Quantitative Modeling of Time to Positivity Following Dosing of Bedaquiline and Rifafour in Patients with Pulmonary Tuberculosis Infection

8th International Workshop on Clinical Pharmacology of TB drugs
September 17, 2015

JF Marier, PhD, FCP
VP & Lead Scientist, Pharsight, A Certara Company

CRITICAL PATH INSTITUTE

Critical Path to TB Drug Regimens

Background

- There is currently a need to develop quantitative tools to:
  - more **accurately evaluate efficacy** in Phase II clinical trials for combination regimens for TB and
  - more **reliably predict** clinically relevant endpoints for Phase III clinical trials.

- The linkage between early biomarker measurements in Phase II and long-term clinical outcomes in Phase III may help increase efficiency of drug development for TB regimens.

- If successful, this novel approach may reduce the time required to develop an innovative regimen from decades to years.

Time to Positivity (TTP)

- With the development of culture-based TB diagnosis, a parameter has emerged with important potential in the assessment of patient progress during therapy: time to detection (TTD), also known as time to positivity (TTP).
- TTP represents the time to detectable growth of Mycobacterium tuberculosis (Mtb) in culture.
- Potential use of TTP as an early indicator of treatment effectiveness comes from some early work performed by Epstein et al. who showed that TTP of Mtb in sputum culture correlates with the response to anti-TB therapy.

Goals

- **Short-Term:** Construct a quantitative model describing the actual shape of TTP trajectory over time using a mixed-effects modeling approach based on data collected in 10 Phase II studies.

- **Longer Term:** Evaluate TTP trajectory parameters as potential predictors of durable cure and relapse, based on data from the REMox trial.

- Note: Previous efforts have evaluated the correlation of TTP slope with clinical outcomes. This effort expands on this work in order to assess the actual shape of TTP, recognizing that TTP changes in a non-linear manner, with a saturable effect (i.e., TTP=42 days).

Methodology: Datasets and Populations

- **TTP Data Collected**
  - 10 Phase II Studies
  - 1750 Subjects with TB
- **Treatments**
  - RHZE (Rifafour-Based)
    - RHZE (Rifafour e275): 593 (33.9%)
    - RHZE/BDQ: 79 (4.5%)
    - RHZE/Vitamin A: 77 (4.4%)
  - PHZE: 511 (29.2%)
  - Bedaquiline: 75 (4.3%)
  - Pretomanid-Based (PA-824)
    - Pretomanid (PA-824): 122 (7.0%)
    - PA-824/Z/Moxi: 159 (9.1%)
- **Baseline Characteristics**
  - Male (65.9%) ; Female (34.1%)
  - HIV (9.1%); non-HIV (90.3%)
  - CD4 Counts (cells/µL)
    - Mean(CV%): 654 (47.5)
    - Median (Range): 607 [19.0, 2952]
  - Lung Cavitation
    - Yes (58.2%)
    - No (41.8%)
  - Race
    - White (11.7%)
    - Black or AA (59.4%)
    - Asian (7.5%)
    - Hispanic (1.5%)
    - Other (17.7%), Missing (2.1%)

Methodology: Modeling Approach

- Extensive evaluation of mathematical functions to describe the non-linear and saturable behavior of TTP over time.
  - Linear Models (previously tested)
  - Emax and Gompertz (sigmoidal, asymptotic function)
  - Cubic & Quadratic Models (exponential functions)
  - Weibull Models (a stretched exponential function)

- With and without right censoring for TTP ≥42
  - Right censored data was implemented using M3 method (estimate likelihood for 42)

- Covariate Analysis (Sources of Variability)
  - HIV (Yes/No), CD4 Counts
  - Pulmonary Cavitation
  - Treatments

- Software: Phoenix NLME v1.3 (non-linear mixed effect modeling)

Results: Introducing the Gompertz Model

- A Gompertz model resulted in the best goodness-of-fit.

$$TTP(time) = Alpha * exp^{[-Beta * exp(-\mathbf{Gamma}*Time)]}$$

i.e. the maximum value that can be reached with the incubation time (i.e,. TTP=42 days)

TTP at the starting observation time (i.e., baseline)

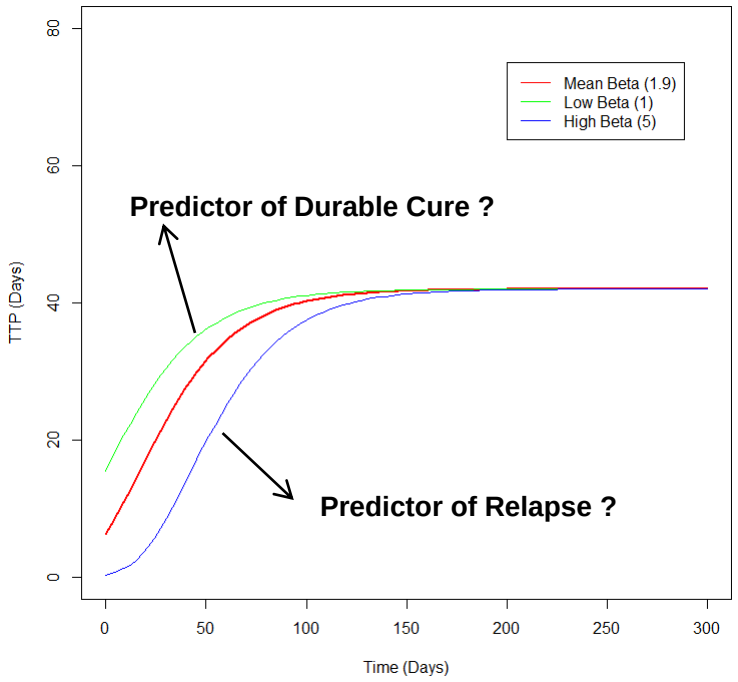
A constant related to the proliferative ability of Mycobacterium tuberculosis (Mtb) in culture (rate of growth)

- Note: Often used in oncology to model tumor size over time (to be used as a predictor of survival).

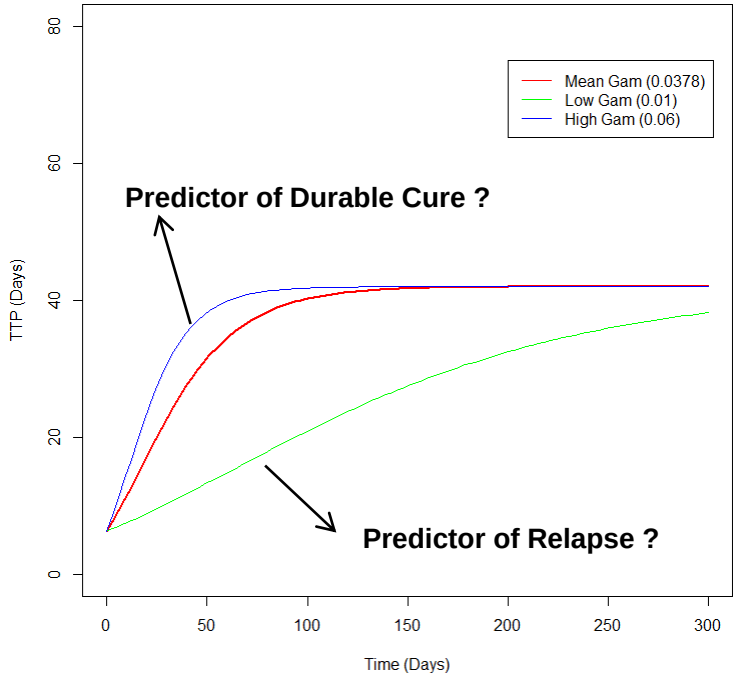
Results: Introducing the Gompertz Model

- Flexibility of a Gompertz model to characterize non-linear profiles

Effect of Beta Parameter on TTP Profiles
Left-Right Shift, Same Steepness



Effect of Gamma Parameter on TTP Profile
Steepness



TTP Population Parameters

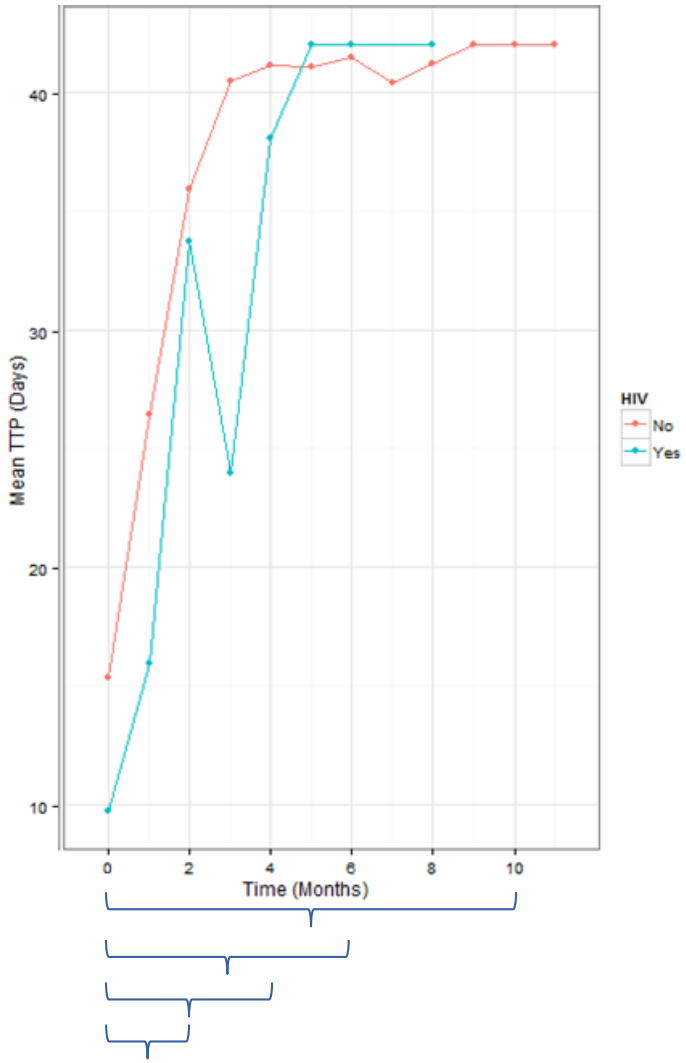
Parameters	Estimate (RSE%)	Between-Subject Variability (%)
Maximum TTP (Days)	42	
Baseline TTP (Day)	1.95 (0.885)	26.8
TTP Growth (Day^{-1})	0.0378 (2.48)	93.1

Half-Life = 18.3 days

- An additional benefit of the Gompertz model is conversion of the gamma factor (rate of TTP) into a half-life i.e., ln2/gamma.
- The above results suggest that TTP doubled every 18 days.
- Residual error: 23.7%

Sensitivity Analysis – Study Duration

- Phase II studies from 2 weeks to 10 months.
- A sensitivity analysis was performed by selecting different period of TTP collection
- TB-1010 (RHZE or PHZE)
  - All Data (0-10 months)
  - 0-6 months
  - 0-4 Months
  - 0-2 Months
- Assessed whether the model was reliable to assess the trajectory based on short- and longer-term Phase II studies.



Sensitivity Analysis – Study Duration

- Results of the sensitivity analysis are presented below.

Parameters	All Data (Reference)	0-6 Months (Test 2)	0-4 Months (Test 3)	0-2 Months (Test 4)
Maximum TTP	42	42	42	42
Baseline TTP (Day)	1.92	1.92	1.85	1.78
TTP Growth (Day^{-1})	0.0494	0.0490	0.0440	0.0407
Half-life (Days)	14.0	14.1	15.8	17.0

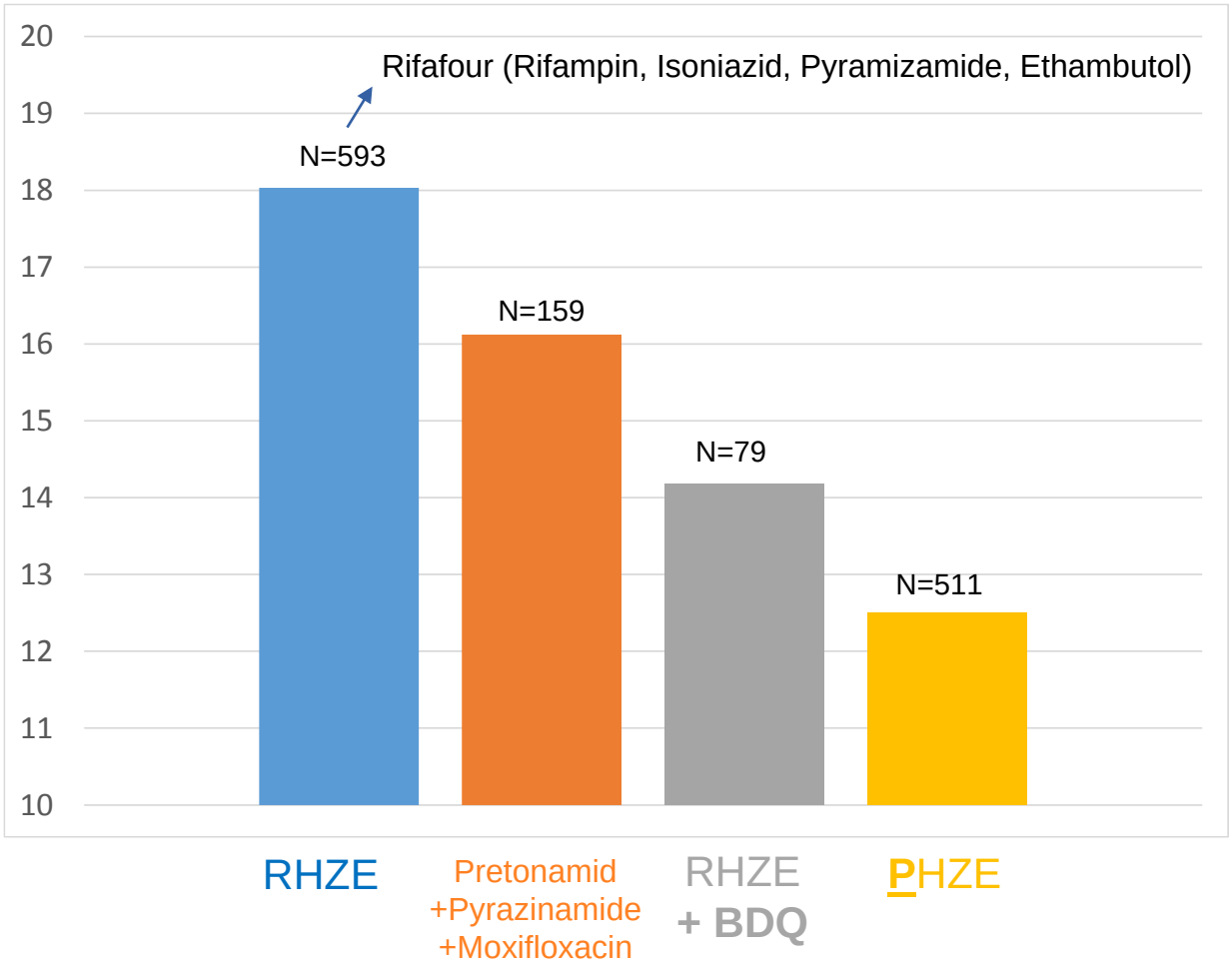
- **Conclusions**
  - The model can adequately capture the shape of TTP over time, independent of the study duration.
  - TTP=42 is not absolutely required for the understanding of the shape of TTP
  - The Gompertz model can be used in short or “long” Phase II studies to adequately characterize the shape of the TTP trajectory.

Sources of Variability in TTP

Treatments: N(%)

- **Rifafour-Based**
  - RHZE (Rifafour e275): 593 (33.9%)
  - RHZE/BDQ: 79 (4.5%)
  - RHZE/Vitamin A: 77 (4.4%)
- **PHZE: 511 (29.2%)**
- **Other**
  - Pyrazinamide (Z): 15 (0.9%)
  - Clofazimine (CZ): 14 (0.8%)
- **Bedaquiline-Based (BDQ)**
  - BDQ: 75 (4.3%)
  - BDQ/Z: 15 (0.9%)
  - BDQ/PA-824: 15 (0.9%)
  - BDQ/PA-824/Z/CZ: 15 (0.9%)
  - BDQ/Z/CZ: 15 (0.9%)
  - BDQ/PA-824/Z: 15 (0.9%)
  - BDQ/PA-824/CZ: 15 (0.9%)
- **Pretomanid-Based (PA-824)**
  - PA-824: 122 (7.0%)
  - PA-824/Z/Moxifloxacin: 159 (9.1%)
  - PA-824/Z: 15 (0.9%)

Treatment Effects on TTP

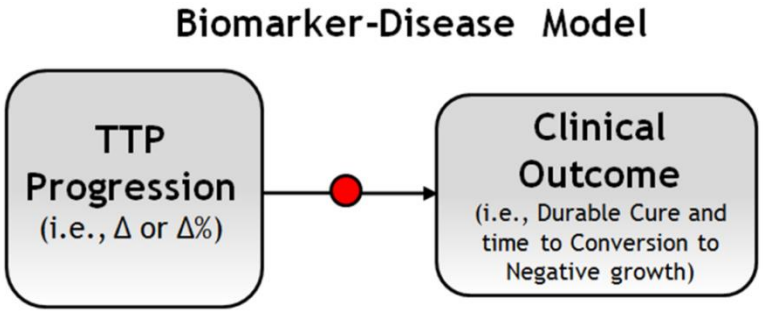


- Adding BDQ to Rifafour (RHZE) deceased the TTP half-life from 18 to 14 days.
- Replacing **R**ifampin (in RHZE) to Rifa**p**entine (i.e., PHZE) resulted in a $t_{1/2}$ of 12 days.
- In addition to treatment, dose information will also be included in the model.

Conclusion

The linkage between early biomarker measurements in Phase II and long-term clinical outcomes in Phase III may help increase efficiency of drug development for TB regimens.

We propose building a biomarker-disease model, linking parameters describing the non-linear behavior of TTP in Phase II to clinical outcomes in Phase III



Application/Value

- Determine early changes in TTP in Phase II (e.g., dose ranging study) and effect on long term clinical outcome in Phase III to guide decisions.
- Use the trial simulation platform as a drug development tool (DDT) to refine the size and cost of clinical trials for TB by shortening the duration of those trials.