PKPD Target Attainment Analysis of Cycloserine in TB Patients

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Background

- In August 2018, WHO reclassified MDR-TB agents
  - CS in group B
  - CS should be added to the MDR-TB regimen (unless it cannot be used)

- Limited PK-PD data on CS in TB patients

- Aim
  - Estimate population PK parameters and perform MCS and target attainment analyses to optimize dosing

Methods – data sources

- Expanded our previous model

Source	Number of patients	Number of samples
Healthy volunteers	12	212
CLIP-TB study (Georgia)	69	337
UVA study (Bangladesh)	42	275
NJC (USA)	54	102
CPTR study, AGH (USA)	27	84
CPTR study, TCID (USA)	28	41
CPTR study, TYLER (USA)	15	18
Total	**247**	**1069**

Methods – PopPK & MCS TA

- Monolix (2018R1) used to build the population PK model
- Final PK estimates used in mlxR package (v3.3.0) in R software
  - simulated 1000 TB patients at steady state for each regimen

- PKPD targets of $T_{>MIC}$ (from Deshpande et al. via Dr. Tawanda Gumbo)
  - ≥30% represents bactericidal activity
  - ≥64% represents EC_{80}.

- Studied MIC ranged from 4 to 64 mg/L
- Selected probability of target attainment (PTA) of at least 90% for the highest MIC (i.e. PKPD breakpoint)

Results – demographic data

Characteristic	N= 247 Mean (SD) or % (n)
Age, years	41.6 (15.1)
Sex, male	74.9% (185)
Weight, kg	60.5 (13.2)
BMI, kg/m^2	21.2 (4.03)
Diagnosis	
Healthy subjects	4.85% (12)
NTM	5.67% (14)
DS-TB	6.48% (16)
RR/MDR-TB	**64.8% (160)**
PreXDR-TB	**14.6% (36)**
XDR-TB	**3.64% (9)**
SrCr, mg/dL	0.93 (0.35)
CrCL, mL/min	93.3 (33.6)

Results – raw data

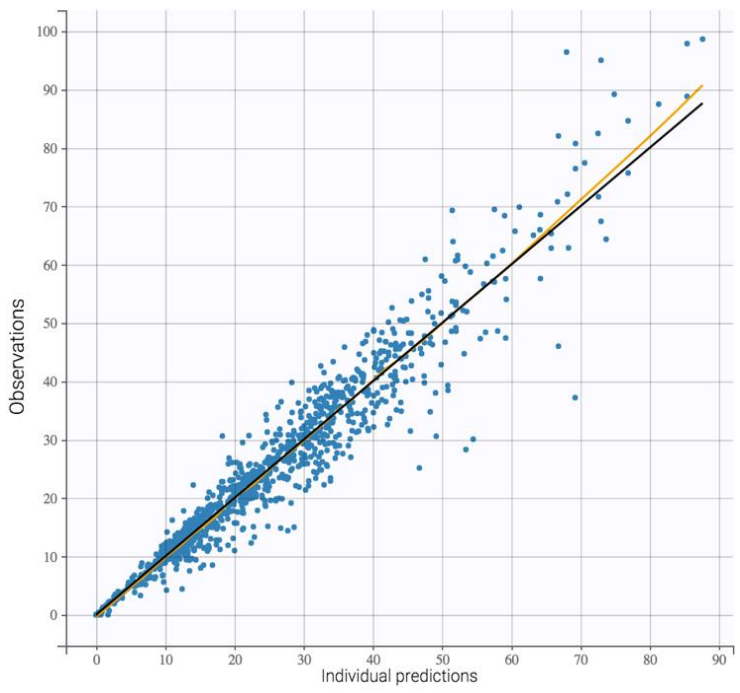
- Typical C_{max} for CS is between 20 to 35 mg/L (250-500 mg dose)
- 6 patients had C_{max} >80 mg/L
  - Due to their low body weight (mean, 55.2 kg) and relatively high doses [500 mg (n=2), 750 mg (n=3), and 1000 mg (n=1)]

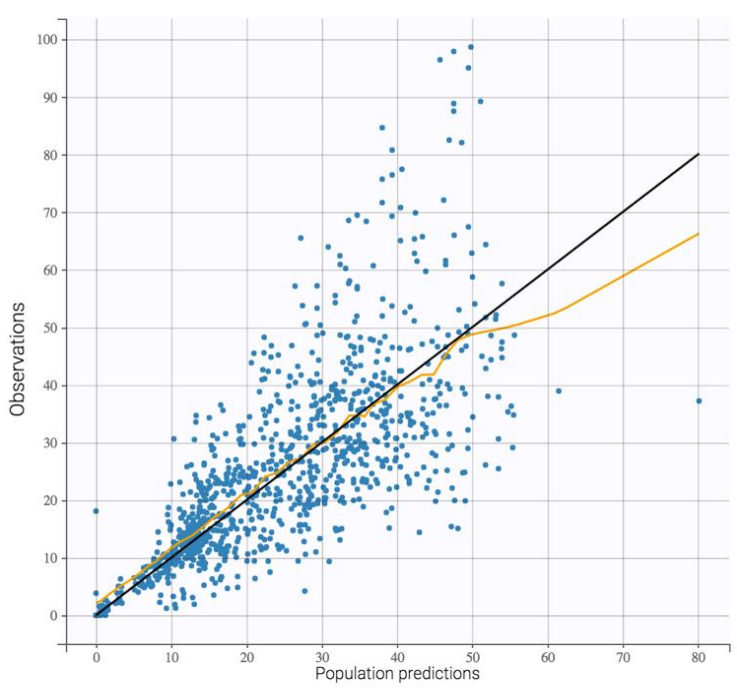
Time (h)	Number of samples	CS concentration (mg/L) median (range)
0 to 1	160	17.0 (0.0 - 98.6)
>1 to 3	362	26.5 (7.5 - 97.9)
>3 to 6	208	28.9 (8.0 - 96.4)
>6 to 12	210	18.0 (4.2 - 65.5)
>12 to 24	108	15.6 (1.9 - 48.3)
>24	21	0.83 (0.0 - 2.6)

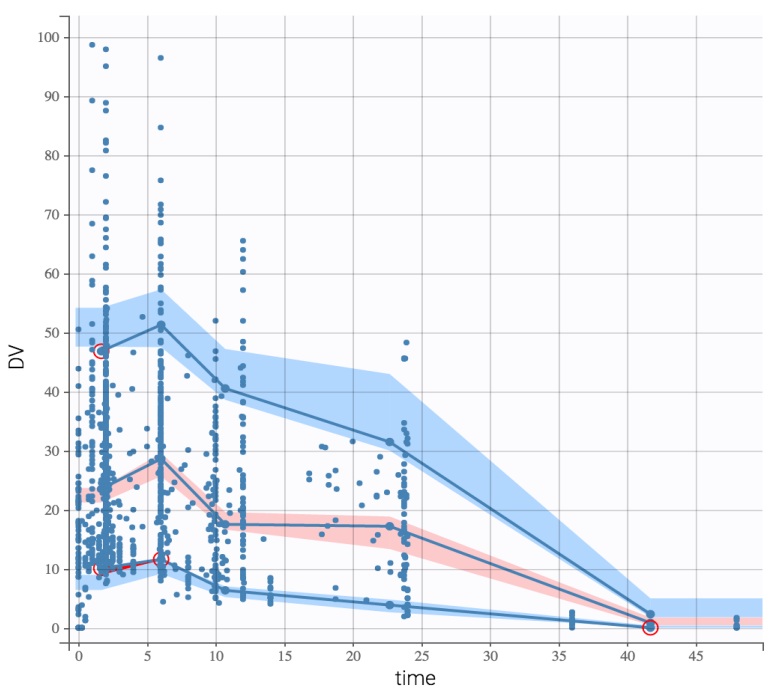
Results – PopPK model

	Base model		Final model		
Parameter	**Estimate**	**RSE (%)**	**Estimate**	**RSE (%)**	**P-value**
Tlag (h)	0.333	10.6	0.326	1.47	
ka (h^{-1})	7.25	34.4	6.61	17.1	
V/F (L)	28.5	4.05	24.9	2.92	
beta, **$WT_{on\ V}$**	-	-	1 (fixed)	-	
CL/F (L/h)	2.00	3.58	2.00	11.9	
beta, **$Cat.\ (pts)_{on\ CL}$**	-	-	-0.66	18.7	8.6×10^{-8}
beta, **$CrCL_{on\ CL}$**	-	-	0.413	18.1	3.1×10^{-8}
ω, Tlag	0.368	61.5	0.409	22.5	
ω, ka	1.08	19.2	1.52	13.6	
ω, V/F	0.242	16.7	0.174	36.6	
ω, Cl/F	0.492	5.59	0.353	9.29	
γ, Cl/F	-	-	0.19	21.1	
Proportional	0.20	3.04	0.19	3.37	
-2LL	4926		4866		

Results – PopPK model

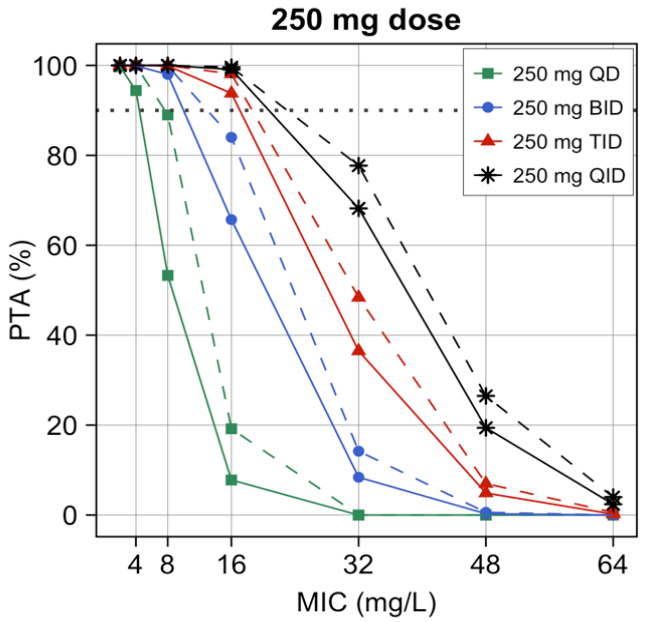


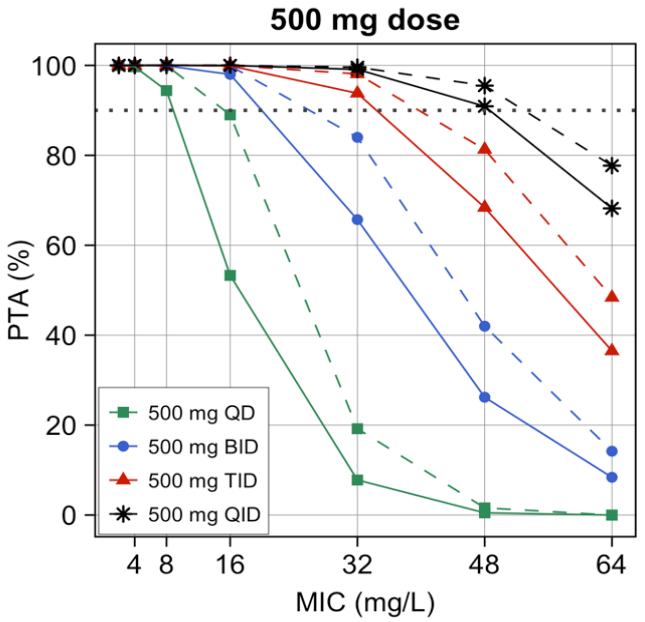


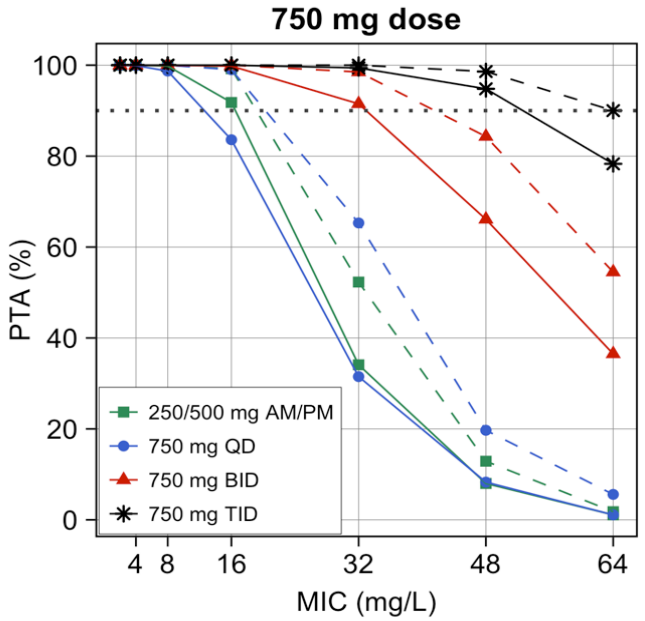


Results – TA

- Increasing the dose → increases PTA
  - QD: 250 mg vs. 500 mg vs. 750 mg
- Dividing the dose → <u>modestly</u> increases PTA
  - Due to long $t_{1/2}$ (~17 h)
  - Exception: dividing 750 mg dose to 250/500 mg BID had an MIC PKPD breakpoint of 16 mg/L, compared to 8 mg/L in the 750 mg QD regimen
    - PTA of 92 vs 84%







PKPD target: T>MIC of ≥30%

PKPD target: T>MIC of ≥64%

PKPD breakpoint of 90%

Results – TA

≥ 90%

Dosage regimen	PTA (%) at each MIC (mg/L)											
	$T_{>MIC}$ ≥30%						$T_{>MIC}$ ≥64%					
	4	8	16	32	48	64	4	8	16	32	48	64
250 mg dose												
250 mg QD	100	89.0	19.2	0.0	0.0	0.0	94.4	53.3	7.8	0.0	0.0	0.0
250 mg BID	100	99.9	84.0	14.2	0.6	0.0	99.9	98.0	65.7	8.4	0.3	0.0
250 mg TID	100	100	98.1	48.4	7.0	0.6	100	99.9	93.8	36.5	4.9	0.2
250 mg QID	100	100	99.6	77.7	26.5	4.0	100	100	99.1	68.2	19.4	2.4
500 mg dose												
500 mg QD	100	100	89.0	19.2	1.6	0.0	99.7	94.4	53.3	7.8	0.5	0.0
500 mg BID	100	100	99.9	84.0	42.0	14.2	100	99.9	98.0	65.7	26.2	8.4
500 mg TID	100	100	100	98.1	81.3	48.4	100	100	99.9	93.8	68.4	36.5
500 mg QID	100	100	100	99.6	95.5	77.7	100	100	100	99.1	90.9	68.2
750 mg dose												
250/500 mg AM/PM	100	100	99.2	52.3	12.9	1.8	100	99.8	91.8	34.1	8.0	1.1
750 mg QD	100	100	99.0	65.3	19.7	5.6	99.9	98.7	83.6	31.5	8.3	1.1
750 mg BID	100	100	100	98.5	84.3	54.5	100	100	99.8	91.5	66.1	36.5
750 mg TID	100	100	100	100	98.6	90.0	100	100	100	99.4	94.8	78.3

Results – safety standpoint

- Dividing the dose reduces C_{max} AND increases PTA
  - 500 mg QD vs 250 mg BID
  - 750 mg QD vs 250/500 mg BID
  - 750 mg QD vs 250 mg TID
- High CS concentrations can result in CNS AEs
- What is the concentration range associated with CNS AEs? No data!

Concentration >45 mg/L

Dosage regimen	C_{max}, mg/L mean (SD)	AUC_{0-24}, mg*h/L mean (SD)
250 mg dose		
250 mg QD	16.4 (4.3)	259.5 (97.9)
250 mg BID	26.4 (8.0)	516.7 (188.3)
250 mg TID	35.5 (10.4)	737.7 (239.1)
250 mg QID	44.4 (12.5)	945.1 (279.8)
500 mg dose		
500 mg QD	32.7 (8.6)	519.0 (195.7)
500 mg BID	52.9 (16.0)	1033.4 (376.7)
500 mg TID	71.0 (20.7)	1475.4 (478.3)
500 mg QID	88.8 (24.9)	1890.1 (559.6)
750 mg dose		
250/500 mg AM/PM	42.2 (11.7)	763.8 (271.0)
750 mg QD	49.6 (13.2)	789.5 (304.6)
750 mg BID	78.4 (22.9)	1527.5 (537.3)
750 mg TID	106.5 (30.6)	2215.0 (702.6)

Conclusion

- Established robust PK model for CS
- Dividing the dose resulted in slight increases in PTA, but it decreased C_{max} significantly, which can potentially reduce CNS AEs

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