emphasis is on modeling/estimation using sophisticated statistics, ongoing analysis + active DSMB
 - Decision rules for adoption are pre-specified
- Very useful for: Dose finding, Sample size re-estimation, Seamless Phase 2/3 trials
- Flexible dose-ranging design allows the dynamic allocation of patients to safe and effective doses
 - Dose demonstrates significant safety issues, drop arm
 - Dose demonstrates positive change in clinical endpoint + no safety issues, expand arm to reach significant numbers.
 - Patients in efficacious arm are included in the expanded-population pivotal trial data.
- Trial can be extended to test duration of therapy, relapse, drug resistance or determine the “generally accepted” dose.


Adaptive Clinical Trial Design

(this is not our idea: we're well behind the curve!)

- Fits FDA “**Critical Path Initiative**”
- FDA to release **2** of 5 position papers on Adaptive Trial Design in Jan 07
 - Guidelines for evaluating multiple trial endpoints
 - How to enrich trials with patients most likely to benefit
- EMEA also working on regulatory guidelines for Adaptive Design clinical trials
- PhARMA formed Adaptive Design Working Group to foster wider use and regulatory acceptance of adaptive design
 - WG participants: Novartis, Pfizer, GSK, Lilly, BMS, J&J, AZ
- PhARMA has a separate Adaptive Dose-Finding Working Group

Adaptive Clinical Trial Design

Adaptive Design Working Group preliminary recommendations:

- Proof-of-concept (PoC) and dose selection should be combined into one seamless trial
 - Early stopping rules, for both efficacy and safety, should be used to allow greater efficiency in adaptive designs
 - Trial simulations should be used to determine appropriate sample sizes, as well as to estimate operational characteristics of designs/methods under consideration
 - Etc...
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Adaptive Trial Phase 2/3 Study Design

- Randomized, double-blind
- Substitute SQ109 for EMB in DOTS intensive phase
- 3 (or more) parallel cohorts randomized 1:1:1 to INH/RIF/PZA/[low dose SQ109], INH/RIF/PZA/[high dose SQ109] or INH/RIF/PZA/EMB.
- Patients Treated for 2 months (Intensive phase), continue with INH/RIF (DOTS) regimen for 4 months
 - Monitor
 - safety
 - drug interaction (PD/PK)
 - Primary clinical endpoint, 2 mo
 - decrease in CFU from sputum cultures or % patients with negative sputum cultures or time to negative sputum culture (pick one)
 - Secondary endpoints
 - Rate of sputum clearance
 - decrease in relapse rate
 - improved safety profile



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