New TB Drugs Now

From Phase II to Phase III trials

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InterTB Meeting SGUL 9th September 2019
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**

A. Preclinical
B. Preclinical
C. Preclinical
D. Preclinical
E. Preclinical
F. Preclinical

**Phase I**

A. SAD
B. SAD
C. SAD
D. SAD
E. SAD
F. SAD

- Dose finding/fractionation, selection of combinations and prediction of duration
- Confirmation of human dose, Evaluation of predicted interactions

**Phase II**

A. IIA Mono
B. IIA Mono + Combo
C. MAD IIA Mono + Combo
D. MAD IIA Mono + Combo
E. MAD IIA Mono + Combo
F. IIC

- 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

**Phase III**

A. IIB
B. IIB
C. IIC
D. IIC
E. IIB/III
F. III

- Evaluation of dose-optimised combination for predicted duration with follow-up
### Safety in drug development

#### Discovery

- Preclinical

#### Phase I/II

- IND

#### Phase III/IV

- NDA

### 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**

- **Death**
- **CFU/MGIT**
- **2-month culture conversion**
- **Time to culture conversion**
- **Time to failure**
- **Failure*”**
- **Cure**
- **Early relapse**
- **Re-infection**
- **Late relapse**
- **Time to relapse**
- **Limit of Detection**

* Treatment failure may occur with or without development of new resistance.
# Metagression of Phase III Endpoints

$R^2 = 35.13\%$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-1.6096</td>
<td>0.2059</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Logit month 2 culture positive rate</td>
<td>1.0817</td>
<td>0.1765</td>
<td>&lt;.0001</td>
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<tr>
<td>Natural log treatment duration</td>
<td>-0.7503</td>
<td>0.2347</td>
<td>0.0014</td>
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<tr>
<td>Natural log treatment</td>
<td>-1.4682</td>
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<tr>
<td>Logit month 2 culture positive rate $\times$ Natural log treatment</td>
<td>-0.8954</td>
<td>0.2157</td>
<td>&lt;.0001</td>
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<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.2900</td>
<td>0.3657</td>
<td>0.4277</td>
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<tr>
<td>Logit month 2 culture positive rate</td>
<td>0.3557</td>
<td>0.1007</td>
<td>0.0004</td>
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<tr>
<td>Natural log treatment duration</td>
<td>-1.3467</td>
<td>0.2885</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Natural log treatment</td>
<td>-0.7314</td>
<td>0.3313</td>
<td>0.0273</td>
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<tr>
<td><strong>End of treatment + Follow-up</strong></td>
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<tr>
<td>Intercept</td>
<td>-0.4732</td>
<td>0.3647</td>
<td>0.1945</td>
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<tr>
<td>Logit month 2 culture positive rate</td>
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<td>0.1184</td>
<td>&lt;.0001</td>
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<tr>
<td>Natural log treatment duration</td>
<td>-1.1984</td>
<td>0.2895</td>
<td>&lt;.0001</td>
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<tr>
<td>Natural log treatment</td>
<td>0.0267</td>
<td>0.3397</td>
<td>0.9373</td>
</tr>
</tbody>
</table>

Ken-Dror G Lancet ID (Submitted)
Reconstruction of Time-to-event endpoints

Ken-Dror G WHO Clinical Trials Workshop 2018
## Metagression: Median time to CC

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

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

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

Ken-Dror G WHO Clinical Trials Workshop 2018
Predicting duration: meta-regression

- Median
- Culture positive at follow-up (%)
- Months 2 positive (%)
- Culture positive at end of treatment plus follow-up (%)
- <6 mo & no R+Z
- =6 mo & R or Z
- >6 mo & R + Z
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

### Phase IIB: Dose-ranging

<table>
<thead>
<tr>
<th></th>
<th>Estimate (logCFU/mL/day)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm mITT (N=174)</td>
<td>-0.011</td>
<td>0.002/-0.025</td>
<td>0.23</td>
</tr>
<tr>
<td>Treatment arm mPP (n=132)</td>
<td>-0.022</td>
<td>-0.002/-0.046</td>
<td>0.022</td>
</tr>
<tr>
<td>Rifampicin AUC(_{0-6p}) mPP (N=126)</td>
<td>-0.017</td>
<td>-0.007/-0.029</td>
<td>0.011</td>
</tr>
<tr>
<td>Rifampicin AUC(<em>{0-6}/MIC</em>{99.9}) mPP (N=126)</td>
<td>-0.010</td>
<td>0.000/-0.021</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Velazquez G CROI 2018
Phase IIB: Adaptation

Time to stable culture conversion on MGIT liquid media

- 35R
- 20RM
- Control
- Q
- 20RQ

Cumulative proportion of patients with culture conversion

Days from randomisation

- 0 7 14 21 28 35 42 49 56 63 70 77 84

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

**Trial design**

<table>
<thead>
<tr>
<th>Start of Recruitment</th>
<th>1st Interim Analysis</th>
<th>2nd Interim Analysis</th>
<th>Final Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Regimen (Arm A)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm D</td>
<td>Stop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm E</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stage 1 Pilot safety and Stage 2 Early efficacy*  
*Stage 3 Qualifying efficacy*  
*Stage 4 Definitive safety and efficacy*
Predicting duration: meta-regression

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**

A. Preclinical
B. Preclinical
C. Preclinical
D. Preclinical
E. Preclinical
F. Preclinical

**Phase I**

A. SAD → MAD/DDI
B. SAD → MAD/DDI
C. SAD → DDI
D. SAD → DDI
E. SAD → DDI
F. SAD → MAD/DDI

**Phase II**

A. IIA Mono → IIA Combo → IIB
B. IIA Mono + Combo → IIB
C. MAD IIA Mono + Combo → IIB
D. MAD IIA Mono + Combo → IIC
E. MAD IIA Mono + Combo → IIB/III
F. IIC → III

**Phase III**

A. III
B. III
C. III
D. III
E. III
F. III

**Notes:**
- **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