



Objective

To characterize changes in albumin and body weight in patients treated for multidrug-resistant tuberculosis (MDR-TB) with bedaquiline (BDQ) and to investigate the potential impact of these changes on BDQ pharmacokinetics.

Methods

- Data were obtained from two phase II studies of BDQ in MDR-TB patients [1,2]
- BDQ is a highly protein bound drug (unbound fraction $f_u < 0.1\%$ [3])
- Observations of albumin, body weight and plasma concentrations of BDQ and the M2 metabolite were available from the 24 weeks treatment period with BDQ plus optimized background therapy (OBT) and from the following period with only OBT (up to week 120)
- Evaluated models:
 - Linear
 - E_{max} and sigmoid E_{max}
 - Self-limiting logistic growth
 - Semi-mechanistic [4] (for albumin only)
- Mechanistically plausible relationships between albumin and body weight and BDQ/M2 PK, including effects of f_u (inversely proportional to albumin concentration), were tested in population models
- NONMEM 7.3 and the FOCE-I method used
- The clinical research had been approved by institutional review boards and all subjects provided written informed consent

Results

- 4684 albumin + 5438 body weight observations from 335 patients
- Albumin at screening typically lower than the reference value for healthy individuals, increasing over time on treatment
- Typical body weight increased 5.8 kg over studied period
- Selected models:
 - self-limiting logistic growth for albumin (Eq. 1)
 - linear for weight (Eq. 2)

$$\frac{dA(t)}{dt} = \frac{\ln(2)}{T_{1/2}} * A(t) * \left(1 - \frac{A(t)}{A_{ss}}\right) \quad \text{Eq. 1}$$

$$A(0) = A_0$$

$A(t)$ =albumin at time t , $T_{1/2}$ = half-life to reach albumin steady state, A_{ss} = albumin at steady state, A_0 = albumin at start of treatment, t =time in weeks

$$BW(t) = BW_0 + k * t \quad \text{Eq. 2}$$

$$k = \frac{BW_{120} - BW_0}{120}$$

$BW(t)$ =body weight at time t , BW_0 = body weight at start of treatment, BW_{120} = body weight 120 weeks after start of treatment, t =time in weeks

- Models fit well (Figures 1 and 2)
- Parameters estimated with good precision (Table 1)
- Box-Cox transformations improved description of the variability
- Significant correlations between albumin and weight

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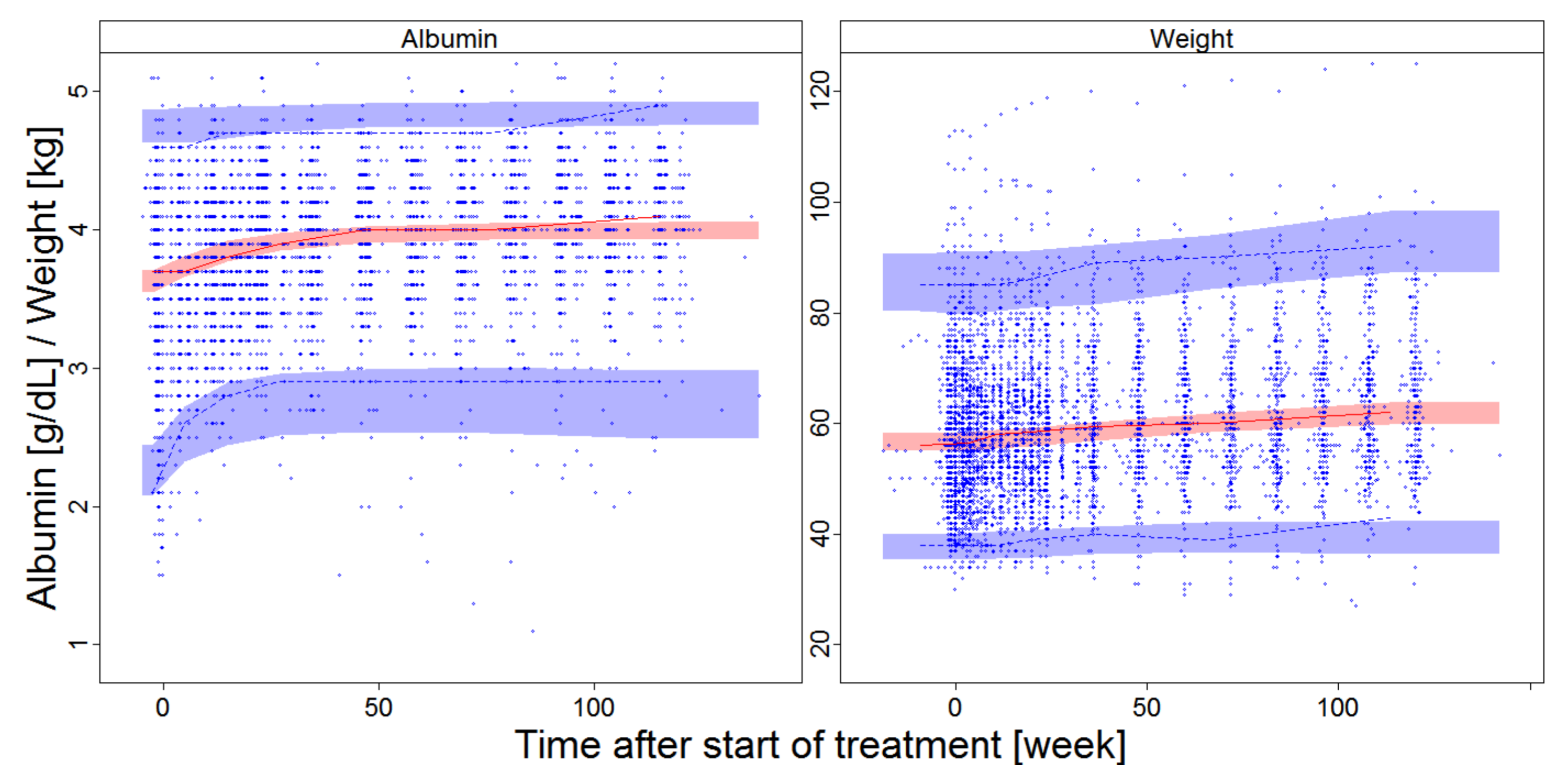


Figure 1. Visual predictive check showing the 5th, 50th and 95th percentiles (lines) of observed data (dots) and the 95% confidence intervals (shaded areas) of the same percentiles of data simulated from the models.

Structural model					
Parameters	Value (RSE)				
A_0 [g/dL]	3.65 (0.9%)				
A_{ss} [g/dL]	4.05 (0.6%)				
$T_{1/2}$ [weeks]	22.3 (16%)				
WT_0 [kg]	56.7 (1.1%)				
WT_{120} [kg]	62.5 (1.3%)				
Stochastic model					
Parameter	Value (RSE)				
BoxCox shape BSV A_0	-2.29 (13%)				
BoxCox shape BSV A_{ss}	-6.39 (23%)				
BoxCox shape BSV WT_{120}	-0.337 (58%)				
BSV A_0 [CV]	16.1% (5%)				
BSV A_{ss} [CV]	40.6% ^a	10.2% (9%)			
BSV $T_{1/2}$ [CV]	-47.6% ^a	24.3% ^a	175% (8%)		
BSV BW_0 [CV]	35.0% ^a	26.5% ^a	-16.3% ^a	20.7% (4%)	
BSV BW_{120} [CV]	14.8% ^a	33.5% ^a	3.4% ^a	81.4% ^a	22.4% (5%)
Prop. error albumin	7.0% (4%)				
Prop. error weight	3.4% (4%)				

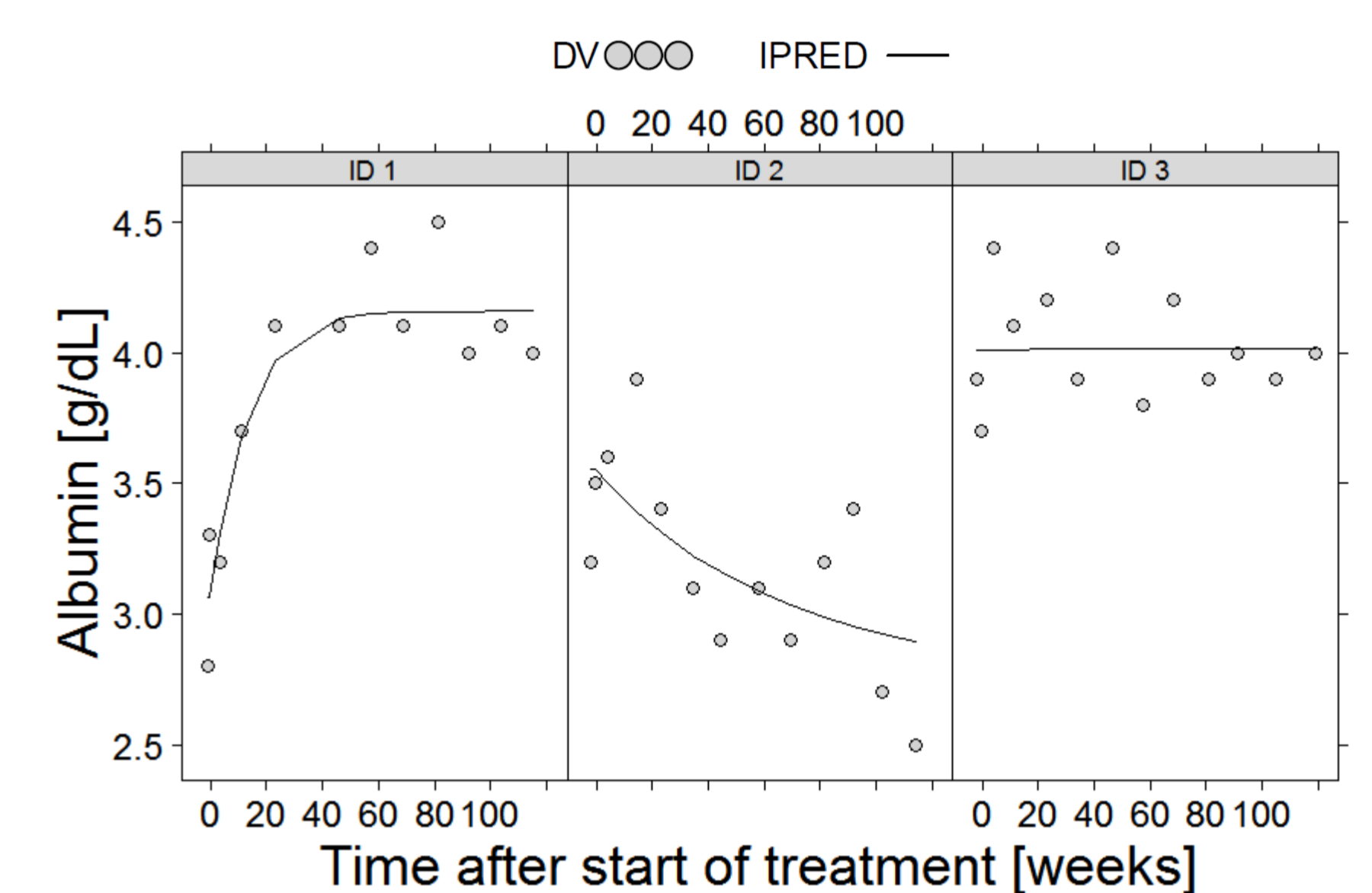


Figure 2. Examples of individual albumin concentration profiles over time after start of treatment.

Table 1. Parameter estimates with precision (RSE). BSV is between subject variability, CV is coefficient of variance. Off-diagonal values marked with ^a are correlations calculated as covariance($\text{ETA}(X) - \text{ETA}(Y)$)/(stdv($\text{ETA}(X)$)*stdv($\text{ETA}(Y)$)).

- Time varying albumin was used to predict changes in f_u and hepatic capacity which improved description of BDQ/M2 PK data significantly
- Using time varying weight instead of weight at baseline improved fit, the allometric coefficients were 1 for volumes (fixed) and 0.18 (estimated, $p < 0.05$) for clearances

Conclusions

- Models describing typical and individual albumin concentrations and body weights were developed
- Time-varying albumin and body weight impacts BDQ/M2 PK
- Incorporating both effects simultaneously and accounting for changes over time aided the characterization of influence of body weight on BDQ patient PK which has not previously been described

References

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