Clinical Pharmacology Aspects of Anti-infective Drugs – Regulatory Experiences

March 23, 2018

Dakshina M. Chilukuri, Ph.D.
Office of Clinical Pharmacology
Office of Translational Sciences
CDER/FDA

Disclaimer

- The opinions expressed during this presentation are those of the speaker, and do not necessarily represent those of the Food and Drug Administration.

Outline

- Tuberculosis
  - Specific features related to TB drug development
  - Regulatory example
- Malaria
  - Regulatory challenges in malaria drug development
  - Regulatory example

Dose Selection for Pivotal Trials – Clinical Pharmacology Considerations for TB drugs

- Nonclinical studies
  - Animal models that identify PK/PD relationships
  - Extent of tissue distribution
- Microbiology evaluations
  - MIC determination
- In vitro models of PK/PD – hollow fiber system
  - quantitative model to inform drug doses, exposures, susceptibility breakpoints and optimize combination regimens

Dose Selection for Pivotal Trials – Clinical Pharmacology Considerations for TB drugs

- Early Bactericidal Activity (EBA) Study[1]
  - Monotherapy to establish proof of concept
  - Usually performed over a 14-day period
  - Define the PK/PD properties
  - Provide justification for future trials
- Phase 2 dose-finding studies
  - Measurement of systemic and sputum concentration of the TB drug (and relevant metabolites) in the trials
  - Attempt to evaluate exposure-efficacy and exposure-safety relationships

Andreas H Diacon & Peter R Donald (2014), Expert Review of Anti-infective Therapy

Clinical Pharmacology Considerations for Development of Combination Regimens

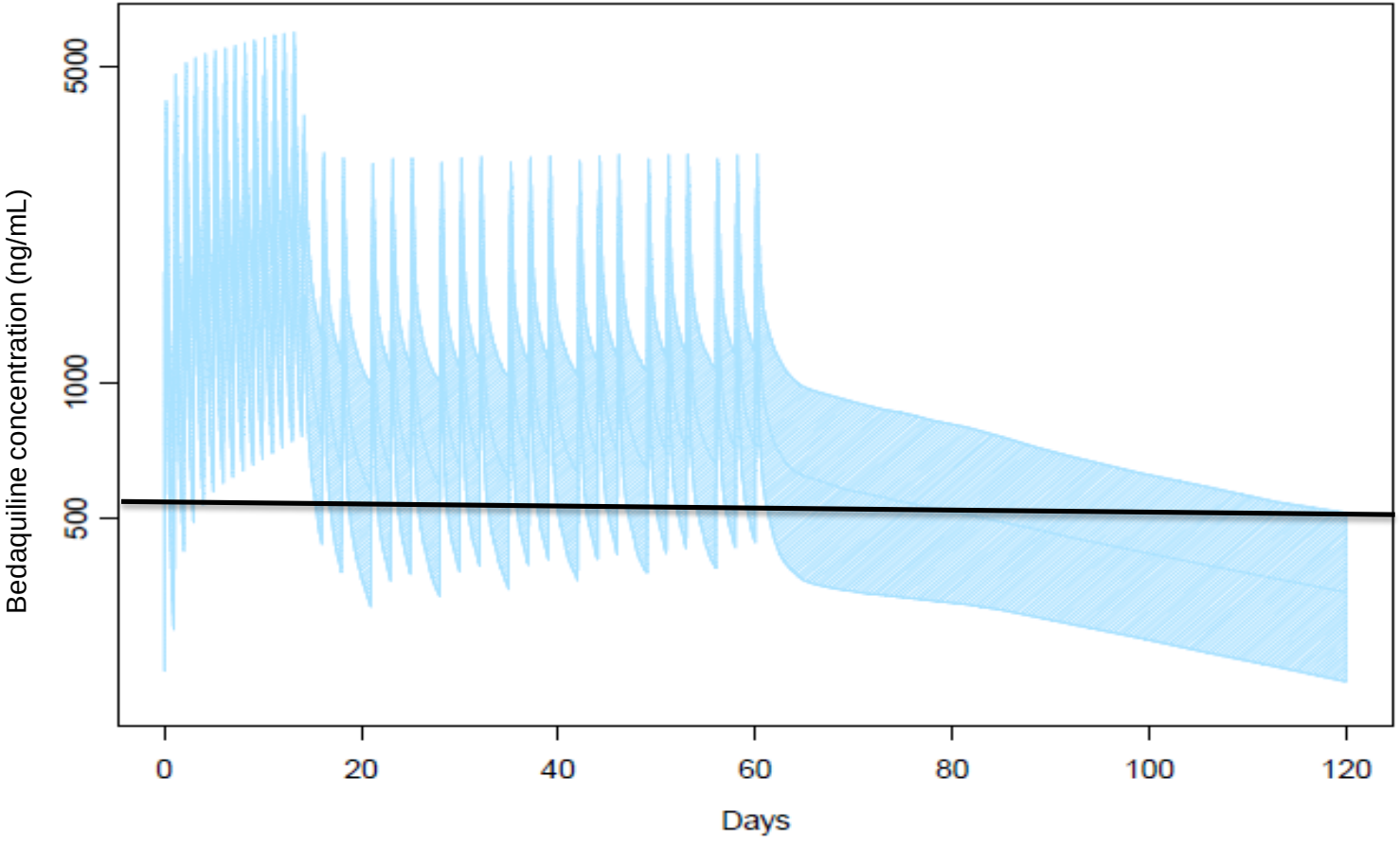
- Adequately characterize drug interaction potential of new TB agents
- Evaluate drug-drug interactions between the existing regimen and newly added drugs
- Evaluate the contribution of each new drug to be used in the combination
- Select the right dose of each new drug used in the combination
- QT monitoring to determine labeling recommendations

Regulatory Example

Sirturo™(bedaquiline)

- Indication: Treatment of MDR-TB
- Approved by FDA in 2013
- Dosing regimen:
  - 400 mg daily for the first 2 weeks
  - 200 mg 3 times/week for the following 22 weeks
- Food increases systemic exposure 2-fold
  - Administered with food in clinical trials
  - Label: administer with food
- Long terminal elimination half-life (4-5 months)
- 99% protein bound

Simulated Bedaquiline Plasma Concentrations for a 9-Week Dosing Regimen, (400 Subjects)



Trial Design

- Trial 1: Phase II, multicenter, stratified, double-blind, randomized, placebo-controlled trial with two consecutive but completely separate stages
  - Stage 1: Exploratory Stage, with an 8-week Bedaquiline/placebo investigational treatment phase
  - Stage 2: Proof-of-efficacy Stage, with a 24-week Bedaquiline/placebo investigational treatment phase
- Trial 2: Single-arm, open-label trial

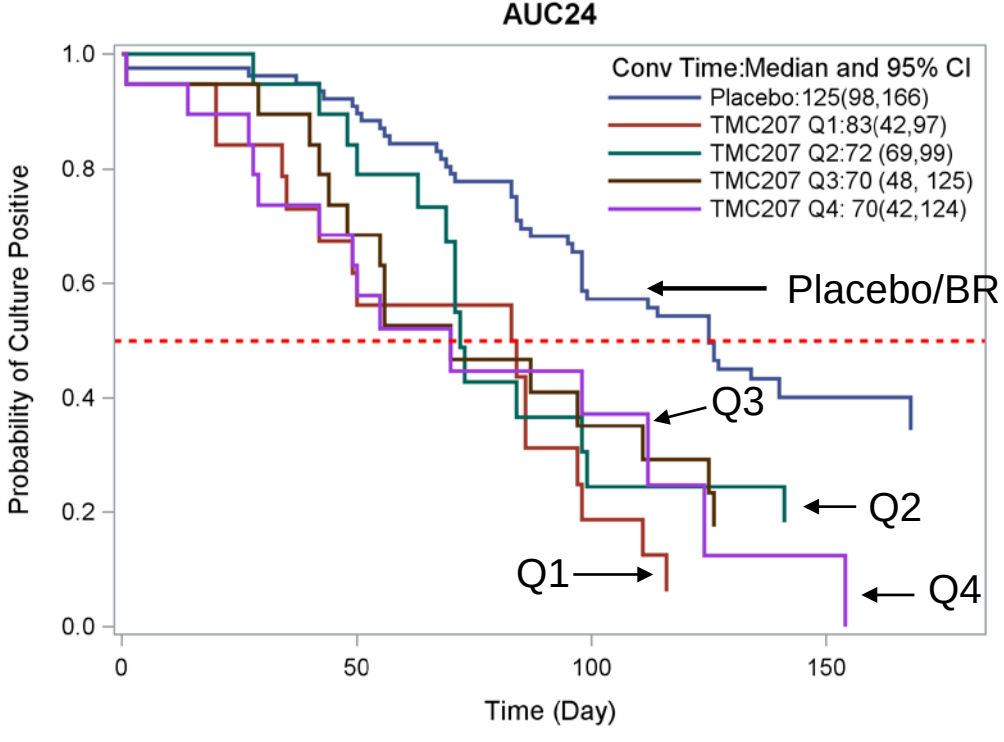
- Bedaquiline was added to an MDR-TB drug regimen

Exposure-Response Analysis

Is there evidence of exposure-response relationship?

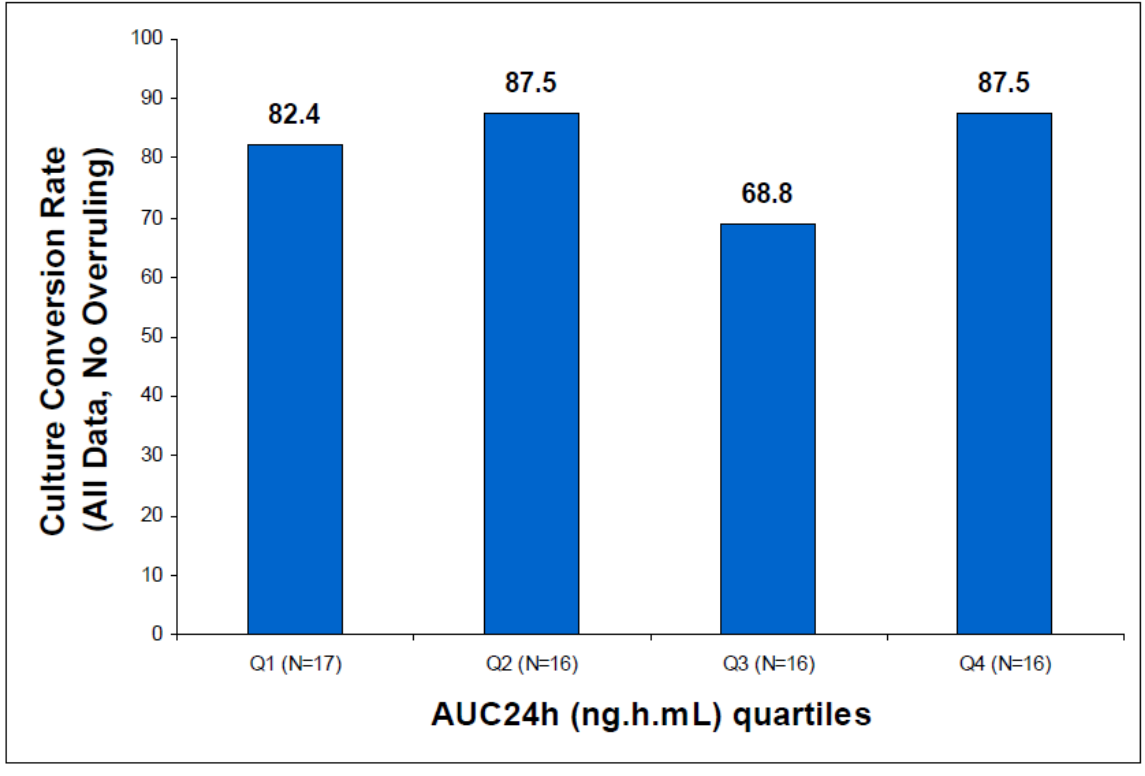
Are there specific populations and situations that require dose adjustments?

Higher exposure to bedaquiline is not associated with greater efficacy over the systemic exposure range



BDQ	N	AUC_{24h} (ng-h/mL)
Pla/BR	81	-
Q1	19	23624
Q2	19	29931
Q3	19	34299
Q4	19	43915

Secondary analysis: No relationship between conversion rate at week 24 vs. bedaquiline AUC (at Week 2)



Patients of black race have clearance that is 52% higher than other patients

Summary of Individual estimates based on population PK analysis

Parameters		N	Mean	SD
CL/F (L/h)	Caucasian	134	3.61	1.54
	Black	**149**	**5.28**	**2.39**
	Hispanic	41	3.7	0.88
	Asian	99	2.73	0.84
	Other	57	3.84	2.15

Study 1, Stage 2: Subgroup Analyses

Week 24 Culture Conversion Rate by Race

Race	Bedaquiline	Placebo
Black	17/24 (70.8%)	18/25 (72.0%)
Caucasian/White	4/6 (66.7%)	4/8 (50.0%)
Hispanic	4/6 (66.7%)	5/10 (50.3%)
Asian	8/9 (88.9%)	5/6 (83.3%)
Other	11/15 (73.3%)	6/17 (35.3%)

Key Questions

- Is there evidence of exposure-response relationship?

  No significant relationship between exposure to bedaquiline and efficacy, suggesting that the exposure may lie at the top of the ER curve.

- Are there specific populations and situations that require dose adjustments?

  No dose adjustment in black patients is recommended. The culture conversion rate is not significantly lower than patients of other races.

Malaria Drug Development

Malaria Treatment

- Current WHO malaria treatment guidelines
  - "*all episodes of malaria should be treated with at least two effective antimalarial medicines with different mechanisms of action*"
  - the combination of a short-acting agent to promote rapid parasite reduction and a long-acting agent to prevent recrudescence
- FDA approved malaria treatments:

  COARTEM™ (artemether + lumefantrine) [2009]

  MALARONE™ (atovaquone + proguanil) [2000]

  Mefloquine [1989]
  - serious psychiatric AEs often limit usage

Regulatory Challenges in Malaria Drug Development

- Prevalence of malaria is non-US
- Recommended malaria treatments are always combinations of a minimum of two drugs
- Children and pregnant women represent at-risk population and are in most need of new and effective therapies
- Development of resistance

Landscape of Malaria Drug Development

- In vitro growth of *P. falciparum* parasites
- Humanized severe combined immunodeficiency mice (SCID huMouse) experiments
- Controlled human malaria infection (CHMI) in healthy volunteers
  - Sporozoite induced malaria (infected Anopheles bites)
  - Induced blood stage malaria (venous inoculation of blood stage malaria)
  - Provide an opportunity to obtain key information about the PK/PD properties of a drug in a controlled setting that can be directly translatable to later clinical studies to estimate an efficacious dose.
- Clinical trials in endemic settings
  - Dose-finding trials
  - Confirmatory trials

Regulatory Example

- Drug X
  - $T_{1/2}$ >2 days (*fast-acting agent*)
- Drug Y
  - $T_{1/2}$ >10 days (*sustained effect*)

- Aim of combination is to have a single administration product with rapid and potent effect from Drug X with sustained antimalarial effect from Drug Y

Proposed Clinical Development Plan for Justifying the Combination of X and Y

- Use existing human data to develop a PK/PD parasitemia clearance model
- In a Phase II trial, efficacy at day 30 post baseline to illustrate the increased treatment effect of the combination vs. X alone.
- Perform simulations to show that the combination of X+Y is superior to X and Y alone
- Phase 3 trials: Non-inferiority to standard of care with artemisinin-based combination therapy in patients with uncomplicated falciparum malaria.

Contribution of Individual Components

- Monotherapy treatment was evaluated
  - Results suggest monotherapy X is not feasible

Endpoint	**X + Y**			**X**
	D1 mg (N=70)	D2 mg (N=72)	D3 mg (N=65)	D4 mg (N=62)
Day 30 Cure Rate	**85%**	**90%**	**99%**	**50%**

Contribution of Individual Components

- **Human challenge study**: Controlled study using blood stage *P. falciparum* challenge inoculum to assess activity of X in healthy subjects.
  - Among the four doses tested (A1, A2, A3 and A4), only the highest dose of A4 mg cleared parasites within 72 h
    - A1 mg -- no change in parasitemia
    - A2 mg -- decrease in parasitemia until 3 days, then recurrence
    - A3 mg -- decrease in parasitemia until 6 days, then recurrence
    - A4 mg -- during the 14 days follow-up, 60% of the participants experienced recurrent parasitemia after 8 days

PK/PD Model of X

- Model-based simulations to predict probability of X monotherapy treatment response
  - Model predictions are based on short-term monotherapy treatment data along with X data
- X is not predicted to be effective as a monotherapy treatment

Endpoint	X [mg]				
	A	B	C	E	F
Day 28 Cure Rate	**2%**	**5%**	**15%**	**30%**	**45%**

Proposed Phase II Evaluations

- Additional dose exploration was recommended as part of the proposed Phase II trial to better elucidate contribution of each component

		Y				
		0 mg	A1 mg	A2 mg	A3 mg	A4 mg
X	0 mg					
	B1 mg		X	X	X	X
	B2 mg		X	X	X	X
	B3 mg		X	X	X	X

- Secondary measures, such as time to alleviation of fever, could further support contribution of the individual components

PK/PD modeling approaches

Semi-mechanistic PK/PD modeling using PD endpoints, such as parasite clearance, recrudescence and clinical cure

– Limitations
  - Stage-specific action of the anti-malarial treatment
  - Host immunity
  - The utility of these models depends on how well the model can predict the patient data

Simpson et al. AAPS J. 2014 Sep;16(5):962-74.

Impact of Model-informed Drug Development (MIDD)

- Mechanistic-based PK/PD models based on preclinical data to assist dose determination in humans that avoids emergence of resistance
- Potential to use population PK approach to support dose selection in children and pregnant women
- Exposure-response analyses may help support evidence of efficacy in addition to other clinical trial data
  - Requires robust models that describe the E-R relationship

Summary

- Both TB and malaria drug development programs are utilizing MIDD principles
- Modeling and simulation results are supportive in demonstrating efficacy of combination of the agents
- FDA has published a DRAFT TB guidance in 2013 and the malaria guidance is under development

Acknowledgements

Philip Colangelo

Jeff Florian

John Lazor

Fang Li

Chao Liu

Kellie Reynolds

Luning (Ada) Zhuang

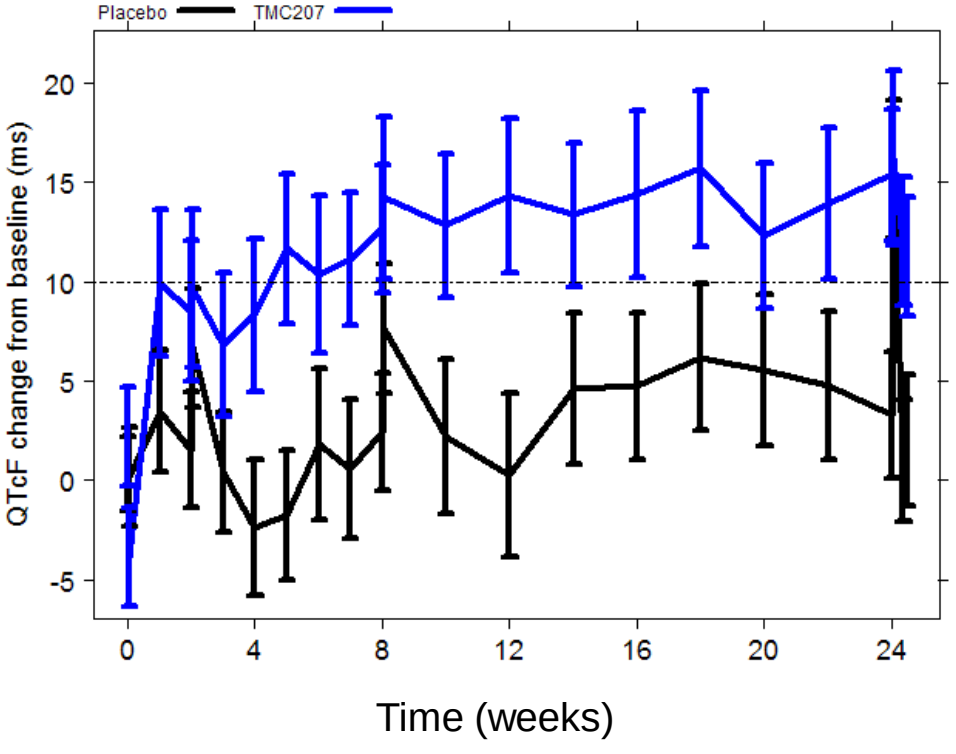
Questions

Thorough QT Study

- **Population:** 88 healthy volunteers
  - 44 bedaquiline
  - 44 placebo
- **Dose:** *Single* 800 mg dose
  - bedaquiline: Cmax in TQT trial was 3-fold higher than at therapeutic dose
  - M2: Cmax in TQT trial was 1/5 of Cmax at therapeutic dose
- **Results:** No significant QT prolongation (< 10 ms)

31

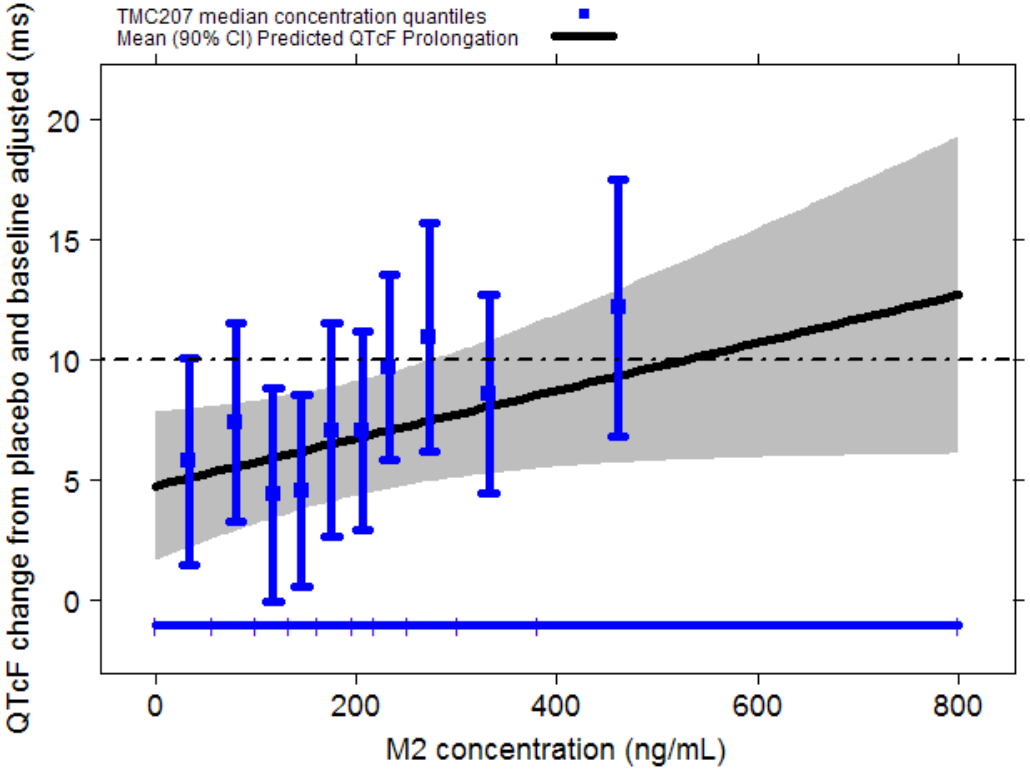
QTc Prolongation Was Observed in Trial 1



Conclusion: Bedaquiline **does** prolong the QTc Interval

32

Relationship between M2 Concentration and QTc Interval Also Observed in Trial 1



33

Bedaquiline Metabolism

- Bedaquiline is mainly metabolized via CYP3A
- M2 is the major metabolite of bedaquiline in vitro and in vivo (~20% of the bedaquiline AUC in humans)
- M2 is 4-6 times less potent than bedaquiline
- Effect on enzymes – bedaquiline is neither an inhibitor nor an inducer of major CYP enzymes