Population Pharmacokinetics of Delamanid and its Main Metabolite DM-6705 in Drug-Resistant Tuberculosis Patients Receiving Delamanid Alone or Coadministered with Bedaquiline

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Abstract
Background and Objective Delamanid is a nitroimidazole, a novel class of drug for treating tuberculosis, and is primarily metabolized by albumin into the metabolite DM-6705. The aims of this analysis were to develop a population pharmacokinetic (PK) model to characterize the concentration-time course of delamanid and DM-6705 in adults with drug-resistant tuberculosis and to explore a potential drug–drug interaction with bedaquiline when coadministered.

Methods Delamanid and DM-6705 concentrations after oral administration, from 52 participants (of whom 26 took bedaquiline concurrently and 20 were HIV-1 positive) enrolled in the DELIBERATE trial were analyzed using nonlinear mixed-effects modeling.

Results Delamanid PK were described by a one-compartment disposition model with transit compartment absorption (mean absorption time of 1.45 h [95% confidence interval 0.501–2.20]) and linear elimination, while the PK of DM-6705 metabolite were described by a one-compartment disposition model with delamanid clearance as input and linear elimination. Predicted terminal half-life values for delamanid and DM-6705 were 15.1 h and 7.8 days, respectively. The impact of plasma albumin concentrations on delamanid metabolism was not significant. Bedaquiline coadministration did not affect delamanid PK. Other than allometric scaling with body weight, no patients’ demographics were significant (including HIV).

Conclusions This is the first joint PK model of delamanid and its DM-6705 metabolite. As such, it can be utilized in future exposure–response or exposure–safety analyses. Importantly, albumin concentrations, bedaquiline coadministration, and HIV co-infection (dolutegravir coadministration) did not have an effect on delamanid and DM-6705 PK.

Key Points

The pharmacokinetics of delamanid, a new drug against tuberculosis, and its main metabolite DM-6705 in adults, has been described by a population modeling approach.

No pharmacokinetic drug–drug interaction was found with bedaquiline or dolutegravir coadministration.

Even though delamanid has been showed to be metabolized into DM-6705 by albumin in vitro, individual plasma albumin levels were not found to impact delamanid/DM-6705 kinetics in this population of patients.
1 Introduction

With approximately 10 million new cases and 1.4 million related deaths reported in 2019, tuberculosis (TB) is one of the most common causes of death globally due to an infectious disease [1]. The public threat is aggravated by resistance to first-line treatment and limited therapeutic options for patients with drug-resistant (DR) TB. Fortunately, in the last decade, new drugs have been registered for the treatment of DR TB.

Delamanid was registered by the European Medicines Agency (EMA) in 2014 as a new treatment for DR TB [2]. Its mechanism of action (inhibition of mycolic acid synthase [3]) and tolerability make it a good candidate for combination with other recently marketed anti-TB drugs, such as bedaquiline. This combination may improve outcomes for DR TB by acting on different targets in Mycobacterium tuberculosis [4], and could allow other more toxic and less effective second-line TB drugs to be phased out. Both delamanid and bedaquiline are oral agents that may be of key importance for new, shorter, all-oral regimens against DR TB [5–7]. However, both delamanid and bedaquiline have the cardiotoxic potential to prolong QTc interval (by blocking the hERG potassium channels during cardiac repolarization). This can lead to tachyarrhythmias, such as torsade de pointe, which are a risk factor of sudden death, so are important to detect. However, this effect has not primarily been attributed to delamanid and bedaquiline themselves, but to their main metabolites, DM-6705 for delamanid and M2 for bedaquiline [8–10].

Delamanid is a nitroimidazole compound metabolized into DM-6705 by albumin. This metabolic pathway has been determined in vitro [9, 11, 12], but patients’ plasma albumin levels have, to our knowledge, never been directly linked to the metabolism of delamanid in humans. In one recent analysis including 744 patients receiving delamanid, hypoalbuminemia appeared to increase delamanid clearance [13]. This may be explained by the high protein binding of delamanid and DM-6705 (> 99.5%) [11]. It follows that hypoalbuminemia could, in turn, lead to decreased protein binding and to an increase in total delamanid clearance [13].

Other key properties of delamanid pharmacokinetics (PK) are that absorption is highly influenced by food (approximately two fold higher bioavailability when administered with food [9]) and that cytochrome P450 (CYP) enzymes play an important role only for the metabolism of metabolites [11, 14, 15]. Furthermore, while the elimination half-life of delamanid is 30–38 h, DM-6705 has a longer terminal half-life of 121–322 h [9]. Sex, race, age, and renal impairment have not been found to affect delamanid PK [15].

The purpose of this analysis was to develop a population PK model for delamanid and its main metabolite DM-6705, to examine the potential drug–drug interaction between delamanid and bedaquiline, to evaluate the role of plasma albumin concentrations, and to test possible covariate relationships that could influence the PK profiles. The model can then be used for future analyses of pharmacokinetic/pharmacodynamic (PK/PD) and PK-toxicity relationships, such as the relationship between DM-6705 and QTc prolongation.

2 Methods

2.1 Data

Data were obtained from the DELIBERATE (DELamanId BEdaquiline for ResistAnt Tuberculosis) clinical trial, a phase II, open-label, randomized, controlled study in adults with multidrug-resistant (MDR) TB (ClinicalTrials.gov identifier: NCT 02583048). The trial was approved by the local Ethics Committees at each site, and participants gave written informed consent [16].

PK data for delamanid and its main metabolite DM-6705 were collected from participants with MDR TB who received delamanid with or without bedaquiline, together with a multidrug background regimen. Participants had to have received the background regimen for at least 7 days prior to enrolment. Participants were randomized to groups of 28 to receive delamanid, bedaquiline or delamanid plus bedaquiline. Delamanid was administered immediately after a standard meal at 100 mg twice daily for 24 weeks, and bedaquiline was administered at the approved dosing regimen (400 mg once daily for 2 weeks, then 200 mg three times weekly for 22 weeks), 1 h after the meal with the other anti-TB drugs. Rich PK sampling was performed at weeks 2, 8 and 24 (immediately after the meal but prior to the morning drug dosing [predose], at 4 [± 0.5] h, 6 [± 0.5] h, 8 [± 0.5] h, 11 [± 1] h and 23 [± 1] h), and a single sample 4 h postdose was drawn every 2 weeks (Fig. 1). PK concentrations were determined by a validated liquid chromatography tandem mass spectrometry assay developed at the Division of Clinical Pharmacology, University of Cape Town, with a lower limit of quantification of 1 ng/mL for both delamanid and DM-6705 (more details are given in Online Resource 1). Participants living with HIV had to have a CD4+ count of at least 100 cells/μL at baseline and were treated with a dolutegravir-based antiretroviral treatment once daily. Albumin levels in all participants were collected at baseline.

Exact times and dates were recorded for the three doses preceding each PK sampling. Pill count and adherence questionnaires (documenting if a dose was missed, and, if so, whether the dose was missed in the last 4 days and how many pills were missed since the last visit) were performed.
weekly between weeks 1 and 8, and every second week between weeks 10 and 24.

### 2.2 Population Pharmacokinetic Modeling

The time course of delamanid and DM-6705 concentrations was analyzed using a nonlinear mixed-effect approach, where both parent drug and metabolite were modeled simultaneously.

#### 2.2.1 Structural and Stochastic Model Development

For both parent and metabolite, one- and two-compartment disposition models were investigated. All disposition parameters were allometrically scaled with body weight using exponents of 0.75 and 1 for clearances and volumes, respectively. Both baseline body weight and time-varying body weight (recorded at weeks 2, 4, 8, 12, 16, 20 and 24) were tested in the allometric relationships. Models with lag time or transit compartments were explored to describe delamanid absorption. The typical bioavailability as well as the fraction of delamanid metabolized to DM-6705 were fixed to 1 in the analysis, thus generating apparent disposition parameters.

The stochastic model included interindividual variability (IIV), interoccasion variability (IOV), and residual unexplained variability (RUV). An occasion was defined as a rich PK sampling visit (i.e. IOV was not included for sparse sampling visits). IIV and IOV were included assuming lognormal distribution, and a proportional model was used for RUV. IIV in RUV was evaluated to allow the residual variability to be different between participants. The residual error of delamanid and DM-6705 observations from the same sample was correlated (by the use of L2 data item in the NONMEM code).

#### 2.2.2 Covariate Model Development

The covariate model-building procedure included a mechanism-based evaluation of the impact of albumin on delamanid metabolism and an exploratory search.

The mechanism-based analysis tested the expected action of albumin, metabolizing delamanid into DM-6705, with both linear and power functions on clearances and the fraction of delamanid metabolized into DM-6705. Both the observed albumin concentrations at baseline and individual model-predicted time-varying albumin concentrations (where the change

![Observed delamanid and DM-6705 concentrations over the study period](image-url)
from the observed baseline was derived using a published model [17] were evaluated in the covariate relationships.

The exploratory search consisted of the evaluation of an effect of bedaquiline coadministration (study arm), adherence (based on the answers of the adherence questionnaires), drug intake time of the day (morning vs. evening), as well as participants’ demographics, such as age, sex, race, and HIV co-infection status (dolutegravir coadministration). Assessment of patients’ demographic covariate relationships was undertaken using the stepwise covariate model procedure (using significance levels of 0.05 and 0.01 in the forward and backward steps, respectively) [18]. Continuous covariates were tested with a linear function (Eq. 1), as well as categorical covariates, where \( \text{cov}_i = 0 \) for the most common category (Eq. 2).

\[
\theta_{i} = \theta_1 \times (1 + \theta_2 \times (\text{cov}_i - \text{cov}_{\text{median}})) \tag{1}
\]

\[
\theta_{i} = \theta_1 \times (1 + \theta_2 \times \text{cov}_i) \tag{2}
\]

### 2.3 Data Analysis and Software

The population analysis was carried out using NONMEM software version 7.4.4, with the first-order conditional estimation method with interaction [19]. Data management, model diagnostics, and graphical visualization were supported by R software version 4.1.0 [20] and the PsN toolkit version 5.2.6 [21, 22]. Missing covariate values (see Table 1) were imputed by replacing them with the median of the population for continuous covariates and by the most common category for categorical covariates.

### 2.4 Model Selection and Evaluation

Model selection was based first on a significant difference (5% confidence level) in objective function value (OFV) between two nested models (\( \Delta \text{OFV} \geq 3.84 \) points or \( \geq 5.99 \) points for 1 or 2 degrees of freedom, respectively, representing the difference in the number of parameters between

### Table 1 Summary of patient demographics

|                        | Delamanid-alone arm [\( n = 26 \)] | Delamanid + bedaquiline arm [\( n = 26 \)] | Total [\( n = 52 \)] |
|------------------------|-----------------------------------|------------------------------------------|----------------------|
| Age, years             | Median (min, max)                 | Median (min, max)                        | Median (min, max)    |
|                        | 35 (18, 73)                       | 35.5 (18, 55)                            | 35 (18, 73)          |
| Sex                    | Male                              | 19 (73)                                  | 20 (77)              | 39 (75) |
|                        | Female                            | 7 (27)                                   | 6 (23)               | 13 (25) |
| Race                   | Black African                     | 9 (35)                                   | 11 (42)              | 20 (38) |
|                        | Colored                           | 10 (38)                                  | 12 (46)              | 22 (42) |
|                        | Mestizo                           | 1 (4)                                    | 2 (8)                | 3 (6)   |
|                        | White                             | 1 (4)                                    | 0 (0)                | 1 (2)   |
|                        | Others                            | 1 (4)                                    | 0 (0)                | 1 (2)   |
|                        | Missing                           | 4 (15)                                   | 1 (4)                | 5 (10)  |
| HIV-1                  | Negative                          | 14 (54)                                  | 15 (58)              | 29 (56) |
|                        | Positive                          | 10 (38)                                  | 10 (38)              | 20 (38) |
|                        | Missing                           | 2 (8)                                    | 1 (4)                | 3 (6)   |
| Baseline albumin, g/L  | Median (min, max)                 | 33.00a (23, 44)                          | 33.30b (23, 43)      | 33.00c (23, 44) |
|                        | Baseline weight, kg               | Median (min, max)                        | 54.00a (38, 83)      | 52.35b (41, 71.5) | 52.65c (38, 83) |
| Weight, maximal change from baseline over the study period, kg | Median (min, max) | 1.3a (− 7, 10.5) | 1.75 (− 4, 15) | 1.5b (− 7, 15) |

Data are expressed as \( n \) (%) unless otherwise specified

| min minimum, max maximum |
|--------------------------|
| \( ^a n = 24 \)          |
| \( ^b n = 25 \)          |
| \( ^c n = 49 \)          |
| \( ^d n = 50 \)          |
| \( ^e \) Normal range: 34.00–54.00 g/L |

△ Adis
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Acceptable goodness-of-fit plots and scientific plausibility were also used to discriminate between models. Models were qualified using visual predictive checks (1000 replicates) stratified by parent or metabolite and rich or sparse sampling occasions. Parameter precision was obtained with the R covariance (Hessian) matrix.

3 Results

3.1 Data

A total of 52 participants were included in the analysis, and a summary of the participants’ demographics are provided in Table 1. Four participants (two in each arm) were excluded from the analysis because they had no PK observations. The original dataset contained 2442 PK observations, of which 78 observations were excluded because sampling occurred after the end of delamanid treatment and the date of the last delamanid dose was not recorded; 21 observations (0.8%) were excluded because they were below the limit of quantification. The final analysis dataset contained 2343 observations (1170 delamanid and 1173 DM-6705 concentrations) and representation of the raw data of concentrations of delamanid and DM-6705 over the study period can be seen in Fig. 1. Self-reported adherence was analyzed by deriving constant or time-varying variables: whether doses were missed since the last visit, and, if so, how many doses were missed; or whether a patient ever reported to have missed a dose during the delamanid treatment period. A summary is provided in Table 2.

3.2 Population Pharmacokinetic Model

Visual predictive checks and final parameter estimates with uncertainty can be found in Fig. 2 and Table 3, respectively. The NONMEM code of the final model can be found in Online Resource 2.

3.2.1 Structural and Stochastic Model

The final structural model comprised of a one-compartment disposition model with linear elimination for both delamanid and DM-6705 (Table 3). The absorption of delamanid was best described by a model with a transit compartment, with a mean absorption time (MAT; i.e., typical time to 90% complete absorption) of 1.45 h. Predicted terminal half-life values for delamanid and DM-6705 were 15.1 h and 187.2 h (7.8 days), respectively. Correlations were significant between the IIVs in the clearances of delamanid and DM-6705. Residual variabilities for delamanid and DM-6705 were proportional and correlated, with the use of NONMEM level 2 data item, where delamanid and DM-6705 observations at the same timepoint (same blood sample) were grouped together.

3.2.2 Covariate Model

Disposition parameters were allometrically scaled with baseline body weight. During the mechanism-based covariate analysis, none of the attempts to include an effect of albumin on delamanid metabolism resulted in a significant improvement of model fit to the data; neither observed baseline albumin levels nor model-derived dynamic albumin levels over the study period had a significant correlation with delamanid clearance (or with DM-6705 clearance) [see Table 4 for confidence intervals of the estimated baseline albumin effects].

The exploratory search found that the daily average relative bioavailability decreased by 60% after the morning intake and increased by 60% after the evening intake; however, note that the only observation time after the evening dose was the morning trough the following day. An effect of adherence allowing changing relative bioavailability after week 8 was included with two different components, depending on whether the participants declared to have missed a dose or not at some point during the delamanid treatment period. A typical reduction in bioavailability of 18% was estimated for participants who declared never to have missed a dose (ADHNMD) versus a typical reduction of 39% in participants who declared to have missed a dose at least once (ADHMD). IIV in the adherence effects was also included on the logit scale. The stepwise covariate model building procedure did not identify further covariate relationships with participants’ demographics. Finally, neither delamanid nor DM-6705 PK were found to be impacted by bedaquiline coadministration, nor HIV with dolutegravir coadministration (Table 4).

Table 2 Summary of self-reported adherence

|                                      |                                            |
|--------------------------------------|--------------------------------------------|
| Number of patients who missed a dose at some point in the study [n (%)] | 25 (48)                                    |
| Total number of pharmacokinetic samples affected by missed doses [n (%)]  | 192 (8)                                    |
| Number of occasions per patient where a dose was missed since last visit [median (min; max)] | 2 (1; 4)                                   |
| Number of doses missed since last visit [median (min; max)]               | 2 (1; 20) [missing: 13]                    |

min minimum, max maximum

△ Adis
4 Discussion

Our analysis characterizes for the first time the population PK of both delamanid and its main metabolite DM-6705 in adult participants with MDR TB, following the approved dosing regimen of 100 mg twice daily, with or without coadministration of bedaquiline. Neither albumin level nor bedaquiline coadministration had an impact on delamanid PK.

Our final model provided a good description of the PK data, as seen in Fig. 2. For comparison, we applied a published model (developed with data from 744 patients included in three phase II trials and one phase III trial [13]) to our data but that model did not describe all our data.

Fig. 2 Visual predictive checks of the final model for both delamanid and DM-6705 concentrations, for the sparse sampling occasions only (a) and stratified by the three rich sampling occasions (b). The solid and dashed lines represent the median, and 2.5th and 97.5th percentiles of the observed data (black circles), respectively, and the shaded areas represent the simulation-based 95% confidence intervals for the corresponding percentiles. Dashed vertical lines represent the time of dosing.
adequately, especially the trough concentrations (Online Resource 3).

Our model is different from other evaluations of delamanid PK, in several ways. The trend of decreasing concentrations over the study period depicted in Fig. 2a has not been reported elsewhere in the literature. To describe this phenomenon, an effect of adherence has been implemented in our model. After week 8, all participants involved in the study were outpatients, which means higher risk to miss a dose. The impact of missing doses on PK was described by decreased bioavailability. This bioavailability factor was significant in both participant groups (see Online resource 4): those who reported missing a dose at least once during the delamanid treatment period (39% reduction) as well as in those who declared to never have missed a dose (18% reduction). The latter might be a consequence of the limited sensitivity of adherence questionnaires. The fact that the decrease in concentrations was more pronounced for the metabolite than for the parent could be explained by a combination of a white coat effect where adherence is improving just before a clinical visit and DM-6705 having a longer half-life than delamanid, therefore a missing dose would affect DM-6705 PK longer than delamanid PK. Thus, the ratio parent/metabolite could potentially be used as an indicator of adherence. A significant body weight increase (which is often observed in treated TB patients) over the study period could also have explained this phenomenon but the median maximal change from baseline weight in this study was 1.5 kg and time-varying weight was not significant in the allometric relationships.

Another pattern that was observed in PK profiles were higher delamanid trough concentrations after the evening dose compared with after the morning dose (see Fig. 2b, where concentrations before 0 h and 24 h are after the evening dose, and concentrations before 12 h are after the morning dose). This trend has been previously described for delamanid in the literature and was attributed to a “genuine physiological mechanism … or a difference in the amount and/or composition of food” [13]. In our analysis, this was estimated as a large effect on daily average relative bioavailability (Table 3), probably capturing several and different processes at the same time. Since all PK samples after evening intake were drawn just before the morning dose, there is very sparse information about the night/evening effect on absorption. This morning/evening effect on bioavailability best described the data of the models explored, but it is likely that it is a simplistic description of the changes in absorption occurring at night/evening administration.

Regarding the mechanism-based evaluation of albumin impact on delamanid metabolism, none of the tested scenarios resulted in a significant improvement of the model fit to the data. Given that it has been established in vitro that albumin metabolizes delamanid into DM-6705 [11, 12], clearance of unbound delamanid would be expected to be proportional to plasma albumin levels. On the other hand, delamanid is known to be highly protein bound to albumin, hence the fraction unbound of delamanid would be inversely proportional to albumin levels [23]. Total clearance is equal to unbound clearance multiplied by fraction unbound [24]. That is why, with those two processes counteracting each other, total clearance would then be expected to not be related to albumin changes. Of note, a relationship

### Table 3 Parameter estimates for the final model

| Description, unit | Estimate [RSE%] |
|-------------------|-----------------|
| Population parameter | |
| Mean absorption time, h | 1.45 [0.501; 2.20]$^a$ |
| CL/F, L/h/52.65 kg | 28.8 [4.07] |
| V/F, L/52.65 kg | 626 [6.93] |
| CLM/(F×fm), L/h/52.65 kg | 81.8 [8.34] |
| VM/(F×fm), L/52.65 kg | 22080 [11.5] |
| AM/PM on F, % | ±60.9 [3.54] |
| ADH$_{NMD}$ on F, % | 82.2 [11.4] |
| ADH$_{MD}$ on F, % | 60.7 [25.9] |
| Residual variability | |
| CL/F, %CV | 19.9 [13.5] |
| Correlation IIV CL/F – IIV CLM/(F×fm), % | 71.4 [17.5] |
| CLM/(F×fm), %CV | 41.1 [14.5] |
| V1/F, %CV | 26.1 [26.3] |
| VM/(F×fm), %CV | 47.8 [10.5] |
| ADH$_{NMD}$, SD | 0.345$^b$ [22.6] |
| ADH$_{MD}$, SD | 0.501$^b$ [15.9] |
| Residual variability delamanid, %CV | 32.5 [16.0] |
| Residual variability DM-6705, %CV | 25.8 [19.0] |
| Intercocassion variability | |
| F, %CV | 32.3% [8.81] |
| Residual variability | |
| Proportional residual error delamanid, %CV | 20.9 [8.88] |
| Correlation RUV delamanid—RUV | 42.9 [5.70] |
| DM-6705, % | 16.7 [6.17] |

$^a$95% confidence interval obtained with log-likelihood profiling

$^b$Standard deviation for logit transformed IIV, SD IIV ADH = $\sqrt{(\alpha^2_{ADH})} \times ADH \times (1 – ADH)$
between low albumin and more rapid delamanid clearance has been previously reported [13]. Such a finding could be explained by a combination of fraction unbound increasing with hypoalbuminemia and the existence of additional metabolism pathways for delamanid (other than albumin).

Regarding the covariate analysis, apart from the allometric scaling factors already included in the structural model on all disposition parameters, none of the demographics were significant as covariates (age, sex, race and HIV co-infection). These results are in line with previous publications: age (over 18 years) and sex have not been previously reported to affect delamanid PK; Asian race has been shown to impact bioavailability [13], but none of the participants in our analysis were Asian; and for HIV co-infection, drug–drug interactions with anti-HIV drugs usually influence the PK, rather than the pathology. In this study, all participants with HIV were treated with dolutegravir (no lopinavir/ritonavir coadministration). In addition to no observable drug interaction with dolutegravir, no drug–drug interactions were found with bedaquiline coadministration. While those drug interactions were not anticipated, this study provides assurance that they are not present. We note that delamanid and bedaquiline intakes were spaced by an hour; the results may be different when ingested simultaneously, especially if coadministration impacts the dissolution and absorption of delamanid.

Our study has several limitations. First, this study was designed to primarily explore the safety of delamanid and bedaquiline coadministration. Indeed, this analysis would probably have benefited from drawing PK samples during the absorption phase of delamanid (first PK sample after dose around the expected maximum delamanid concentration), as well as drawing albumin levels over time to better assess the mechanism-based aspect of albumin metabolizing delamanid into DM-6705. Moreover, an objective method (e.g. mobile application, drug dispenser, etc.) to measure patient adherence could have helped to derive time-dependent, more sensible metrics for assessing the role of adherence in delamanid PK.

### 5 Conclusion

In summary, the PK of delamanid and DM-6705 in adults with DR TB was adequately described using a combined model, where no effect of bedaquiline coadministration, HIV (with dolutegravir-based treatment), or albumin levels could be identified. This is the first joint population PK model of delamanid and its main metabolite DM-6705, and it can be utilized in future exposure–response or exposure–safety analyses (e.g. relation between DM-6705 concentrations and QT prolongation).

### Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s40262-022-01133-2.

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### Declarations

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**Conflicts of interest** LT, MOK, AHD, JS, JDLR, LW, CMU, KED, GM, and EMS have no conflicts of interest to declare.

### Table 4

Summary of the nonsignificant effects of bedaquiline coadministration, HIV co-infection (dolutegravir coadministration) and baseline albumin levels on disposition parameters

|                  | F  |          |          |                  | CL |          |          |                  | CLM|          |          |
|------------------|----|----------|----------|------------------|----|----------|----------|------------------|----|----------|----------|
| **Effect estimate** |    | 95% CIa  | 95% CIa  | **Effect estimate** |    | 95% CIa  | 95% CIa  | **Effect estimate** |    | 95% CIa  | 95% CIa  |
| Bedaquiline coadministration | −0.306% | (−13.1%, 12.5%) | +0.726% | (−14.6%, 16.1%) | −5.43% | (−29.1%, 18.2%) |
| HIV co-infection/ dolutegravir coadministration | −5.33% | (−14.8%, 4.13%) | +5.34% | (−4.86%, 15.5%) | −0.877% | (−21.6%, 19.8%) |
| Baseline albumin | +1.02% | (−1.02%, 2.14%) | −0.908% | (−1.90%, 0.09%) | +0.778% | (−1.39%, 2.95%) |

*CI confidence interval, CL clearance, CLM metabolite clearance, F bioavailability*

aCoded with a linear function:

\[
PAR = TVPAR * (1 + THETA(X) * (COV - median)) \text{ for continuous COV}
\]

\[
PAR = TVPAR * (1 + \text{THETA}(X) \times \text{COV}) \text{ for 0–1 categorical COV}
\]

where PAR is the disposition parameter (F, CL, or CLM) and THETA(X) is the estimate of the effect

bCIs containing zero, the changes in parameter estimates were not statistically significant.
Ethical approval and consent The clinical data were available from both the DELIBERATE trial (NCT02583048) and the report of the results of the clinical trial already published [16]. The trial was approved by the local Ethics Committees at each site, and participants gave written informed consent.

Consent for publication Not applicable.

Availability of data and material and Code availability Deidentified participant data were shared to the modeler. Top-line study results for delamanid and DM-6705 PK can be found in the electronic supplementary material.

Author contributions LT, MOK and EMS designed the research in conjunction with AHD, KED and GM; AHD, JS, JDLR and CMU conducted the clinical trial; LW analyzed the PK samples; LT performed the posterior data management, the analysis and wrote the first draft of the manuscript; and MOK and EMS reviewed and supervised the analysis and the manuscript preparation. All authors reviewed the key steps of the analysis and commented on intermediate versions of the manuscript, and read and approved the final manuscript.

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References

1. World Health Organization. Global tuberculosis report 2020. 2020. https://www.who.int/publications/i/item/9789240013131.
2. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012;366:2151–60.
3. Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med. 2006;3:e466.
4. Hoagland DT, Liu J, Lee RB, Lee RE. New agents for the treatment of drug-resistant mycobacterium tuberculosis. Adv Drug Deliv Rev. 2016;102:55–72.
5. Mohr E, Ferlazzo G, Hewison C, De Azevedo V, Isaakidis P, Bedaquiline and delamanid in combination for treatment of multidrug-resistant tuberculosis. Lancet Infect Dis. 2019;19:470.
6. Kim CT, Kim T-O, Shin H-J, Ko YC, Hun Choe Y, Kim H-R, et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. Eur Respir J. 2018;51:1702467.
7. Migliori GB, Ponteï E, Sotgiu G, Centis R, D’Ambrosio L, Tiberi S, et al. Combined use of delamanid and bedaquiline to treat multidrug-resistant and extensively drug-resistant tuberculosis: a systematic review. Int J Mol Sci. 2017;18:341.
8. Tanneau L, Svensson EM, Rossenu S, Karlsson MO. Exposure–safety analysis of QTc interval and transaminase levels following bedaquiline administration in patients with drug-resistant tuberculosis. CPT Pharmacometrics Syst Pharmacol. 2021;10(12):1538–49.
9. Liu Y, Matsumoto M, Ishida H, Ohguro K, Yoshitake M, Gupta R, et al. Delamanid: From discovery to its use for pulmonary multidrug-resistant tuberculosis (MDR-TB). Tuberculosis. 2018;111:20–30.
10. Pontali E, Sotgiu G, Tiberi S, D’Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J. 2017;50:1701462.
11. Sasahara K, Shimokawa Y, Hirao Y, Koyama N, Kitano K, Shibata M, et al. Pharmacokinetics and metabolism of delamanid, a novel anti-tuberculosis drug, in animals and humans: importance of albumin metabolism in vivo. Drug Metab Dispos. 2015;43:1267–76.
12. Shimokawa Y, Sasahara K, Koyama N, Kitano K, Shibata M, Yoda N, et al. Metabolic mechanism of delamanid, a new anti-tuberculosis drug, in human plasma. Drug Metab Dispos. 2015;43:1277–83.
13. Wang X, Mallikaarjun S, Gibiansky E. Population pharmacokinetic analysis of delamanid in patients with pulmonary multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2020;65:e01202-e1220.
14. Mallikaarjun S, Wells C, Petersen C, Paccaly A, Shoaib SE, Patil S, et al. Delamanid coadministered with antituberculous drugs shows no clinically relevant drug-drug interactions in healthy subjects. Antimicrob Agents Chemother. 2016;60:5976–85.
15. EMEA. Public assessment report—deltyba. 2013. https://www.ema.europa.eu/en/documents/assessment-report/deltyba-epar-public-assessment-report_en.pdf.
16. Dooley KE, Rosenkranz SL, Conradie F, Moran L, Hafner R, von Groote-Bidlingmaier F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. Lancet Infect Dis. 2021;21(7):975–83.
17. Svensson E, Dosne A, Karlsson M. Population pharmacokinetics of bedaquiline and metabolite M2 in patients with drug-resistant tuberculosis: the effect of time-varying weight and albumin. CPT Pharmacometrics Syst Pharmacol. 2016;5:682–91.
18. Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM. Pharm Res. 1998;15:1463–8.
19. Beal SL, Sheiner LB, Boeckmann AJ, Bauer RJ. NONMEM 7.4 Users Guides (1989-2017). Gaithersburg, MD: ICON plc. 2017. https://nonmem.iconplc.com/nonmem743/guides.
20. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. 2020. https://www.r-project.org/.
21. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005;79:241–57.
22. Karlsson MO, Hooker A, Nordgren R, Hartling K, Freiberga S. Perl-speaks-NONMEM (PsN). 2016. https://uapharmacometrics.github.io/PsN/.
23. Gabrielson J, Weiner D. Pharmacokinetic and pharmacodynamic data analysis: concepts and applications. Fourth Edition. Taylor & Francis; 2007.
24. Benet LZ, Zia-Amirhossein P. Basic principles of pharmacokinetics. Toxicol Pathol. 1995;23:115–23.