Population PK Model development for bedaquiline and M2

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Bedaquiline (BDQ) is a novel anti-mycobacterial agent approved in US, EU and other countries as part of combination therapy in adult (≥18 years) and pediatric patients (5 years to <18 years, ≥15 kg) with pulmonary multi-drug resistant Mycobacterium tuberculosis (MDR-TB). A popPK model for BDQ was previously developed based on data from 9 clinical studies in healthy volunteers (HVs) and 2 Phase 2 b MDR-TB patients [1]. Also, a parent-metabolite (BDQ-M2) model had been developed on the same MDR-TB Phase 2 studies data but without HVs and single dose (SD) data[2].

Objectives

1. Perform an exploratory graphical analysis of BDQ and M2 in HVs and patients with tuberculosis (TB).
2. Expand the previously developed model for BDQ by incorporating metabolite compartment(s) (CMT) to describe the observed BDQ and M2 PK data.
    - Quantify popPK parameters, including typical parameter values, inter-individual variability, and residual variability.
    - Identify and quantify covariate effects which contribute to the variability in the PK of BDQ and M2.
3. Validation of the BDQ-M2 model on data from a Phase 3 study

Methods

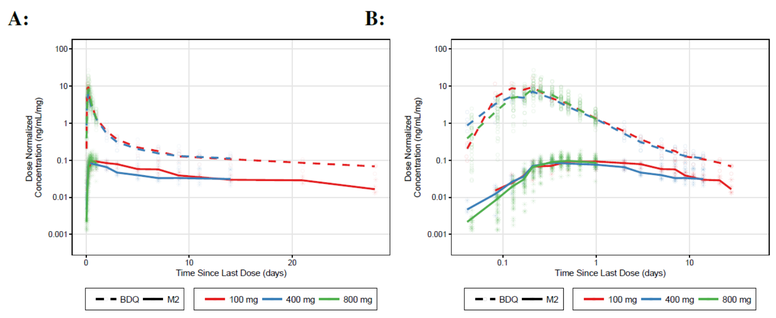
The original dataset used to develop the popPK model for BDQ was expanded by including M2 data from the same studies: PK data from HVs recruited in 6 phase 1 studies and patients recruited in 3 phase 2 studies. The model building dataset consisted of 5222 BDQ concentrations and 4717 M2 concentrations from 479 adult participants (111 HVs and 368 patients with TB) with weight range of 30 kg – 113 kg. The data set for the external validation included 3087 BDQ concentrations and 3068 M2 concentrations from 282 MDR/Rifampicin-resistant-TB patients 16 years and older with weight range of 28-123.4 kg from the STREAM Stage 2 phase 3 trial [3].

An exploratory graphical analysis was conducted prior to the BDQ-M2 model development using the previously developed popPK model for BDQ as a starting point. The BDQ structure was reassessed, and the parameters were re-estimated after the inclusion of the M2 data. Covariates (i.e. race, population, study, and BDQ formulation) included in the prior model were retained, with additional covariates evaluated.

The external validation of the BDQ-M2 model was performed with the parameters fixed to the final estimates obtained for MDR-TB patients, using GOFs, VPCs, and individual profiles.

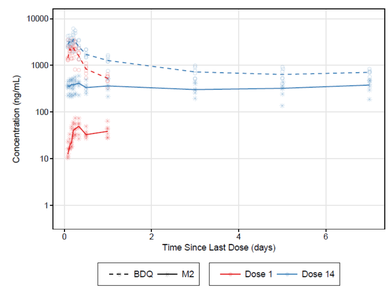
Results and discussion

Figure 1. Dose Normalized Concentration-time Profiles by Dose – Single Dose (HVs)



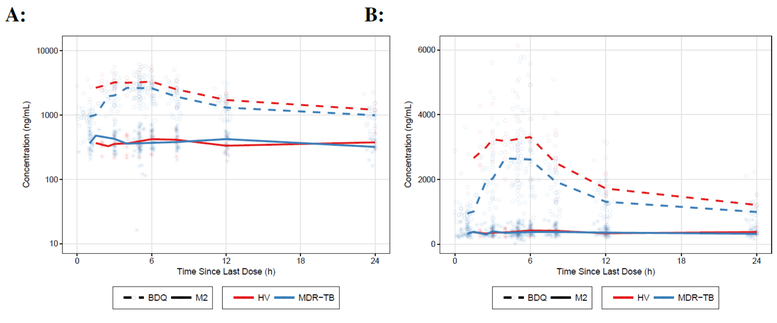
Solid and dashed lines show the median of M2 and bedaquiline with symbols representing the observed data. (A) Y-axis on log scale. (B) log-log scale. Data below the LLOQ were excluded. Note: only data from single dose studies were included (i.e., studies TMC207-TiDP13-C110, TMC207-TiDP13-C111 and TMC207-TBC1003). BDQ = bedaquiline.

Figure 2. Concentration-time Profiles – Multiple-dose (HVs – 400 mg QD)



Solid and dashed lines show the median of M2 and bedaquiline with symbols representing the observed data. Data below the LLOQ were excluded. Note: only data following dose 1 and dose 14 from study R207910-CDE-102 were included for visualization. BDQ = bedaquiline. Log Y-axis is used.

Figure 3. Concentration-time Profiles by Population – Multiple-dose (400 mg QD)



Solid and dashed lines show the median of M2 and bedaquiline with symbols representing the observed data. (A) Y-axis on log scale, (B) Y-axis on linear scale. Data below the LLOQ were excluded. Note: PK data following bedaquiline 400 mg on Day 14 from studies R207910-CDE-102 and TMC207-TiDP13-C208 were included and truncated at 24 h for visualization. BDQ = bedaquiline, HV = healthy volunteer, MDR-TB = patients with multi-drug resistant *Mycobacterium tuberculosis*.

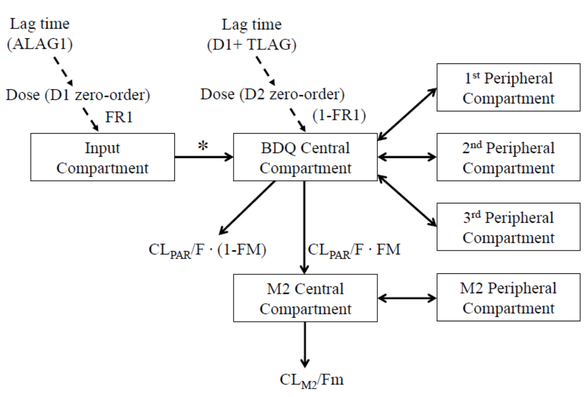
The **graphical analysis** (Fig. 1, 2 and 3) showed that BDQ exposure increased proportionally with dose and was higher in HVs than patients with MDR-TB. M2 exposure was comparable between the two populations but lower than BDQ (M2 peak following SD was about 100-fold lower). M2 had flatter profiles with almost no peak to trough fluctuations compared to BDQ. After 14 days of 400 mg QD, BDQ and M2 accumulation were 2-fold and 14-fold, respectively.

The previously developed **structural model** for BDQ was retained with consistent re-estimated parameter values. Fig. 4 and Table 1 present the model details. A two-CMT model with linear input to the BDQ central CMT and linear elimination adequately described M2 data. To avoid identifiability issues, the central volume of distribution of M2 was fixed to BDQ and the fraction metabolized (FM) parameter was estimated with a covariate effect to describe the differences in parent:metabolite ratios observed between HVs and patients, allowing BDQ to be eliminated as is and via metabolism to M2.

Typical apparent parameters for CLMET/Fm, clearance between the central and peripheral CMT for the metabolite (CLp1,MET/Fm), central and peripheral volumes of distribution for M2 (Vc,MET/Fm and Vp1,MET/Fm) were 4.95 L/h, 164L, and 862L. The long half-lives of BDQ and M2 arise from their low clearance (2.62 and 4.95 L/h, respectively) and their large peripheral volume of distribution (7670 and 862 L for the largest CMTs, respectively).

The VPCs showed that the popPK BDQ-M2 model provided an adequate description of the phase 3 data, despite a minor under-prediction of M2 at the population level (Fig. 5).

Figure 4. Schematic of the Final BDQ-M2 popPK Model



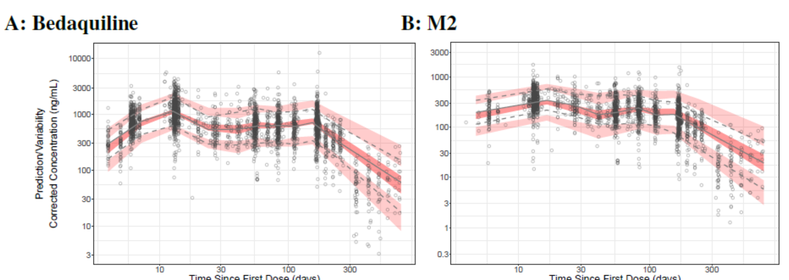
CL_{PAR}/F = apparent clearance for the parent, CL_{MET}/Fm = apparent clearance for the metabolite, F = bioavailability, FM = fraction metabolized, Fm = bioavailability corrected with fraction metabolized (i.e., Fm = F · FM), D1 = duration of zero-order input into the first compartment, D2 = duration of zero-order input into the second compartment, ALAG1 = absorption lag time for the first pathway, TLAG = absorption lag time for the second pathway, FR1 = fraction of the dose absorbed via the first pathway, BDQ = bedaquiline. * Rate parameter was fixed to 1000. Note: $V_{c,MET}/Fm$ was fixed to $V_{c,PAR}/F$ to avoid parameter identifiability problem.

Table 1. Parameter Estimates for the Final BDQ-M2 popPK Model

Parameter Name (Unit)	Parameter Description	Prior BDQ PK Model Estimate Value (%RSE†)	Final BDQ-M2 PK Model Estimate Value (%RSE‡‡)	95% CI‡‡
Bedaquiline				
CL_{PAR}/F (L/h)	Apparent clearance	2.78 (5.1)	2.62 (4.4)	2.40 – 2.85
$Effect_{Black,CL_{PAR}/F}$ (%)[a]	– Effect of black race on CL_{PAR}/F	52.0 (21.2)	71.1 (13.4)	51.9 – 89.2
$Effect_{HV,202,CL-PAR/F}$ (%)[b]	– Effect of HVs or study C202 on CL_{PAR}/F	37.5 (35.2)	45.0 (28.6)	23.9 – 72.6
$V_{c,PAR}/F$ (L)	Apparent central volume of distribution	164 (5.0)	117 (8.0)	98 – 134
$Effect_{Sex,Vc_{PAR}/F}$ (%)[c]	– Effect of sex on $V_{c,PAR}/F$	-15.7 (42.5)	-25.8 (35.9)	-42.7 – -6.2
CL_{p1}/F (L/h)	Apparent clearance between the central and first peripheral compartment	11.8 (7.6)	23.3 (6.8)	20.1 – 26.6
V_{p1}/F (L)	Apparent volume of distribution for the first peripheral compartment	178 (8.1)	124 (5.0)	113 – 137
CL_{p2}/F (L/h)	Apparent clearance between the central and second peripheral compartment	8.03 (4.9)	8.61 (3.8)	8.01 – 9.25
V_{p2}/F (L)	Apparent volume of distribution for the second peripheral compartment	3010 (9.0)	2770 (5.6)	2466 – 3062
CL_{p3}/F (L/h)	Apparent clearance between the central and third peripheral compartment	3.58 (9.0)	3.35 (4.3)	3.11 – 3.68
V_{p3}/F (L)	Apparent volume of distribution for the third peripheral compartment	7350 (5.8)	7670 (3.0)	7255 – 8166
FR1*	Fraction of the dose absorbed via the first pathway	1.41 (11.1)	1.06 (11.9)	0.85 – 1.34
D1 (h)	Duration of zero-order input for first absorption pathway	2.22 (1.0)	2.53 (4.0)	2.33 – 2.71
$ALAG1_{solution}$ (h)	Absorption lag time (solution)	0.541 (5.7)	0.48 (10.6)	0.38 – 0.59
$ALAG1_{tablet}$ (h)	Absorption lag time (tablet)	0.917 (0.6)	0.921 (0.5)	0.911 – 0.930
D2 (h)	Duration of zero-order input for second absorption pathway	1.48 (3.2)	2.31 (5.8)	2.07 – 2.60
TLAG (h)**	Lag time for second absorption pathway	1.48 (3.2)	0.815 (13.7)	0.525 – 0.989
$F_{208,209}$	Relative bioavailability for studies C208 and C209	1 Fixed	1 Fixed	–
F_{HV-MD}	Relative bioavailability for studies 102 and C104	1.51 (7.5)	1.49 (9.7)	1.23 – 1.82
$F_{HV-SD,DS-TB}$	Relative bioavailability for studies C109, C110, C111, C202, and TBC1003	2.03 (4.7)	1.93 (5.3)	1.74 – 2.14
FM_{TB}	Fraction metabolized for patients with MDR-TB	–	0.542 (6.3)	0.471 – 0.603
$Effect_{HV,FM}$ (%)[d]	– Effect of HV on FM	–	48.1 (10.2)	38.1 – 57.4
M2 Metabolite				
CL_{MET}/Fm (L/h)	Apparent clearance	–	4.95 (6.9)	4.21 – 5.65
$Effect_{Black,CL_{MET}/Fm}$ (%)	– Effect of black race on CL_{MET}/Fm	–	Fixed to $Effect_{Black,CL_{PAR}/F}$	–
$V_{c,MET}/Fm$ (L)	Apparent central volume of distribution	–	Fixed to $V_{c,PAR}/F$	–
$CL_{p1,MET}/Fm$ (L/h)	Apparent clearance between the central and peripheral compartment	–	104 (15.7)	77 – 140
$V_{p1,MET}/Fm$ (L)	Apparent peripheral volume of distribution	–	862 (6.7)	748 – 970
$BSV_{CL_{PAR}/F}$ (%)	Between subject variability for CL_{PAR}/F	50.4 (12.3)	44 (7.7)	40.8 – 47.4
$BSV_{V_{c,PAR}/F}$ (%)	Between subject variability for $V_{c,PAR}/F$	39.1 (15.6)	71.1 (13.5)	61.1 – 81.3
BSV_{FR1} (%)	Between subject variability for FR1	113 (15.9)	97 (16.1)	81.2 – 112.8
BSV_F (%)	Between subject variability for F	39.6 (9.3)	36.9 (7.4)	33.9 – 39.5
$BSV_{CL_{MET}/Fm}$ (%)	Between subject variability for CL_{MET}/Fm	–	45.3 (8.5)	41.4 – 48.8
BSV_{FM} (%)	Between subject variability for FM	–	27.9 (14.6)	24.1 – 31.8
$BSV_{CL_{p1,MET}/Fm}$ (%)	Between subject variability for $CL_{p1,MET}/Fm$	–	158 (18.4)	124 – 183
	– Correlation Between CL_{PAR}/F – CL_{MET}/Fm	–	0.908 (7.5)	0.852 – 0.957
$RUV_{BDQ,HV}$ (%)	Residual unexplained variaibility for BDQ in HVs	20.6 (3.3)	23.9 (2.3)	23.5 – 24.5
$RUV_{BDQ,TB}$ (%)	Residual unexplained variaibility for BDQ in Patients with MDR-TB (%)	27.7 (3.2)	28.8 (1.9)	28.3 – 29.3
RUV_{M2} (%)	Residual unexplained variaibility for M2 (%)	–	24.8 (0.9)	24.5 – 25.0
	– Correlation Between $RUV_{BDQ,HV}$-RUV_{M2}	–	0.652 (2.7)	0.624 – 0.678
	– Correlation Between $RUV_{BDQ,MDR-TB}$-RUV_{M2}	–	0.492 (2.8)	0.470 – 0.518

RSE = relative standard error, CI = confidence interval, BDQ = bedaquiline. [a]Effect of Black race on CL_{PAR}/F was parameterized as $1 + 0.711^{Effect}$ where Effect = 1 for Black race and 0 for non-Black race. [b]Effect of HV or study R207910-CDE-102 on CL_{PAR}/F was parameterized as $1 + 0.450^{Effect}$ where Effect = 1 for HV or study R207910-CDE-102 and 0 for other subjects. [c]Effect of sex on $V_{c,PAR}/F$ was parameterized as $1 + 0.450^{Effect}$ where Effect = 1 for female and 0 for male. [d]Fraction metabolized for HVs was parameterized as $FM_{MDR-TB} \cdot (1\text{-}0.481)$. * Parameterized as FR1/(1+FR1), ** Parameterized as ALAG2 = D1 + TLAG. † Derived from $COV in NONMEM. ‡‡ Derived from sampling importance resampling (SIR). [2]

Figure 5. pvcVPC for the Final BDQ-M2 popPK Model – Patients with TB



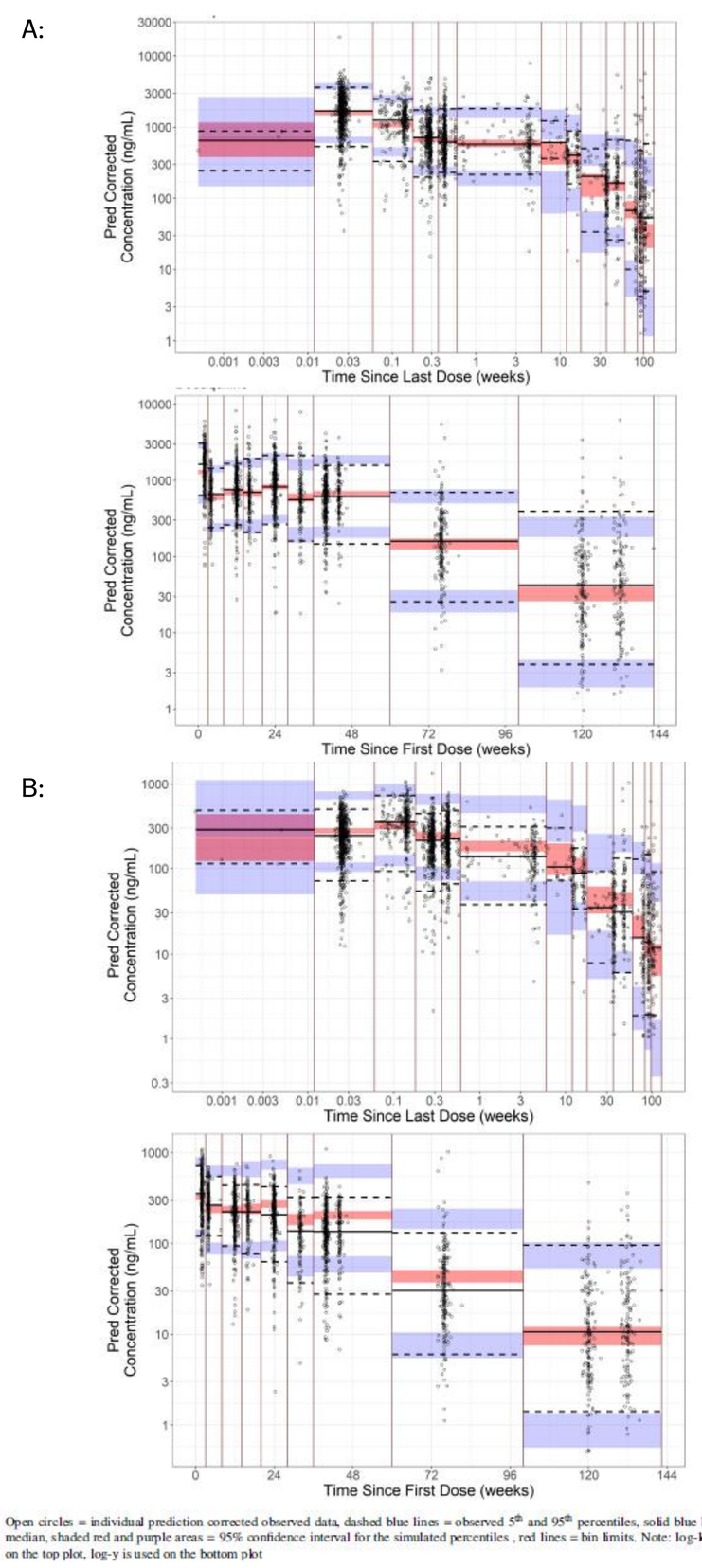
Open circles = individual prediction/variability corrected observed data, dashed lines = observed 10th and 90th percentiles, solid line = observed median, shaded red area = 95% confidence interval for the simulated percentiles. Note: log-log scale is used. Data from studies TMC207-TiDP13-C202, TMC207-TiDP13-C208, and TMC207-TiDP13-C209 were included.

External validation on the phase 3 data

The parent-metabolite model for BDQ and M2 provided an adequate description of the observed data from the phase 3 study STREAM Stage 2 (Fig. 6).

A minor under-prediction of M2 was evident at a population level (Fig. 6B) and subsequently a sensitivity analysis was conducted where the fraction of BDQ metabolized to M2 (and its BSV) where re-estimated (FM was re-estimated at 0.449 (2.5%RSE) compared to 0.542). Although re-estimating FM improved the model and the model diagnostics, it made no meaningful difference to the derived individual exposure metrics.

Figure 6. pcVPC for BDQ (A) and M2 (B) using the STREAM stage 2 phase 3 trial



Open circles = individual prediction corrected observed data, dashed blue lines = observed 5th and 95th percentiles, solid blue line = observed median, shaded red and purple areas = 95% confidence interval for the simulated percentiles , red lines = bin limits. Note: log-log scale is used on the top plot, log-y is used on the bottom plot

Conclusion

A BDQ-M2 popPK model was developed using data from 9 phase 1 and 2 clinical studies and validated on phase 3 data.

The model described the BDQ and M2 data in adult HV and patients with MDR-TB adequately, had good parameter precision, and can be used for simulation purposes.

References

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3. Goodall, Ruth L., et al. "Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial." The Lancet 400.10366 (2022): 1858-1868.