Pharmacokinetics/ Pharmacodynamics of Delamanid

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Understanding Delamanid PK/PD Relationship

To understand the relationship between drug exposure and efficacy of delamanid, using criteria set by European Medicines Agency*.

1. Determine the range of MICs
2. Identify PK-PD indices from non-clinical studies, and PD target (PDT)
3. Determine the probability of target attainment (PTA), using clinical PK data and PDT
4. Evaluate clinical exposure-response relationships

*European Medicines Agency. Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products. EMA/CHMP/594085/2015. 21 July 2016

Delamanid, a nitroimidazooxazole anti-TB drug

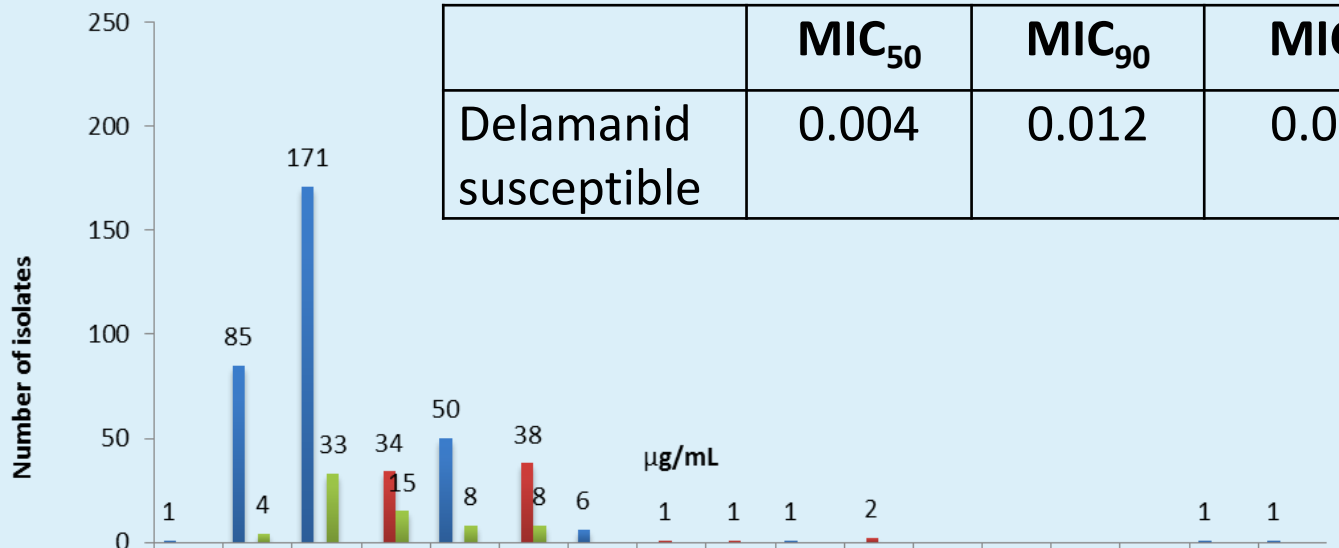
Delamanid is a nitroimidazooxazole which has activity against MTB bacilli in log-phase growth, Wayne and intra-cellular macrophage models

Indication: treatment of adult pulmonary multi-drug resistant (MDR)-TB when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (EMA & others)

Posology: 100 mg BID administered with food

MICs from 460 clinical isolates (DS, MDR, XDR)

	MIC_{50}	MIC_{90}	MIC_{95}	MIC_{99}
Delamanid susceptible	0.004	0.012	0.012	0.016



	0.001	0.002	0.004	≤0.006*	0.008	0.012	0.016	0.024	0.025	0.031	0.05	0.063	0.125	0.25	0.5	1	>8
204 Isolates	1	85	171		50		6			1						1	1
EBA Study Isolates				34		38		1	1		2						
Other Clinical Isolates		4	33	15	8	8											
Grand Total	1	89	204	49	58	46	6	1	1	1	2					1	1

*MICs of 0.006 and ≤ 0.006 µg/mL were combined

Stinson K, Kurepina N, Venter A, Fujiwara M, Kawasaki M, Timm J, et al. MIC of delamanid (OPC-67683) against mycobacterium tuberculosis clinical isolates and a proposed critical concentration. Antimicrob Agents Chemother. 2016;60(6):3316-22

Nonclinical PK-PD analysis: mouse model

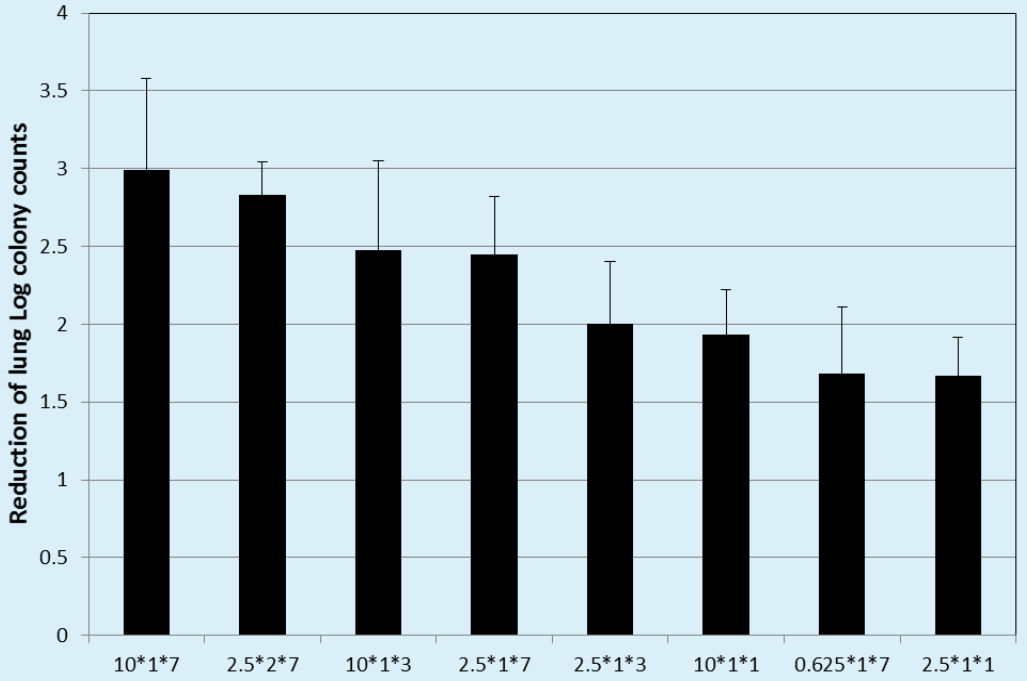
PK: The single dose PK data obtained from the uninfected mice were used to simulate PK parameters after various dosing regimens tested in the mouse efficacy study by the nonparametric superposition method using Phoenix WinNonlin.

PD: mouse lung CFU counts reduction by various dose regimens in a mouse (ICR mice) chronic TB (*M. tuberculosis* Kurono) model

Dose regimens

Delamanid (mg/kg)	Twice Daily	Once Daily	3 Days/Week	1 Day/Week
0.625		X		
2.5	X	X	X	X
10		X	X	X

Efficacy



PK/PD Analysis of Nonclinical Data

PKIndex and lung log reduction analyzed using nonlinear regression (WINNONLIN) and the maximum efficacy Θ_1 (E_{max}) calculated.

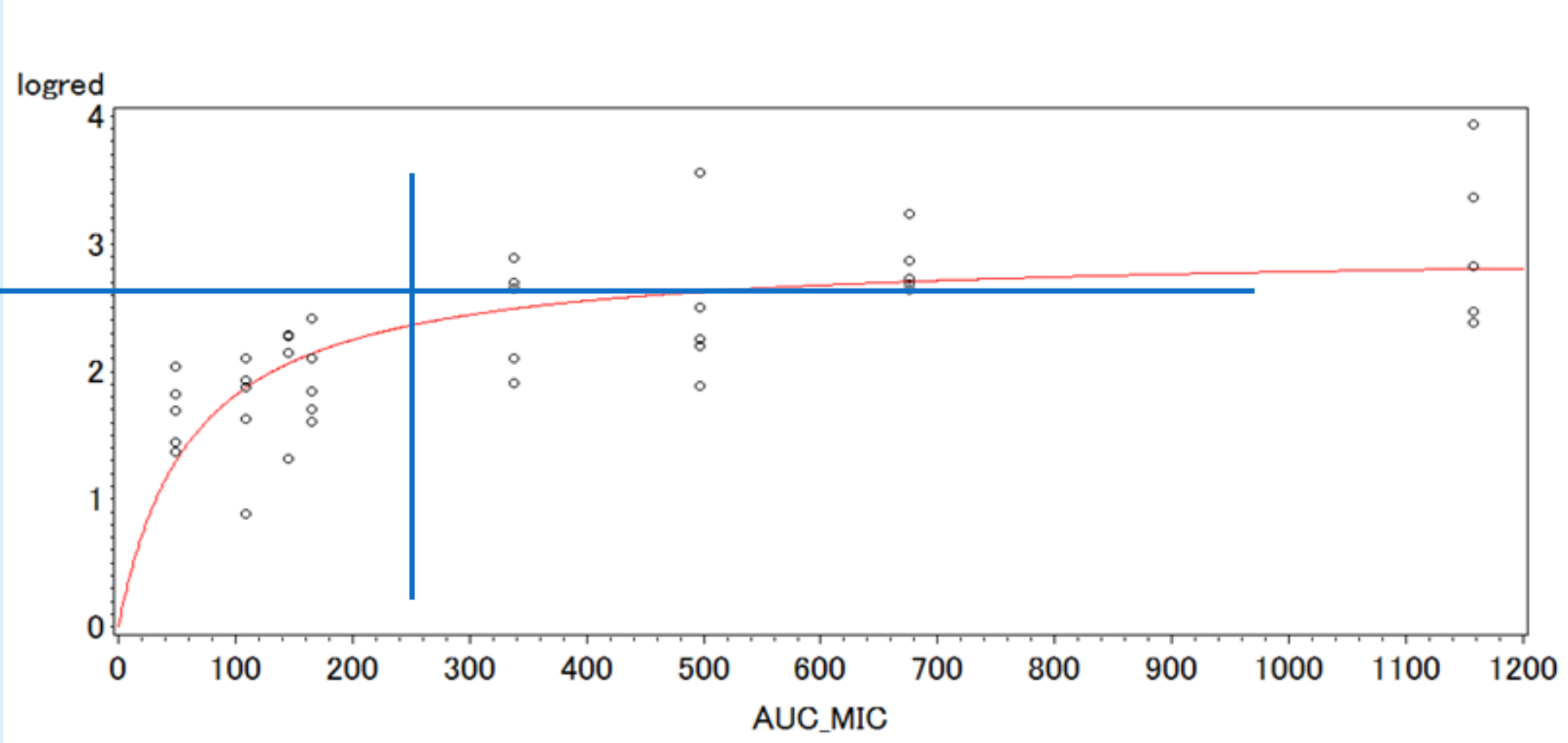
$$\text{Log}_{10}\text{CFU reduction} = \frac{\Theta 1 \text{ X PKIndex}}{\Theta 2 + \text{PKIndex}}$$

PKindex: AUC/MIC or C_{max}/MIC or %T>MIC
Θ1: maximum lung Log_{10}CFU reduction
Θ2: 50% PKIndex for maximum lung Log_{10}CFU reduction

	AUC_{24h}/MIC	**%T > MIC[#]**	**C_{max}/MIC**
Correlation coefficient	0.97	0.53	0.59
p value	<0.0001	<0.01	0.1246

P was calculated using Pearson or Spearman correlation coefficient (SAS, v9.1 and v9.3)
[#]%T>MIC was calculated by the nonparametric superposition method (Phoenix WinNonlin Ver 6.3, Pharsight Corp)

PK/PD Analysis of Nonclinical Data



X-axis = $AUC_{0\text{-}24}$/MIC; Y-axis = Log_{10}CFU reduction

- AUC/MIC is the parameter best correlated with CFU decline
- The EC_{80} was determined to be an AUC/MIC of 252 (Nonclinical PDT)

Exposure-Response Modeling of EBA Data

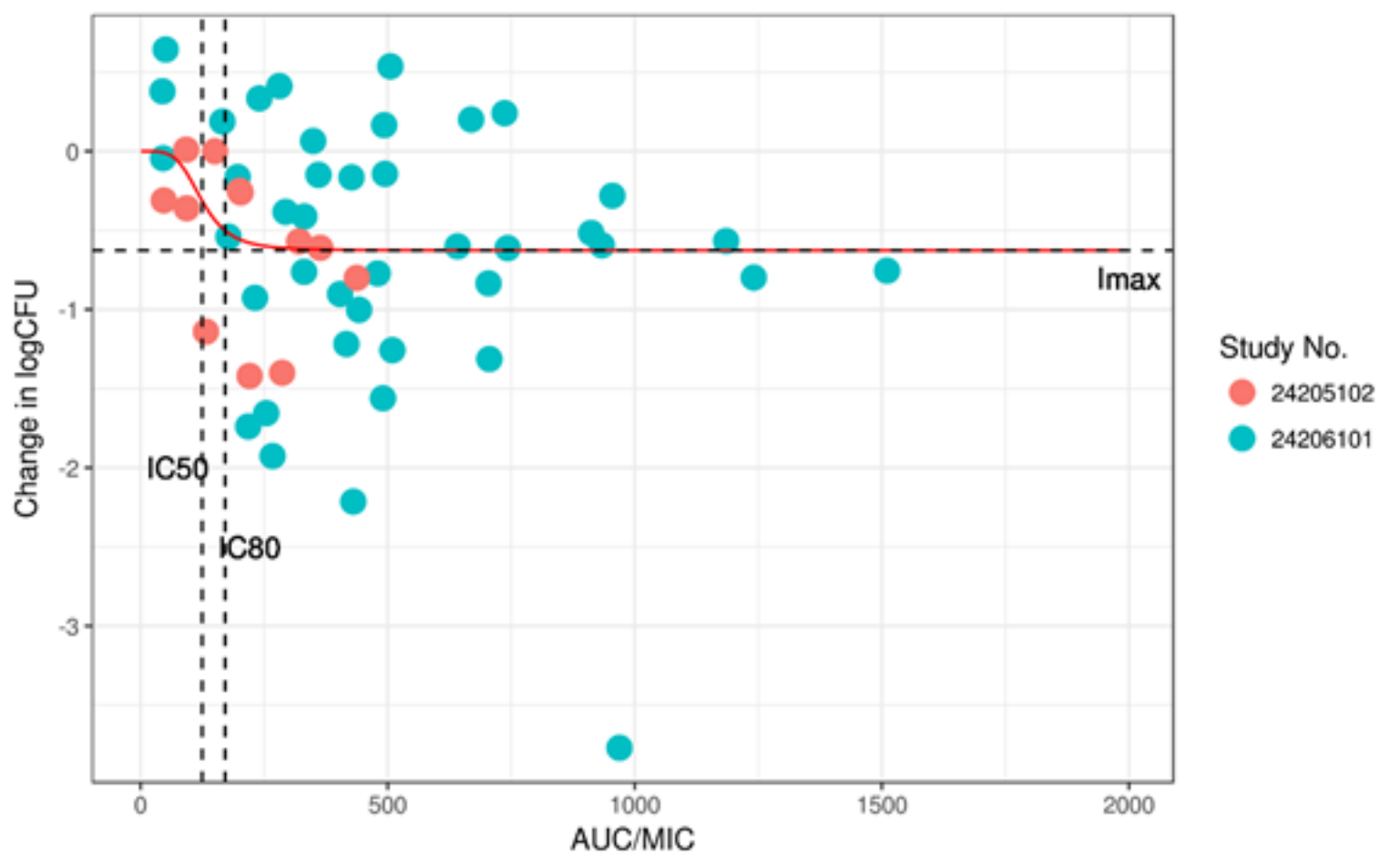
- An inhibitory sigmoidal E_{max} model and nonlinear mixed effect analysis using NONMEM was used to model EBA data from a 7-day and a 14-day EBA trials.
- The structural model used was as follows

$$\text{Reduction in } \log_{10}\text{CFU} = \text{Base} - \frac{I_{max} \times CAUC^{Hill}}{ICAUC_{50}^{Hill} + CAUC^{Hill}}$$

Base = baseline $\log_{10}$CFU
I_{max} = maximum inhibition, CAUC = cumulative AUC
$ICAUC_{50}$ = cumulative AUC required for 50% reduction of the maximum Log_{10}CFU
Hill = Hill coefficient which determines the shape of the response curve

- The AUC/MIC parameter was also tested using the same model, where AUC/MIC replaced CAUC, using the individual daily AUC divided by individual MIC at baseline determined for each individual in the trials.

Exposure-Response Modeling of EBA Data



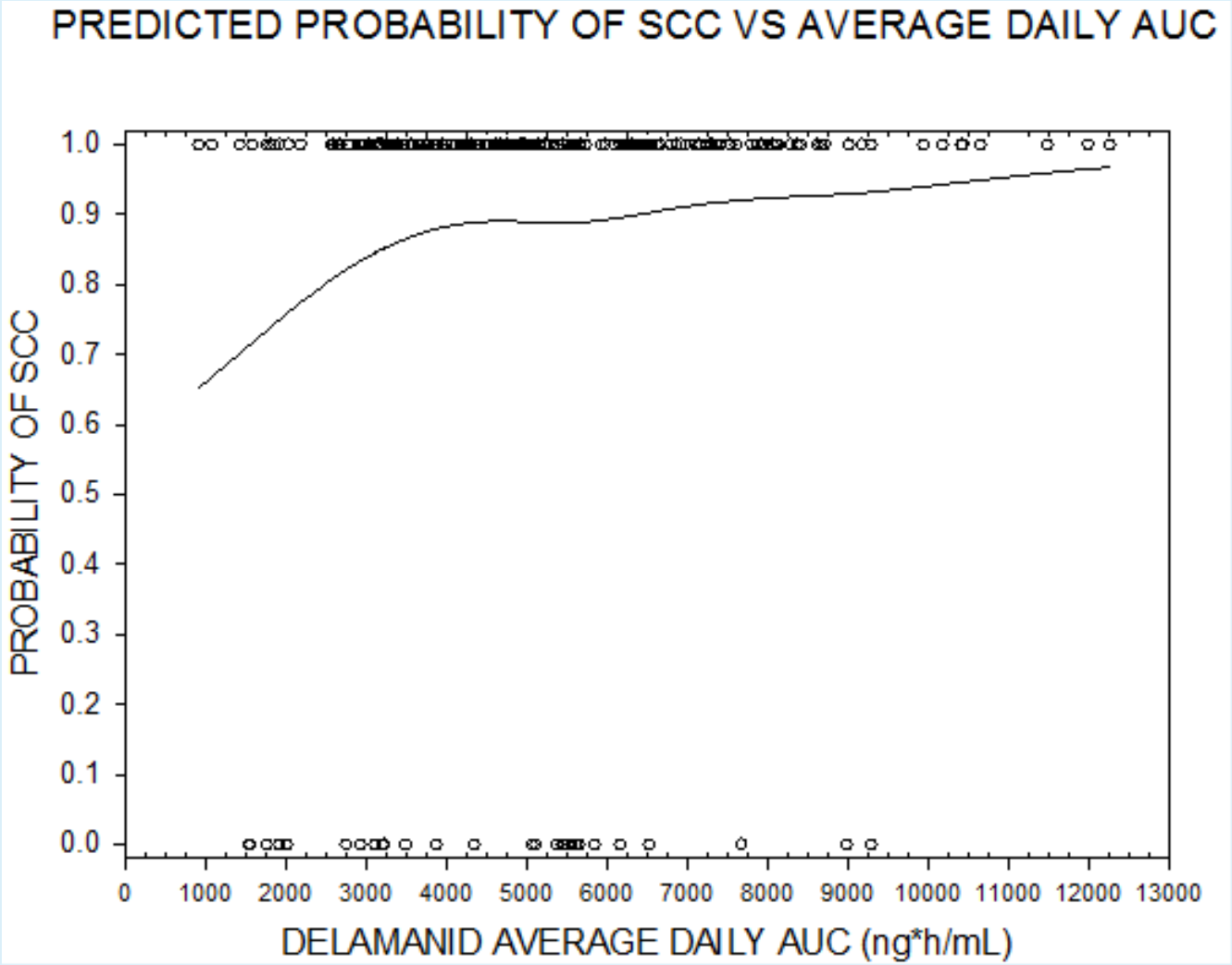
- AUC/MIC is the parameter best correlated with CFU decline
- The IC_{80} (AUC/MIC) was determined to be 171 (Clinical PDT)

Probability of Target Attainment (PTA) in Trials 242-07-204 and 242-09-213 Based on Delamanid Pharmacodynamic Target (PDT)

- Delamanid dosed for 8 weeks at 100 mg BID in both trials – probability of target attainment determined
- Using a population PK approach, the cumulative AUC over 8 weeks was estimated and used to determine the average daily $AUC_{0\text{-}24h}$ over 8 weeks during the 100 mg BID dosing period
- MIC_{95} was determined to be 0.012 µg/mL from 460 isolates including 316 MDR-TB isolates from trial 242-07-204; $AUC_{0\text{-}24}$/MIC was calculated.
- PTA for Nonclinical PDT: 94% of subjects in trial 242-07-204 and 93% in trial 242-09-213 were at or above nonclinical PDT
- PTA for Clinical PDT: 100% of subjects in trial 242-07-204 and 98.5% of subjects in the 242-09-213 trial were at or above the clinical PDT

Delamanid Exposure and Outcome in Trial 242-09-213

- In the phase 3 trial of delamanid (242-09-213), MDR-TB subjects were administered either placebo + OBR or delamanid 100 mg BID + OBR for 8 weeks followed by 200 mg once daily (QD) + OBR for 18 weeks.
- The daily average delamanid $AUC_{0\text{-}24}$ over 26 weeks estimated using a population pharmacokinetic approach and correlated with the time to SCC for 225 subjects.
- A generalized additive model for SCC by 6 months as dependent variable, and the daily average $AUC_{0\text{-}24}$ as independent variable with a logit link function was used to obtain the predicted probability of 6 month conversion for each subject, using SAS.
- The additive model includes a linear term for $AUC_{0\text{-}24}$ plus a nonparametric smoothing spline function for $AUC_{0\text{-}24}$.
- The predicted probability was then plotted against the $AUC_{0\text{-}24}$ values.



- To understand the change in probability of SCC with AUC, the average steady state AUC following 100 mg BID and 200 mg BID were compared
- The average steady state AUC following a 100 mg BID dose was 7925 ng*h/mL with a probability of SCC of 92%
- The average steady state AUC following 200 mg BID dose was 11837 ng*h/mL with a probability of SCC of 96%
- The QTcF interval prolongation is about 12.7 msec following 100 mg BID and 18.7 msec following 200 mg BID

Summary

- For delamanid, the nonclinical PDT (AUC/MIC) was 252 and the clinical (EBA) PDT was 171
- Following a regimen of 100 mg BID, the probability of target attainment (PTA) was > 98% for the clinical PDT
- Delamanid 100 mg BID is expected to achieve near maximum efficacy
- PK/PD modeling indicated that the QTcF interval prolongation will increase by about 50% from 12.7 msec following 100 mg BID to 18.7 msec following 200 mg BID
- Therefore, increasing the dose of delamanid beyond 100 mg BID is likely to increase cardiac risk with no corresponding significant increase in efficacy