# Population pharmacokinetic analysis of doxecitine and doxribtimine in patients with thymidine kinase 2 deficiency and in healthy volunteers

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## Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial myopathy resulting from pathogenic variants of the thymidine kinase 2 gene (*TK2*)[1,2]
- *TK2* variants lead to depletion in levels of deoxycytidine triphosphate and deoxythymidine triphosphate, interfering with the synthesis of mitochondrial DNA and causing mitochondrial DNA depletion and/or multiple deletions[3,4]
- Patients with TK2d experience progressive skeletal muscle myopathy with bulbar muscle weakness and respiratory insufficiency, leading to premature death[4]
- There are no approved treatments for TK2d, with current management focused on supportive care[4]
- Data suggest that treatment with doxecitine and doxribtimine, a powder for oral solution consisting of a 1:1 mixture by weight of deoxycytidine (dC) and deoxythymidine (dT), can improve survival and positively change TK2d disease trajectory, with improvement and/or stabilization across key clinical outcomes, especially in patients with age of TK2d symptom onset ≤12 years[5–8]

## Objective

- To describe the pharmacokinetics (PK) of dC and dT, quantifying the associated interindividual variability (IIV) and investigating the effect of relevant covariates on their systemic exposure in healthy volunteers and patients with TK2d

## Methods

### Data

- PK data were collected from 120 participants from phase 1 (24-day study in healthy adult volunteers) and phase 2 (~14-day study in adult and paediatric [≥2–18 years] patients with TK2d) clinical trials to assess the pharmacokinetics, safety, tolerability and food effect of dC and dT
- Doxecitine and doxribtimine was dosed based on body weight up to a maximum of 800 mg/kg/day (dC at 400 mg/kg/day and dT at 400 mg/kg/day) as follows:
  - in healthy adult participants, escalating single doses of 86.6, 173.4 and 266.6 mg/kg after an overnight fast (≥10 hours), and a single dose of 266.6 mg/kg within 5 minutes of consuming a standard high-fat, high-calorie meal; all treatments were separated by a 2-day washout period
  - in adult participants with moderate or severe renal impairment (but without TK2d) and in matched healthy adult controls, a single dose of 266.6 mg/kg
  - in patients with TK2d, total daily maintenance doses of 260, 520 or 800 mg/kg, given in three equal doses
- In participants without TK2d, PK was sampled intensively after each dose; in patients with TK2d, up to four PK samples were taken at month 1, 3 or 6 at their daily maintenance dose

### Modelling

- Population PK modelling analyses of dC and dT in healthy and patient populations were performed using Non-Linear Mixed Effects Modeling (NONMEM, version 7.5 [ICON, Gaithersburg, MD, USA] facilitated by Perl-speaks-NONMEM [version 5.3.2])
- Data management and post-processing was carried out using R (version 4.2.2)
- Body weight and food intake were included in the models as mechanistic covariates
- Other covariate–parameter relationships were evaluated using a stepwise covariate model procedure including demographics, organ impairment and disease-related variables

## Results

### Participants

- Baseline demographics and clinical characteristics of patients with TK2d and healthy volunteers can be found in **Supplementary Table 1**

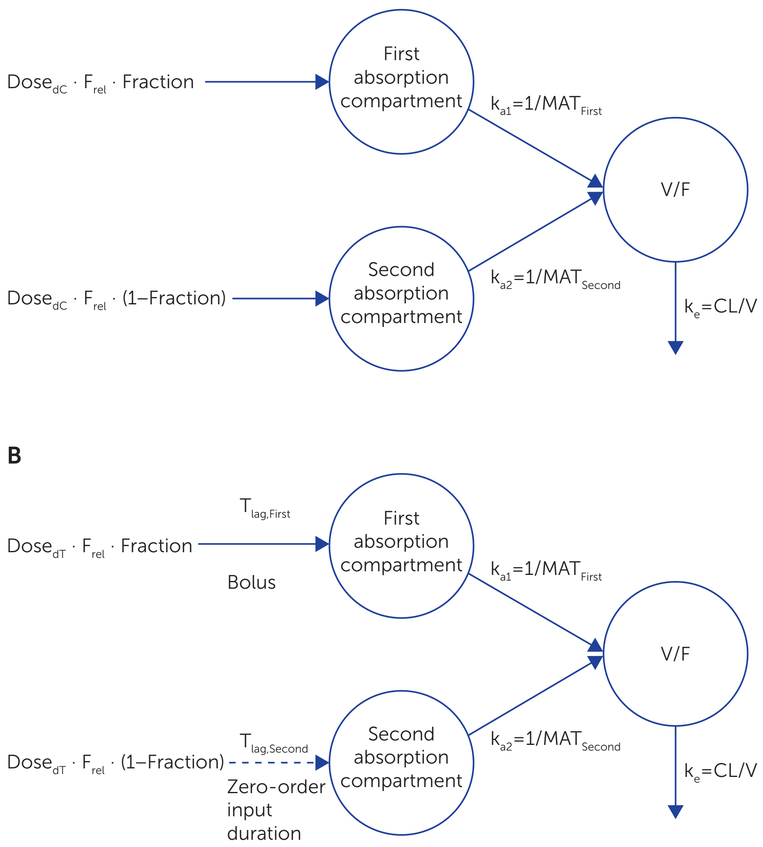
### Deoxycytidine

- dC pharmacokinetics were adequately characterized by a one-compartment disposition model with two parallel first-order absorption processes and a first-order elimination (**Figure 1A**)
  - The predictive performance of the dC population PK model was satisfactory (**Figure 2A**)
- The following covariate–parameter relationships were included:
  - body-weight-based allometric relationships with estimated exponent for clearance (CL)
  - fixed exponent for volume of distribution (V)
- Alanine aminotransferase and moderate and severe renal impairment had statistically significant effects on CL, food status and dose on relative bioavailability ($F_{rel}$), food status on mean absorption time associated with the first absorption compartment ($MAT_{First}$), time after dose on mean absorption time associated with the second absorption compartment ($MAT_{Second}$) and age on estimated baseline plasma concentration (BASE)
- Compared with healthy volunteers, patients with TK2d had higher IIV for $F_{rel}$ and residual unexplained variability
  - dC population PK model parameter estimates are reported in **Supplementary Table 2**
- The largest covariate impact on dC exposure was due to food status, with a median increase of >100% in the predicted 24-hour area under the curve at steady state ($AUC_{0-24,ss}$) in the fed state compared with in the fasted state (**Figure 3A**)
- Dose effect on $F_{rel}$ was such that increase in dC exposure was less than dose proportional

### Deoxythymidine

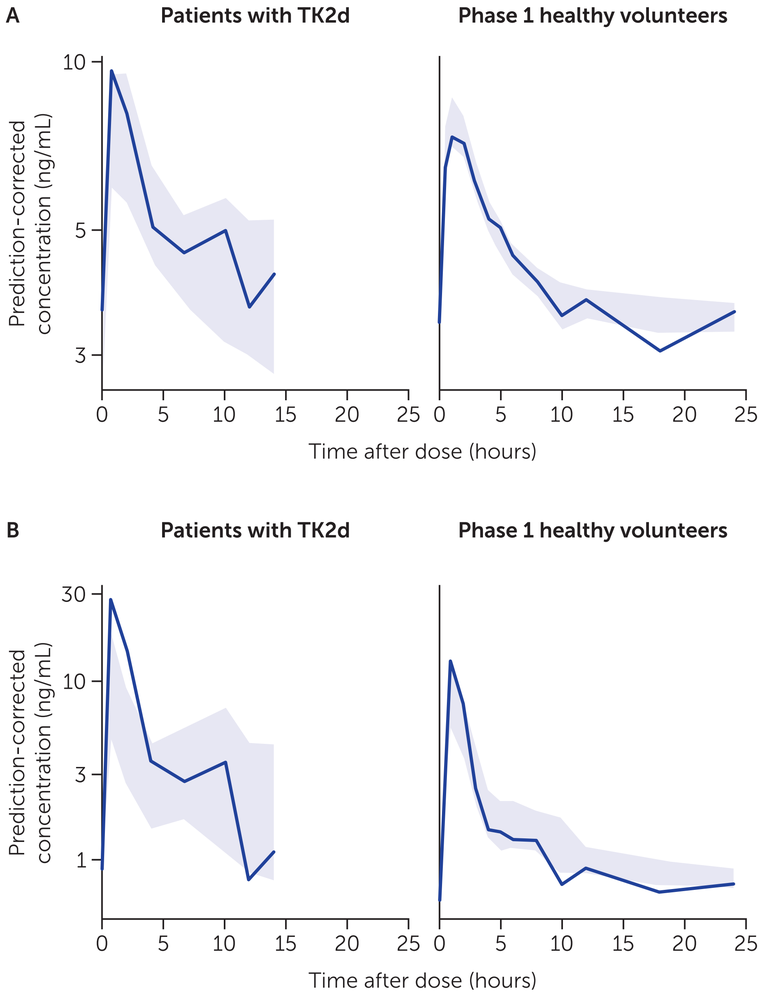
- dT pharmacokinetics were best described by a one-compartment disposition model with two parallel first-order absorption processes and first-order elimination. A bolus input with lag time ($T_{lag1}$) was added to the first absorption compartment, whereas a zero-order input with lag time ($T_{lag2}$) was applied to the second absorption compartment (**Figure 1B**)
  - The predictive performance of the dT population PK model was satisfactory (**Figure 2B**)
- The model included the following covariate–parameter relationships: body-weight-based allometric relationships with estimated exponent on CL and fixed exponent on V. Ethnicity was added on $F_{rel}$, food status was added on $F_{rel}$, $MAT_{First}$, $MAT_{Second}$, $T_{lag1}$, $T_{lag2}$ and Fraction, and age was added on BASE. In addition, patients with TK2d had a higher magnitude of IIV for $F_{rel}$ than healthy volunteers
  - For dT, 'Fraction' represented the fraction going into the rapid-absorption (first absorption) compartment when in the fasted state and the second-absorption compartment when in the fed state
  - dT population PK model parameter estimates are reported in **Supplementary Table 3**
- dT median $AUC_{0-24,ss}$ in fed was approximately 100% greater than that in fasted conditions (**Figure 3B**). Unlike dC, dT dose effect on $F_{rel}$ led to an increase in exposure that was more than dose proportional

**Figure 1. Illustrations of the final (A) dC and (B) dT PK models**



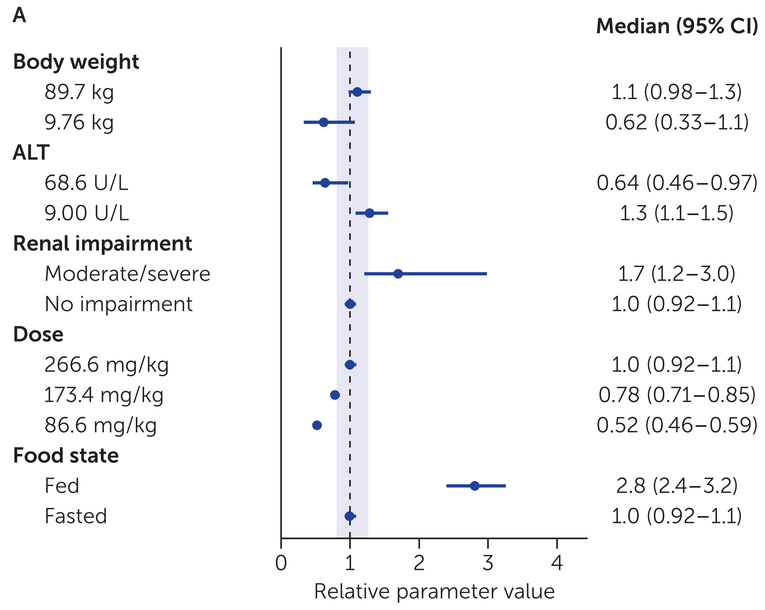

CL, clearance; dC, deoxycytidine; dT, deoxythymidine; Fraction, fraction of the bioavailable dose absorbed through the first absorption compartment (fixed to 1 in fasted); $F_{rel}$, relative bioavailability; $k_{a1}$, first-order absorption rate constant associated with the first absorption compartment; $k_{a2}$, first-order absorption rate constant associated with the second absorption compartment; $k_e$, first-order elimination rate constant from the central compartment; $MAT_{First}$, mean absorption time associated with the first absorption compartment; $MAT_{Second}$, mean absorption time associated with the second absorption compartment; PK, pharmacokinetic; $T_{lag,First}$, lag time associated with the first absorption compartment; $T_{lag,Second}$, lag time associated with the second absorption compartment; V, volume of distribution; V/F, apparent volume of distribution.

**Figure 2. Prediction-corrected VPC of PK plasma concentrations vs time after dose for the PK analysis dataset using the final PK model, stratified by population for (A) dC and (B) dT**




Data are presented on semi-logarithmic scales. Time points associated with BLQ observations were included in the VPC. BLQ values were censored for the observed data and are only plotted for the simulated data. Blue areas show 90% confidence intervals of the model-predicted median.
BLQ, below the limit of quantification; dC, deoxycytidine; dT, deoxythymidine; PK, pharmacokinetic; TK2d, thymidine kinase 2 deficiency; VPC, visual predictive check

**Figure 3. Forest plots illustrating effects of covariates on (A) dC and (B) dT $AUC_{0-24,ss}$ based on the final PK model**




Reference participant parameters: body weight 60 kg, ALT=19.76 U/L, normal renal function, dose 266.6 mg/kg, fasted state and Hispanic or Latino. Data points represent medians of the predicted relative change from the reference participant; horizontal lines depict 95% CIs; dotted vertical lines represent parameter values for a reference participant; shaded blue reference areas depict 80–125% margins relative to the reference participant, based on the standard bioequivalence limits.
ALT, alanine aminotransferase; $AUC_{0-24,ss}$, 24-hour area under the curve at steady state; CI, confidence interval; dC, deoxycytidine; dT, deoxythymidine; PK, pharmacokinetic; U/L, units per litre.

## Conclusions and Outlook

- The models effectively characterized the plasma pharmacokinetics of dC and dT in both paediatric and adult participants after administration as an oral solution
- The interindividual variability in dT pharmacokinetics was large and greater than for dC
- Food intake had a substantial effect on dC and dT absorption processes, leading to a >100% increase in dC and dT $AUC_{0-24,ss}$ values in the fed state than in the fasted state
- With increasing dose, less than and more than dose-proportional increases in exposure were observed for dC and dT, respectively
- No age-related effect was identified on the pharmacokinetics of dC or dT once body weight and other covariates were included in the models; therefore, dose adjustments with age were not necessary

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**Disclosures:** **Salim Bouchene**, **Himanshu Naik**, **Pinky Dua** and **Akash Khandelwal** are employees of UCB. **Aravind Mittur** is an employee and stockholder of UCB. **Ida Neldemo** is an employee of Pharmetheus. **Jakob Ribbing** and **Martin Bergstrand** are employees and stockholders of Pharmetheus.

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