

# **Population Pharmacokinetics of AZD-5847 in Patients with TB**

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# Introduction

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- AZD5847 is an oxazolidinone antibiotic, with *in vitro* activity against *Mycobacterium tuberculosis*
- Recently completed a phase II EBA study
- EBA activity was very modest

# Objective

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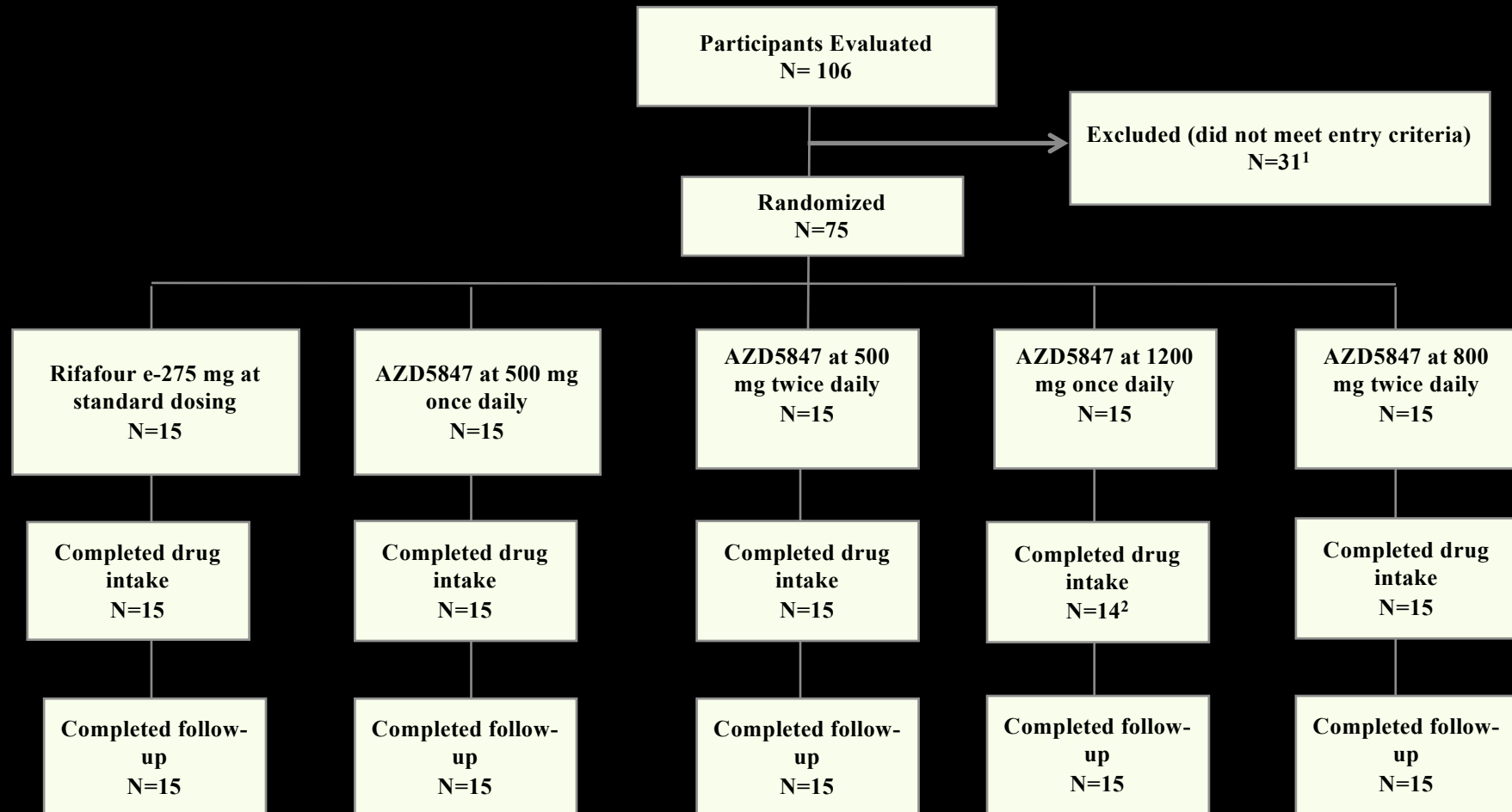
- **Develop a population pharmacokinetic model for AZD-5847 using data from the Phase 2 EBA study**

# Study Design

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- The study includes 60 subjects receiving AZD-5847
- Study included 4 different AZD arms, 15 subjects per arm
  - 500 mg QD
  - 500 mg BID
  - 800 mg BID
  - 1200 mg QD

# Study Design



# Sampling

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- **Participants underwent intensive PK sampling for 24 to 48 hours after dosing on days 1 and 14**
- **Trough concentrations also were measured within 30 minutes prior to dosing on days 3, 5, and 10**

# Modeling

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- **Modeling performed using Monolix 4.3 (SAEM)**
- **First, model data for day 1 only**
- **NCA results showed F might be dose dependent; initially F was fixed at 1**

# Modeling

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- Dose was modeled as a categorical covariate for F
- First, develop model for day 1, then predict concentrations on day 14 to assess any time dependent changes in  $Cl / F$  or F



# Results

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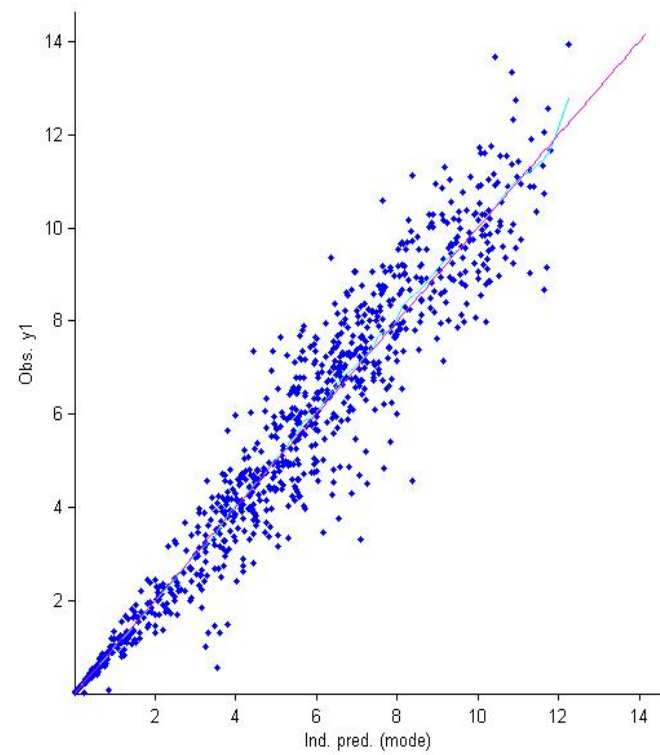
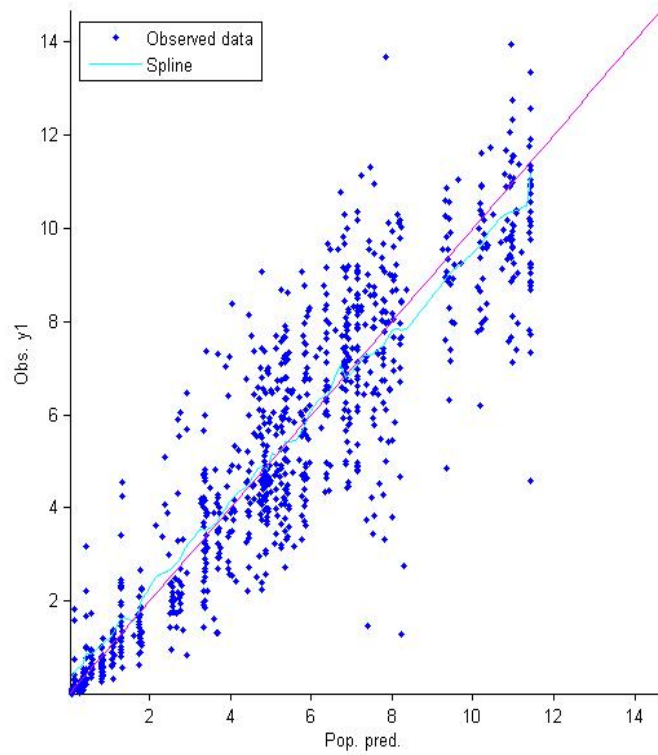
- **Total number of observations is 1723**
- **Average body weight was 53.6 kg and average age was 35 years**
- **The study included 10 females and 50 males receiving AZD-5847.**

# Results

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- Data were adequately described with a two compartment model and tlag for absorption
- Dose added as a covariate for F
- F is capped at 800 mg dose
- F at 1200 mg is 67 %

# Predicting day 14



# Modeling full data

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- Then, all data were modeled simultaneously :
- Two compartment and tlag with dose as covariate for F

## Modeling full data

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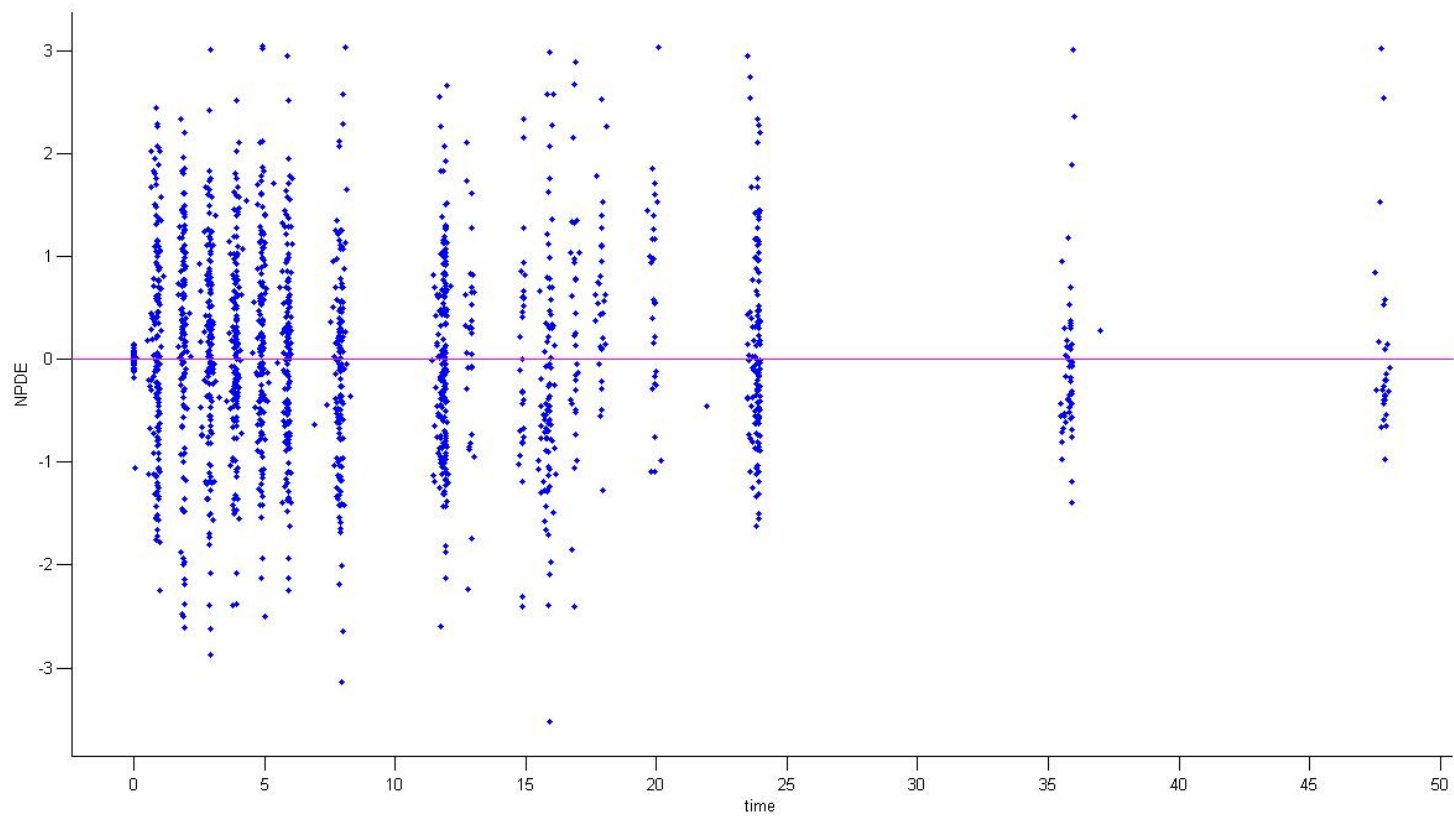
- Typical values ( relative standard error % ) were :
- Tlag 0.27 hours ( 18% )
- Ka 0.38 hour<sup>-1</sup> ( 9% )
  
- Cl 8.0 L/hour ( 3% )
- V1 43.3 L ( 7% )
- Q 8.9 L/hour ( 13% )
- V2 31.9 L ( 9% )

## Modeling full data

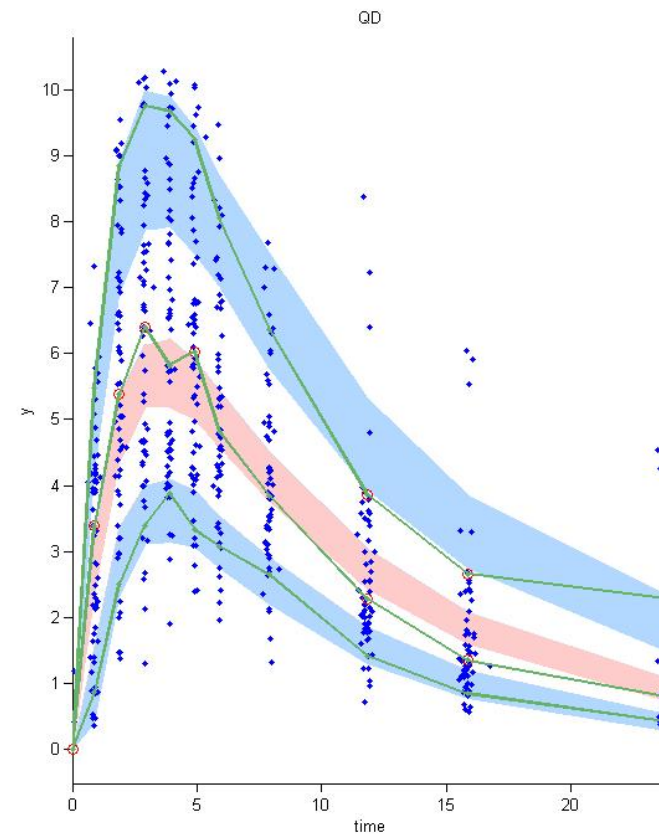
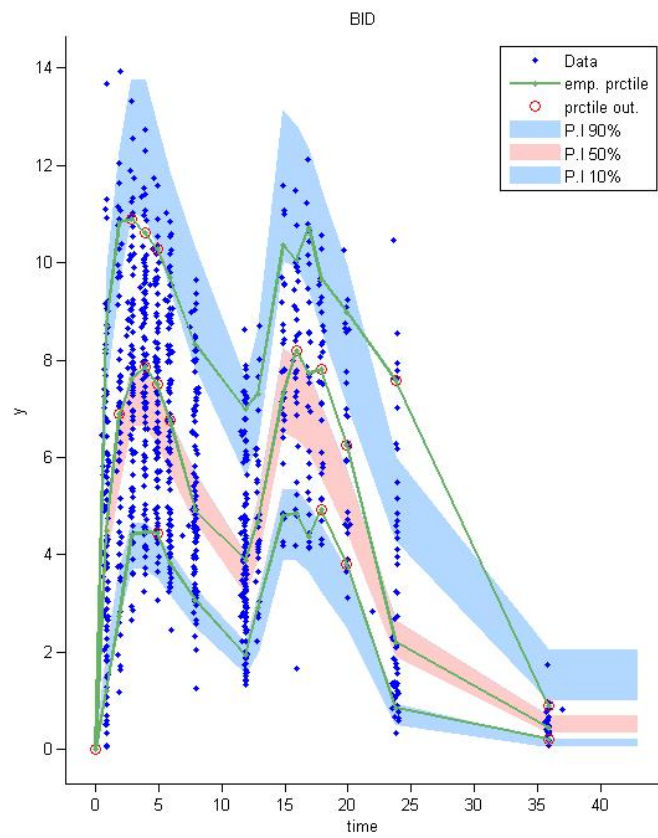
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- The coefficient of variation (r.s.e. %) were :
- Tlag 68.6 % ( 22% )
- Ka 21.6 % ( 19% )
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- CI 22.0% ( 10% )
- V1 14.9% ( 36% )
- Q 47.1% ( 28% )
- V2 55.6% ( 13% )

# Diagnostics

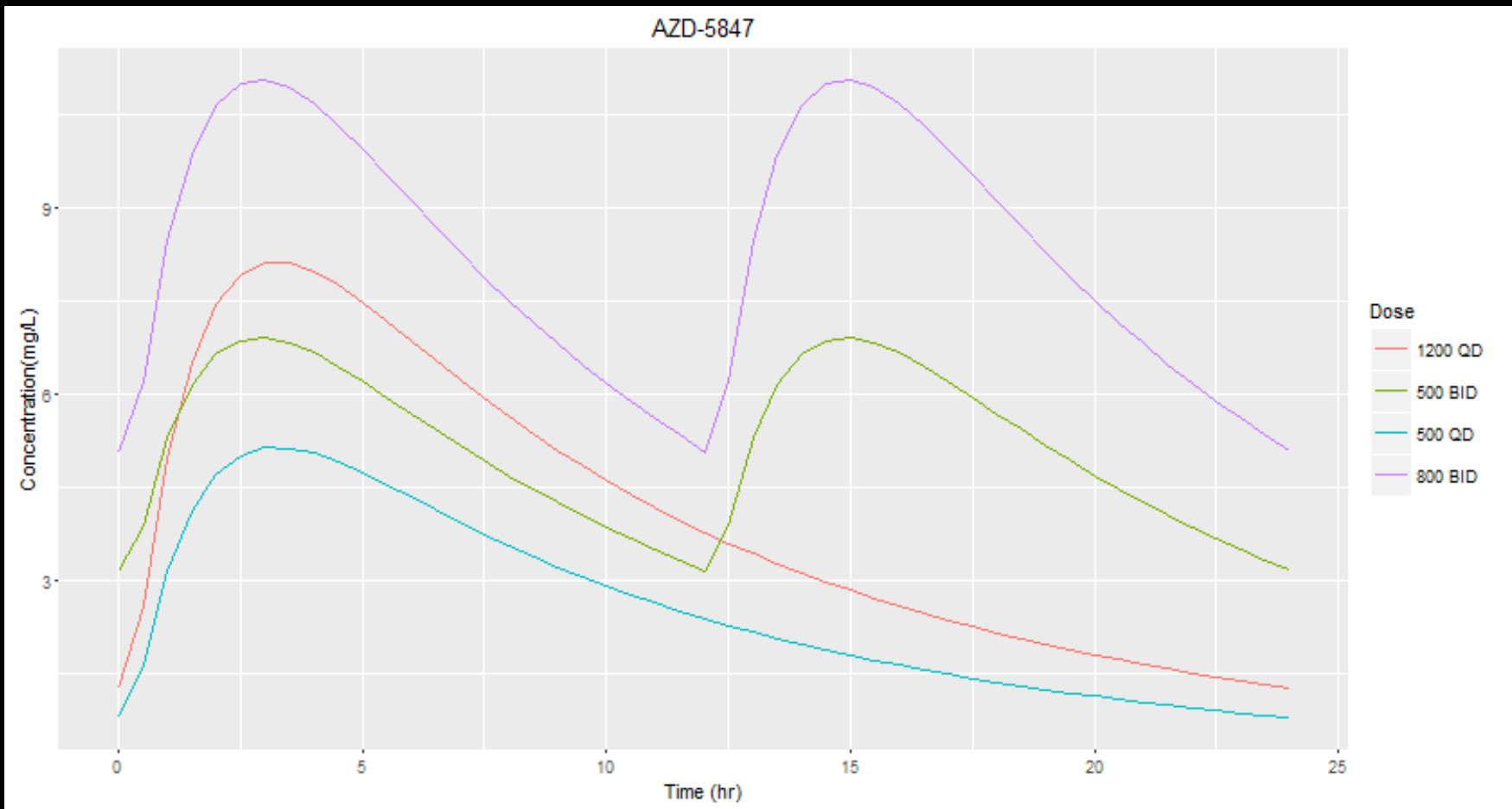


# Diagnostics





# Typical profile



# Predicted AUC

Dose	Observed AUC	Predicted AUC
500 mg QD	56	63
500 mg BID	65	63
800 mg BID	93	100
1200 mg QD	96	100

## Predicted AUC / MIC

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- Protein binding is 80% ; MIC in the EBA study ranged from 1-2 mcg / ml
- In the mouse model, a minimum  $fAUC / MIC > 20$  was required for bactericidal activity

# Predicted AUC / MIC

Dose	<u>fAUC/MIC</u> (MIC = 1)	<u>fAUC/MIC</u> (MIC = 2)
500 mg QD	12.5	6
500 mg BID	12.5	6
800 mg BID	20	10
1200 mg QD	20	10

# Summary

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- **AZD-5847 shows biphasic elimination, and saturable (non – linear ) absorption ; administering doses above 800 mg might not be beneficial**
- **In the mouse model, a minimum  $fAUC / MIC > 20$  was required for bactericidal activity**

# Summary

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- **This could help explain the poor bactericidal activity observed in the phase II study**
- **Given the saturable absorption of AZD-5847, it is difficult to achieve favorable PK / PD targets**