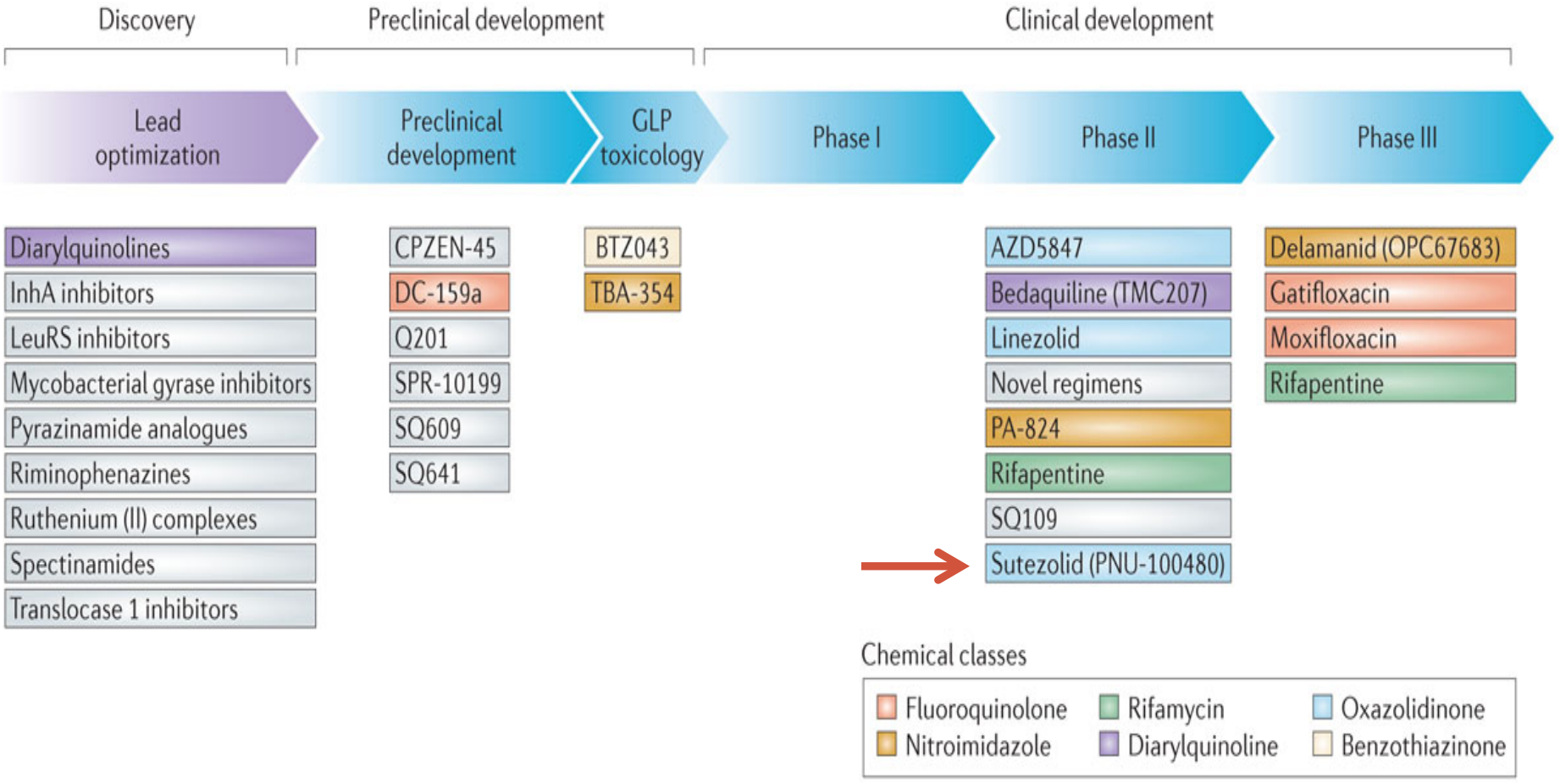
Population pharmacokinetics and bacterial dynamics of sutezolid in patients with active tuberculosis

Kajal B. Larson[1], Kun Wang[1,2], Lisa Beth Ferstenberg[3], Carol Nacy[3] and Edward P. Acosta[1]

[1]Division of Clinical Pharmacology, University of Alabama at Birmingham, Birmingham, Alabama
[2]Center for Drug Clinical Research, Shanghai University of Chinese Medicine, China
[3]Sequella, Inc

Pipeline of TB drugs



Nature Reviews Drug Discovery 12, 388–404 (2013) doi:10.1038/nrd4001

Oxazolidinone family

- Linezolid
  - Has activity against DR TB
  - Optic neuropathy, myelosuppresion
- Sutezolid (PNU-100480)
  - More potent than linezolid in murine models
  - Safe and well-tolerated in healthy human volunteers
  - Active metabolite: PNU-101603
    - Median plasma concentration is ~7 times higher than parent*

*range, 1-28; reference: Antimicrob Agents Chemother. 2014 Jun;58(6):3306-11

Sutezolid Clinical Studies

- Study B1171001
  - Phase 1, single ascending doses, healthy volunteers, fasted/fed (35-1500 mg)
- Study B1171002
  - Phase 1, placebo-controlled, multiple ascending doses, healthy volunteers (100, 300, 600 mg BID, 1200 mg QD)
- Study B1171003
  - Phase 2a, open-label, randomized, treatment-naïve sputum smear positive subjects with drug-sensitive pulmonary TB to assess early bactericidal activity (EBA) and whole blood activity (WBA); 600 mg BID, 1200 mg QD

Question

- What is the optimal sutezolid dose and dosing interval when administered as a single agent?
  - Second look at the EBA, WBA, and parent and metabolite concentration-time data collected in the B1171003 study

Methods

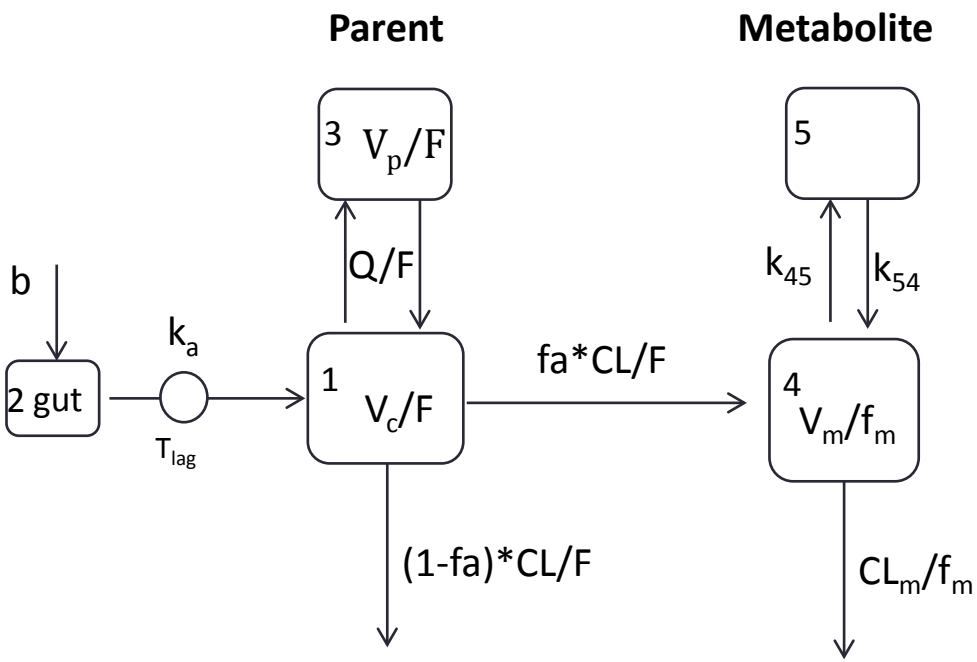
- Fifty treatment-naïve adults, sputum smear positive with drug sensitive TB
  - 14-day monotherapy
  - 25 received sutezolid at 600 mg BID
  - 25 received sutezolid at 1200 mg QD
- Patient demographics:

Parameters	Sutezolid 600 mg BID	Sutezolid 1200 mg QD
Number of subjects	25	25
Age (years, mean ± SD)	32.3 ± 9.0	34.1 ± 11.7
Male	20	20
Race (Black/other)	11/14	8/17
BMI (kg/m^2, mean ± SD)	19.6 ± 2.9	18.3 ± 1.8

Methods

- Drug concentration measured by HPLC-MS/MS
- Sputum was collected for CFU counts
- Blood was also collected for WBA
- ADAPT 5 (MLEM algorithm) was used to
  - Develop a population pharmacokinetic model to describe the drug (parent and metabolite) concentrations
  - Link the PK model to bacterial dynamic model

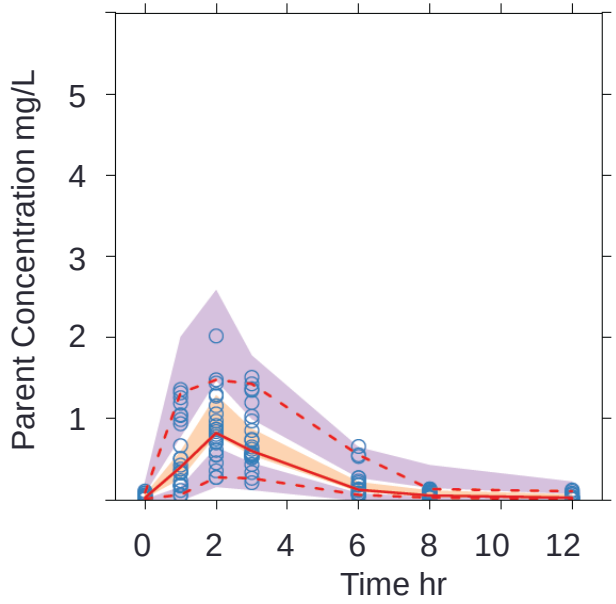
PK model

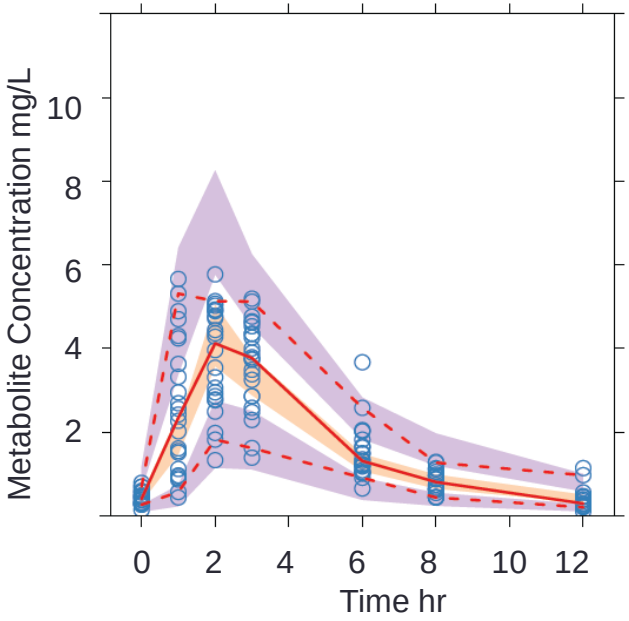


t1/2-parent	6.72 hrs
t1/2-metabolite	5.71 hrs

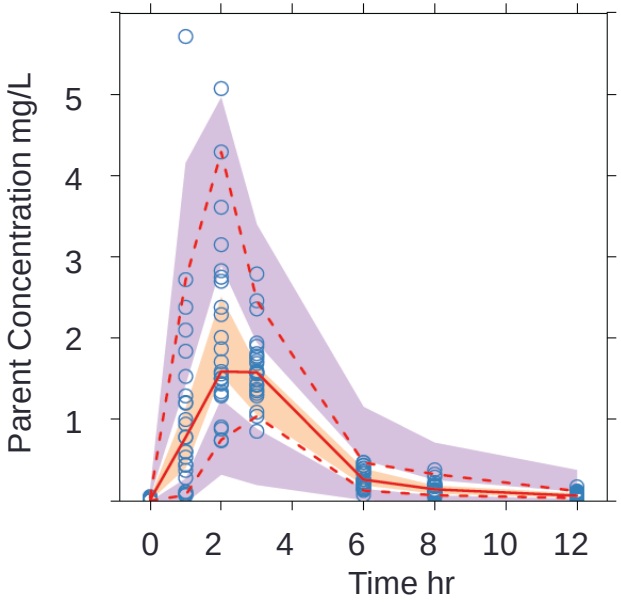
Parameter	Mean (%RSE)	IIV CV% (%RSE)
CL_t (L/h)	165 (5.33)	27.8 (16.8)
V_c/F (L)	162 (20.3)	71.1 (26.2)
Q/F (L/h)	32.4 (8.65)	14.8 (131)
K_a (1/h)	0.876 (7.23)	6.38 (210)
V_p /F(L)	258 (10.4)	33 (41.6)
T_{lag} (h)	0.846 (3.39)	10.7 (32.8)
CL_m/F_m (L/h)	17.5 (68.8)	16.5 (81.3)
V_m/F_m (L)	0.157 (92)	15.6 (193)
K_{45} (1/h)	59.4 (62.1)	3.68 (2520)
K_{54} (1/h)	0.347 (12.2)	26.5 (58.4)
fa	0.562 (67.5)	1.93 (2130)

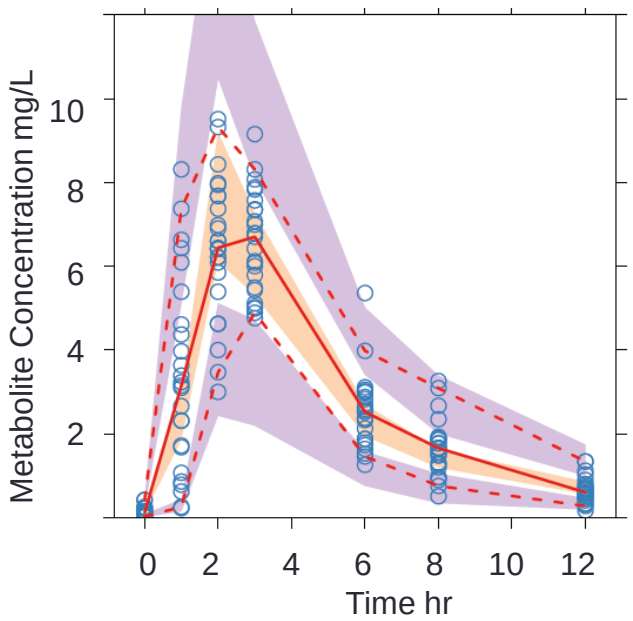
PK Model Visual Predictive Check





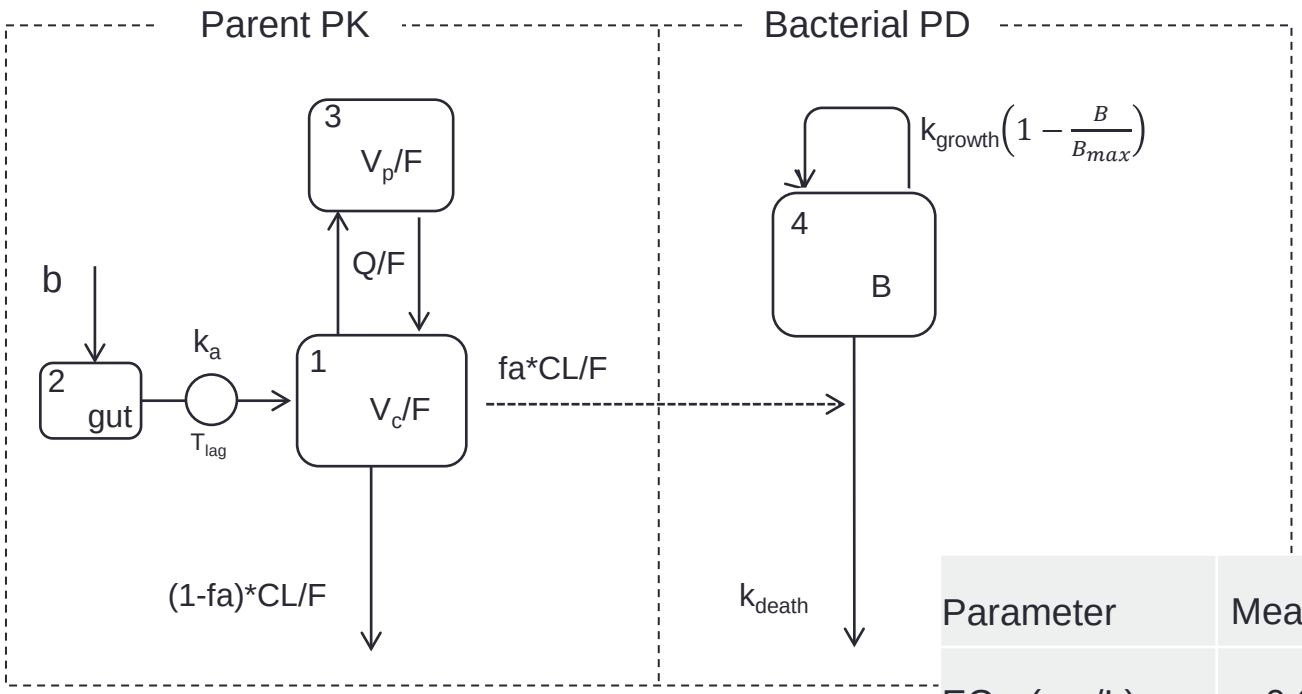
dose= 600 mg BID





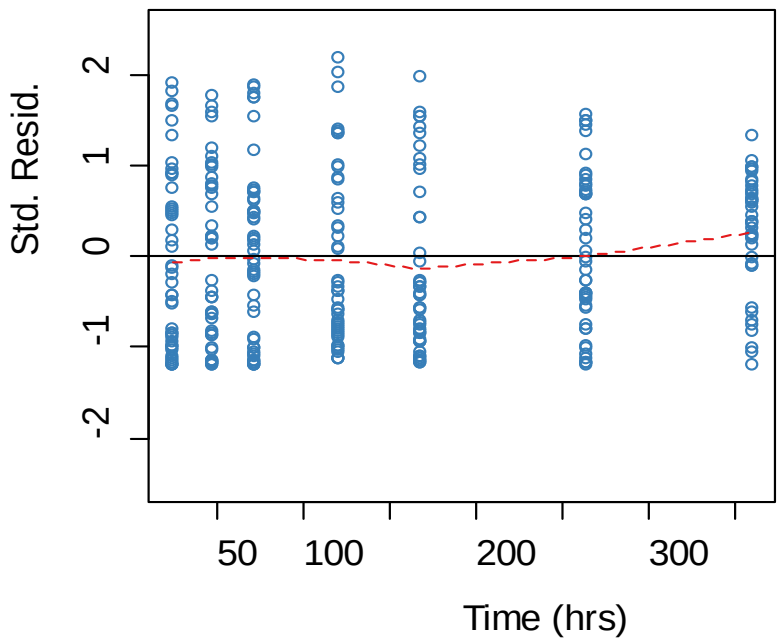
dose=1200 mg QD

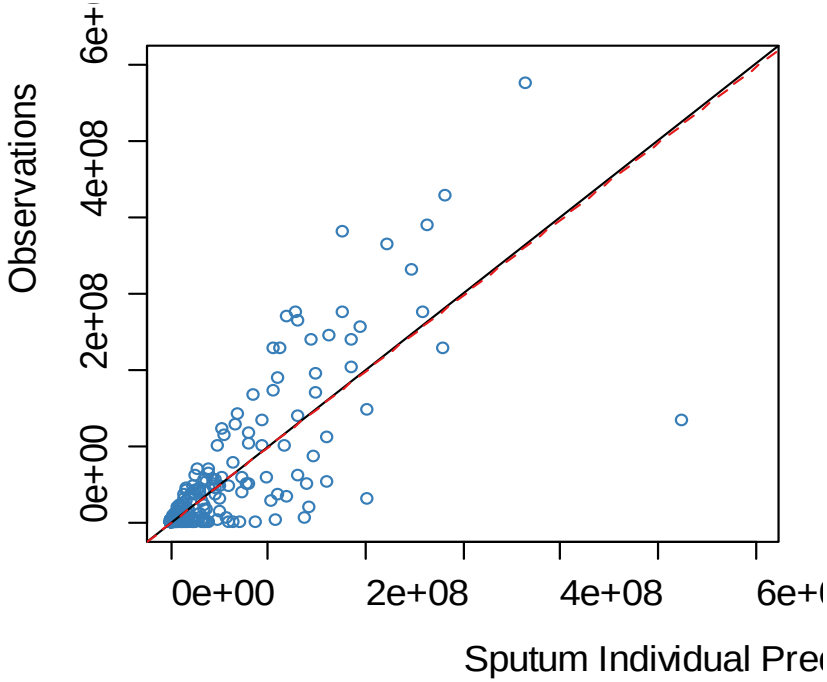
PK model linked to bacterial model



Parameter	Mean (%RSE)	IIV CV% (%RSE)
EC_{50} (mg/L)	0.02 (105)	63.6 (174)
k_{death} (day^{-1})	0.0281 (19.4)	31 (31.5)
k_{growth}(day^{-1})	0.0133	Fixed
B_{max} (CFU/mL)	10^9	Fixed

Bacterial Model Goodness of Fit





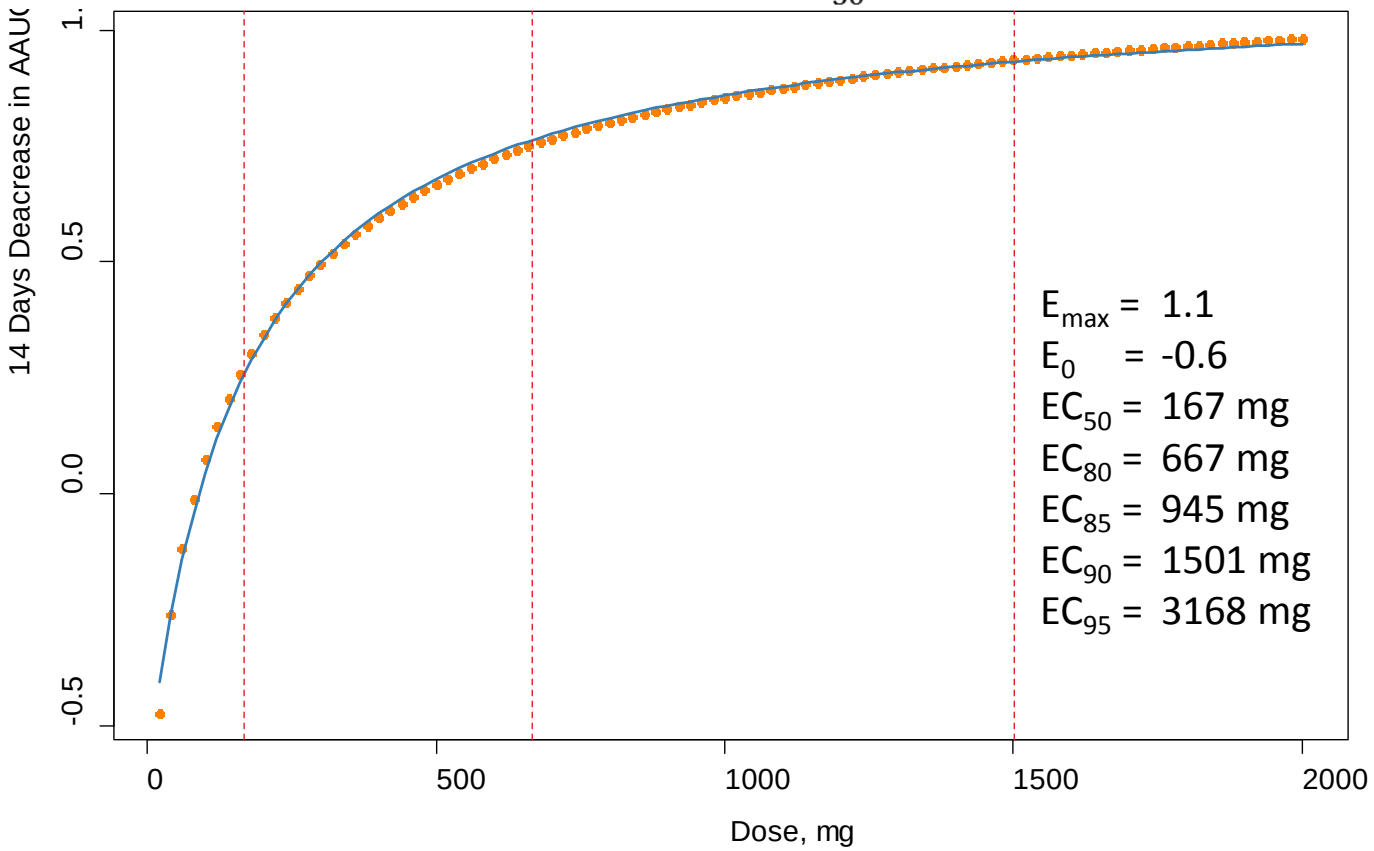
Dose-Response Simulation of Linked PK/Bacterial Model

- Simulation studies were conducted to explore exposure–response relationships using population mean parameters of the linked PK/Bacterial Model.
- Simulated doses ranged from 20 to 2000 mg twice daily (100 different doses).
- The pharmacodynamic determinant of response was the decrease in the time-averaged area under the $\log_{10}$ sputum–time curve from 0 to 14 days minus baseline (AAUCMB).
- Simulated doses were linked to the bacterial model to calculate corresponding changes in AAUCMB and to determine the dose required to produce the EC_{50}, EC_{80}, EC_{85}, EC_{90}, and EC_{95} of the maximum drug effect (E_{max}).

Exposure-relationship curve

- The exposure–response relationship of dose and the decrease in AAUCMB was fitted using the following Emax model:

$$Decrease\ in\ AAUCMB = E_0 + \frac{(Emax - E_0) \cdot Dose}{EC_{50} + Dose}$$



Summary

Parameter	**EBA AAUCMB** (BID, mg)
EC_{50}	167
EC_{80}	667
EC_{85}	945
EC_{90}	1501
EC_{95}	3168

Conclusions

- It is believed that U-480 is most active against intracellular TB and U-603 is more active against extracellular TB
- Our model linked the parent drug to EBA activity; future work will consider the metabolite model
  - It is very difficult to extract individual drug effects when both parent and metabolite are inherently present
- Our modeling and simulation exercises suggest a sutezolid dose of 1000 mg BID as a center point for further dose-ranging trials in patients
- Sutezolid and linezolid are structurally similar
  - Concern for mitochondrial protein synthesis toxicity
    - high exposures and longer duration

Css 001 001-003