**Prediction of Dolutegravir Pharmacokinetics and Dose Optimisation in Neonates via PBPK Modelling**

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**Running Title: Prediction of dolutegravir pharmacokinetics in neonates**

## **Abstract**

**Background:** Only a few antiretroviral drugs (ARVs) are recommended for use during the neonatal period and there is a need for more to be approved to increase treatment and prophylaxis strategies. Dolutegravir, a selective integrase inhibitor, has potential for treatment of HIV infection and prophylaxis of transmission in neonates. The objective of this study was to model the pharmacokinetics of dolutegravir in neonates and to simulate a theoretical optimal dosing regimen.

**Methods:** The PBPK model was built incorporating the age-related changes observed in neonates. Virtual neonates between 0-28 days were simulated. The model was validated against observed clinical data for raltegravir and midazolam in neonates, prior to the prediction of dolutegravir pharmacokinetics.

**Results:** Both raltegravir and midazolam passed the criteria for model qualification, with simulated data within 1.8-fold of clinical data. The qualified model predicted the pharmacokinetics for several multi-dose regimens of dolutegravir. Regimen 6 involved 5 mg doses with a 48h interval from day 1-20 increasing to 5 mg once daily on week 3, yielding AUC and Ctrough values of 37.2 mg.h/L and 1.3 mg/L, respectively. These exposures are consistent with those observed in paediatric patients receiving dolutegravir.

**Conclusions:** Dolutegravir pharmacokinetics were successfully simulated in the neonatal PBPK model. The predictions suggest that during the first 3 weeks of life a 5 mg dose administered every 48 hours may achieve plasma exposures needed for therapy and prophylaxis.

## **Introduction**

Neonates, defined as infants from birth up to 28 days of age, are generally neglected as a population. As a result, data describing the pharmacokinetics (PK) and pharmacodynamics in this vulnerable population of most licensed drugs, are lacking. 1 Efforts have been made to elucidate the significant changes that are observed in the absorption, distribution, metabolism and elimination of drugs from birth to adulthood, yet a great deal remains unanswered. Previously, neonatal dosing regimens were derived from adult doses using allometric scaling based on characteristics such as body surface area or body weight. 2-4 Extrapolation of PK data from older patients using this scaling approach is generally unsuccessful due to the complex physiologic changes that occur in neonates, 4 including insufficient characterisation of the immaturity of metabolic pathways. Investigating drugs directly is required to use drugs safely and effectively, however, researchers are faced with several challenges and clinical constraints which impede the conduct of clinical trials in paediatric patients, and this is particularly true for neonates. 5

Physiologically based pharmacokinetic (PBPK) modelling can be employed to inform the design of clinical trials in neonates, making these trials safer and more efficient. PBPK modelling simulates important drug processes by integrating existing knowledge on patient-specific characteristics and drug-related data. Typically, models comprise distinct compartments which represent the physiology of organs and tissues that are connected by the cardiovascular system. Moreover, age-related changes in physiology, anatomy and molecular processes can be captured mathematically to provide more accurate predictions in neonates. 6, 7 8

In 2017, an estimated 1.8 million (1.3–2.4 million) children younger than 15 years of age were living with HIV. 9 The majority of paediatric HIV infections are caused by perinatal transmission, in utero during birth or afterwards through breastfeeding.10 Of the measures taken to prevent mother to child transmission (PMTCT), initiating or maintaining effective antiretroviral (ARV) therapy in pregnant and breastfeeding women is the most successful. In addition, all neonates with perinatal HIV exposure should receive ARVs as part of PMTCT. Those infants who are infected with HIV despite these efforts at prophylaxis can be detected with successful early diagnosis techniques and early initiation of ART can maintain an undetectable viral load and improve clinical outcomes in these infants.11 9

Current guidelines for ARV use in neonates recommend either a 1 or 2-drug prophylaxis regimen or ‘empiric therapy’, using a 3-drug regimen, including 2 NRTI and a NNRTI or integrase inhibitor (II), in high risk or infected infants. Zidovudine, an NRTI, and/or nevirapine, an NNRTI are currently recommended for prophylaxis of neonates born to women living with HIV.12 Few ARVs have been studied in newborn infants,1and only zidovudine, nevirapine, lamivudine and raltegravir have sufficient neonatal safety and PK data to be recommended for use from birth and lopinavir/ritonavir from 2 weeks of age,12 resulting in limited options for neonatal 3-drug treatment regimens.

Dolutegravir is a highly potent HIV-1 integrase inhibitor13 but is not currently approved for use in neonates. Integrase inhibitors are well known for their safety and high efficacy and are accordingly favoured for first-line treatment in both ARV-naïve and experienced adult patients.13, 14 Safety and PK of dolutegravir have previously been studied in paediatric patients and a recent study investigated the safety in infants older than 4 weeks of age.15Dolutegravir was generally well tolerated in all the cohorts with doses meeting the target concentrations.15 The aim of the current study was to model exposure of dolutegravir in neonates and to identify a dosing regimen for evaluation in neonates.

## **Methodology**

This study is based on virtual patients, therefore no ethical approval was required.

The PBPK model was designed in SimBiology version 5.8, a product of MATLAB R2018a (MathWorks, Natick, MA, USA 2018). 16 Virtual patients between 0 – 28 days were simulated. Neonatal maturation characteristics and a description of physiological and anatomical growth data were incorporated where appropriate. The model was based on the following assumptions: (1) well-stirred compartments with instant distribution of the drug; (2) no absorption of the drug from the colon; and (3) the model is blood flow limited.

### **Anatomy**

WHO reference growth charts relating age to body weight and height were used for male and female neonates 17 (shown in Table S1). The organ weights were collated from multiple sources, 2, 18 these values along with organ density data were used to calculate organ volumes, 6 listed in Table S2. Blood flow data previously described by Bjorkman 2 were integrated into the model, summarised in Table S2. The small intestine fluid capacities from the published paediatric model were allometrically scaled. 16

### **Intestinal Absorption**

For orally administered drugs, a previously defined compartmental absorption and transit model was implemented in the model. 19 Absorption rates were calculated using equations involving the apparent permeability derived from Caco-2 cells or the polar surface area and hydrogen bond donor values. 20

### **Plasma protein binding**

Plasma protein binding of drugs in neonates was calculated using a previously combined database on age-related changes in plasma albumin and α1-acid glycoprotein. 21 The unbound fraction of drug was estimated using the following equation (Eq.1): 22

(Eq. 1)

### **Metabolism**

***Intestinal metabolism***

The expression of CYP3A4 in the gut was estimated using an equation describing the fraction of CYP3A4 present in the neonatal gut in relation to the adult abundance. Clearance of drugs in the gut was evaluated using the *in vitro* intrinsic clearance and the neonatal abundance of CYP3A4. 16, 21

The activity of CYP3A7 is notably higher at birth, however due to the minor role CYP3A plays in the metabolism of dolutegravir 23 and the paucity of data on the effects of CYP3A7, CYP3A7 expression was not included in the model.

***Ontogeny of CYP3A4 and UGT1A1***

Equations for CYP3A4 expression in neonates was calculated as a fraction of adult expression (Table S3). 21 A UGT1A1 ontogeny profile detailing the age-related changes in enzyme maturation elucidated by Miyagi *et al* 24 was digitalised using Plot Digitizer. From this, a polynomial equation describing the fraction of UGT1A1 present in neonates in relation to adult abundance was derived, where age is expressed in days.. The profile was adjusted during the qualification of raltegravir to better characterise UGT1A1 expression in neonates which yielded the following equation (Eq. 2).

UGT1A1 = (-5x10-10 x Age4) + (5x10-7 x Age3) – (0.0002 x Age2) + (0.0203 x Age) + 0.0305

(Eq. 2)

***Prediction of Hepatic Clearance from in vitro data***

Assuming the well-stirred model, hepatic clearance was estimated using the following equations. 20, 25, 26

CLinttotal = (ClintE x Abundance x MPPGL x WLiver)

(Eq. 3)

MPPGL (mg/g) = 101.407+0.0158 x Age - 0.00038 x Age2+0.0000024 x Age3

(Eq. 4)

Total Hepatic Clearance = (Qhv x fu x CLinth)/ (Qhv + CLinth x fu))

(Eq. 5)

Where CLinttotal, ClintE, Abundance, MPPGL, Qhv, fu and CLinth is the total intrinsic clearance of the enzyme(s) involved in metabolism of the drug, *in vitro* clearance of said enzyme(s), abundance of enzyme(s) in neonates, microsomal protein content per gram of liver, hepatic blood flow, fraction unbound of drug and the sum of all CLinttotal values, respectively.

***Dolutegravir clearance***

Due to the difficulty of approximating dolutegravir clearance from *in vitro* experiments, clearance was estimated via retrograde modelling from adult *in vivo* systemic clearance. The liver is the main site of dolutegravir metabolism 23. A large portion of dolutegravir (51%) is estimated to be conjugated into an ether glucuronide by UGT1A1 and approximately 21% is hydroxylated by CYP3A4. UGT1A3 and UGT1A9 are minor routes of elimination, owing to 2.8% and 5.5% of hepatic metabolism, respectively. 23 The remainder of the clearance (19.7%) is suggested to be undertaken by extrahepatic metabolism.23The fractions metabolised by each enzyme were incorporated in the final calculation of dolutegravir clearance. However, data on UGT1A3, UGT1A9 and extrahepatic enzyme expression were inadequate, hence the fraction metabolised by each were totalled and scaled allometrically (Eq. 6).

Clearance = (CLadult x 0.51 x UGT1A1) + (CLadult x 0.21 x CYP3A4) + (CLadult x 0.28)/70 x Weight)

(Eq. 6)

Where CLadult is the systemic clearance of dolutegravir in adults.

### **Distribution**

The volume of distribution was calculated using previously published equations. 27

### **Model Qualification and Simulations**

***Qualification***

Anatomical qualification has been summarised in Table S4 and S5.

As dolutegravir is predominantly metabolised by UGT1A1 and CYP3A4, 23 the PBPK model was validated using physicochemical and *in vitro* data (listed in Table 1) from the surrogate substrates: raltegravir and midazolam, which are metabolised by UGT1A1 and CYP3A4, respectively. Dolutegravir adult and infant clinical data were used for the qualification of the PBPK model.

***Clinical PK data in neonates***

Clinical PK data for midazolam was available in critically ill neonates with respiratory distress syndrome or neonatal infection. 28 The study involved administration of a 0.2 mg.kg-1 intravenous bolus of midazolam in neonates. The effect of the illness on the overall disposition of the drug could not be determined, however due to the lack of data available, it was used for the qualification of CYP3A4. Two cohorts of clinical data were available 29 for the qualification of UGT1A1 activity with raltegravir.

***Simulations***

Simulations were initially carried out for raltegravir and midazolam, in 100 virtual neonates. For raltegravir, the mean maximum plasma concentration (Cmax) and AUC were recorded for comparison against clinical data. For midazolam, the mean AUC, Cmax, trough plasma concentration (Ctrough) and CL values were recorded for comparison.

Each multiple dose strategy for dolutegravir was simulated in 100 healthy term neonates with the aim of achieving plasma exposure comparable to therapeutic levels observed in paediatric patients (Ctrough: 0.99 mg/L and AUC24: 50.1 mg.h/L). 30 Doses ranged from 2 - 5 mg with neonatal weight ranging from 3.0 – 4.5 kg in the model.

For further qualification of the dolutegravir PBPK model, simulations were performed in the adult PBPK model 31 and comparisons were made between clinical 15, 30 and predicted values. Infant PK was simulated by extrapolating from the neonatal PBPK model, for comparison against clinical values.

***Statistical evaluation of the model***

The PBPK model was qualified by calculating the absolute average fold error (AAFE) and root mean squared error (RMSE) where appropriate. AAFE is a useful parameter to assess over or under-prediction of the model, values closer to 1 indicate a closer similarity with observed values. The RMSE calculates the error between the predicted value and the observed value. The model was assumed to be qualified if the predicted values fell within the following criteria: with AAFE < 2 and RMSE < 1 as per convention for the approach.32

## **Results**

### **Model Qualification**

***Raltegravir***

Comparison between observed and simulated PK data of oral raltegravir has been outlined in Table S6. In Cohort 1, the predicted mean AUC12 and Cmax values are within 1.6-fold of observed data. The predicted mean AUC and Cmax values in Cohort 2 were on average within 1.25-fold of the observed data, and Ctrough values were within 1.8-fold of observed data with the simulated concentration-time profile yielding a RMSE value below 1 (Table S7 & Fig. S1).

***Midazolam***

Comparison of intravenous midazolam PK parameters have been detailed (Table S8), with mean simulated values of AUC, Cmax, Ctrough and CL, all within 1.4-fold of observed data.

As both drugs were in sensible agreement with literature values, the model was considered qualified.

**Model Predictions of Dolutegravir**

The qualification of dolutegravir in adults and infants is outlined in Tables 2 and 3, with mean simulated PK parameters falling within the 2-fold acceptance criteria.32

The qualified model predicted the exposure of dolutegravir in neonates, with doses ranging from 2-5 mg (summarised in Table 4 and Figure 1). The predictions indicate that a 5 mg dose may be suitable for neonates. Regimen 6 comprising a 5 mg dose with prolonged intervals between dosing resulted in AUCav and Ctrough values of 37.2 mg.h/L and 1.3 mg/L, respectively. These values are comparable to the paediatric target (AUC24: 50.1 mg.h/L and Ctrough: 0.99 mg/L).30

## **Discussion**

The benefits of initiating ARV therapy shortly after birth may include prevention of infection in at-risk infants and early viral suppression in those infants who are infected. 33 Breastfeeding increases the risk of infection in newborns but has enormous benefits for health and is recommended by WHO for at least the first six months of life. 34 In low- and middle-income countries, breastfeeding is favoured to avoid infant mortality from other life-threatening infections and initiating prophylaxis in breastfed neonates is encouraged for PMTCT. 35 There are only 5 ARVs with adequate neonatal PK and safety data and a formulation suitable for use in neonates, the need for more potent alternatives is essential for effective early treatment and prophylaxis.36 Dose optimisation in neonatal patients is complex and PBPK modelling may help inform knowledge gaps in the absence of empirical data. This is exemplified here with dose prediction for dolutegravir deployment in neonates.

The PBPK model was built incorporating neonatal anatomical and physiological maturation characteristics. Differential equations relating growth to age were derived from existing literature. 2, 17, 21 Some parameters remain underexplored in neonates, hindering the ability to mathematically represent their changes with growth and development. In the absence of such data, parameters from the previously published paediatric model 16 were utilised and assumed to be similar, including solubility, body composition, gastric and intestinal pH. For other parameters like small intestinal transit time, literature suggested there were no significant growth-related changes, thus adult values were implemented. 37 The lack of data on developmental changes in transporter expression make it inherently difficult to replicate this parameter *in silico* and so data on transporters was not included in the model. Although there are data available on the ontogeny of hepatic enzymes, a significant portion of these studies are routinely carried out on small samples with large gaps in different age groups. In some cases, there are only one or two samples in the neonatal age bracket, making it difficult to accurately characterise expression. For this reason, the UGT1A1 maturation profile was adjusted to adequately predict the PK of raltegravir; a probe substrate that allowed the fine-tuning of equations describing age-related maturation. UGT1A1 polymorphism is known to affect dolutegravir exposure,38 certain polymorphisms are responsible for reduced enzyme activity resulting in an increase in exposure. 38A previous study in adults concluded that this reduction in activity did not have a clinically significant impact on the exposure of dolutegravir,38 however this would need exploring further in neonates. The effect of CYP3A7 on dolutegravir has not yet been fully elucidated however CYPs play a minor role in the metabolism of dolutegravir hence was not included in the model.23

The *in vivo* clinical data used for the comparison between predicted and observed values were carried out in a small number of neonates. 28, 29 Qualification of neonatal PBPK models is challenging due to the underrepresentation of clinical PK data in this population. The few clinical studies that have been conducted in neonates have, often by necessity, several limitations from small sample sizes to restricted clinical and demographic detail due to ethical and logical constraints.

Though the presented model predicts the PK of dolutegravir it has some key limitations. Maternal transfer of drug through breast milk or placenta has not been considered by the model. Pregnant women with HIV infection are expected to start or already be receiving treatment which involves a combination of ARVs. A cause for concern in breastfed neonates is maternal transfer of these drugs. The dolutegravir transfer into breast milk in a mother-infant pair was previously estimated to be equal to a daily infant exposure of 0.015 mg/kg.39 Dolutegravir also readily crosses the placenta, therefore mothers receiving this treatment will be exposing neonates to dolutegravir with or without breastfeeding. 40 Based on our findings, the neonate’s first dose may be postponed until 24-48 hours after birth if the mother has received dolutegravir 2-24 hours prior to delivery.

Although dolutegravir exposure from breast milk was not considered in this study, the model does provide information on a range of parameters from absorption through to risk of concentration-dependent foetal toxicity. Several models have previously been published describing infant exposure via breast milk.41-44 The most recent involved a model to estimate isoniazid exposure in infants, a drug used in the first-line treatment of tuberculosis. 44 Two multi-compartment models were coupled together, one adult and one infant; a separate compartment for breast milk was incorporated into the model. Predictions generated from the model suggested infant isoniazid exposure was relatively low and would not result in any clinically significant adverse effects. While progress has been made in the development of these models, similar limitations, arise from the lack of knowledge on specific neonatal characteristics. A recently published review on PBPK modelling in neonates 8 highlighted the importance of cross-talk between modellers and clinicians to bridge the understanding of age-related changes. Clinical observations and modelling can be combined in an attempt to explicate the developmental changes observed in the first month of life, utilising the knowledge that cannot solely be gained from existing *in vitro* and *in vivo* methods. The integration of molecular and clinical approaches represents an ideal interdisciplinary framework for the enhancement of modelling and its translation to various clinical scenarios. 16, 20, 31, 41

Despite limitations, PBPK models are considered validated if predicted mean values lie within 2-fold of observed data.32 Clearly, in the absence of clinical data it was not possible to specifically qualify the presented neonatal dolutegravir model. However, the raltegravir and midazolam qualification does provide some confidence that the ontogeny profiles of CYP3A4 and UGT1A1 appropriately described expression in neonates. Observed differences between simulated and clinical drug concentrations (e.g Cmax and Tmax) can additionally be caused by the model limitations described above but will likely have limited clinical impact. A study evaluating the PK of dolutegravir in pregnant women and their infants reported the median elimination half-life in 21 infants as 32.8 hours, after in utero exposure. 40 Although infants did not directly receive dolutegravir, the half-life provides information on the elimination kinetics of dolutegravir in the first days of life. The simulations generated by our neonatal PBPK model are in keeping with this value with predictions of half-life within 20% of observed data (Table 4). The PK, efficacy and safety of dolutegravir in HIV-infected infants and children aged ≥ 4 weeks to < 6 years was previously investigated. 15 Within this study, 10 subjects were aged between 4 weeks and 6 months receiving a once daily 5 mg dispersible tablet, with the same dose simulated *in silico*. In the absence of a PBPK model for infants, predictions were carried out by extrapolating from the existing neonatal model. To minimise the difference between subpopulations, extrapolations were taken between weeks 4-5. Though the simulated data of dolutegravir in infants were close to the clinical values (within 2-fold), there was a trend to overestimate clearance, resulting in lower mean AUC values. The simulations for dolutegravir were carried out over a 28-day period for several multiple dose regimens outlined in table 4, with a maximum dose of 5 mg set by the adequate AUC and Ctrough values achieved clinically in infants. From the fixed-dose (regimens 1-3) concentration-time profiles, a steady increase in plasma concentrations of dolutegravir is observed during the first week of life, reaching maximum concentrations on day 7 (Fig. 1); this may partly be explained by the immaturity of enzymes. Based on this prediction, a greater initial dose may be needed if the goal is to reach therapeutic concentrations within the first hours of life.

It is also worth noting that the smallest dose formulation currently available for dolutegravir is a 5 mg dispersible tablet, however, administering 5 mg of dolutegravir daily (regimen 1) may lead to over-dosing. Regimens 4-6 propose alternative strategies to accommodate for the formulation restrictions that currently surround dolutegravir. Based on the simulated data, introducing a longer interval between dosing could pose a solution; regimen 6 involved 5 mg doses with a 48h interval from day 1-20 escalated to 5 mg once daily on week 4, yielding AUC and Ctrough values of 37.2 mg.h/L and 1.3 mg/L, respectively (Table 4). These values fall within the target criteria and are comparable to the clinical paediatric exposure.

With the previously stated formulation limitations, an advantage of PBPK modelling is its ability to simulate the PK of novel formulations. 31 Large dose adjustments are commonly observed between adult and paediatric patients, a more robust formulation approach would prove invaluable as drug approval in neonates and infants is often hindered by a lack of suitable formulations. PBPK modelling can be used to evaluate and help direct development of alternative formulations appropriate for use in paediatric patients.

## **Conclusion**

Clinical trials in neonates are difficult to conduct and the risk involved may be reduced by advanced mathematical dose prediction based on PBPK modelling. The presented simulations indicate that a 5mg dose every 48 hours for the first 3 weeks followed by daily dosing during the 4th week may be suitable for prophylaxis or treatment of HIV. These predictions can be used to inform neonatal clinical trials to help accelerate dose optimisation in this population.

**Acknowledgements**

This work has been presented at Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 2019 (Poster 827).

**Funding source**

This work was internally funded by the University of Liverpool.

**Transparency declarations**

Prof. Owen reports grants from Merck, personal fees from Merck, grants from ViiV Healthcare, personal fees from ViiV Healthcare, grants from Janssen, non-financial support from Janssen, grants from AstraZeneca, outside the submitted work; In addition, Prof. Owen has a patent drug delivery issued, and a patent drug delivery pending. Dr. Siccardi reports grants from ViiV Healthcare, grants from Janssen, outside the submitted work. Prof. Mirochnick receives research support from ViiV Healthcare, Gilead Sciences and Merck & Co, outside the submitted work. All other authors: none to declare.

**Author contributions**

All authors contributed to the overall concept, design, and choice of the drugs to be tested. FB performed the modelling and analysis. FB and MS wrote the manuscript with support from RR, AO and MM. All authors reviewed and contributed to the final manuscript.

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Property | Dolutegravir 45 | Raltegravir 46 | Midazolam 21 | |
| Molecular weight, g/mol | 419.4 | 445.2 | 325.8 | |
| Log Po:w | 2.2 | 0.58 | 3.89 | |
| fu | 0.011 | 0.17 | 0.034 | |
| pKa | 8.20 | 6.67 | 6.57 | |
| R | 0.535 31 | 0.60 | 0.55 | |
| Polar surface area, Å2 | 99.2 | 150 | 30.2 | |
| Hydrogen bond donors | 2 | 3 | 0 | |
| Caco-2 permeability, 10-6 cm/sec | 40.17 47 | 6.6 | 32.4 26 | |
| Clearance | 0.776A 48 | NA | NA | |
| CLint CYP3A4 | NA | NA | 3.75 | |
| CLint UGT1A1 | NA | 12.4 | NA |
| Solubility, mg/L | 95 | 70000 49 | 0.134 26 |

**Tables**

Table 1 Physicochemical and in vitro data of dolutegravir, raltegravir and midazolam.

Abbreviations: A, L/h; CLint, intrinsic clearance; CYP, cytochrome P450 (µL/minute/pmol); log Po:w, partition coefficient between octanol and water; NA, not applicable; pKa, logarithmic value of the dissociation constant; R, blood-to-plasma drug ratio; UGT, uridine diphosphate glucuronosyltransferase (µL/minute/106).

|  |  |  |  |
| --- | --- | --- | --- |
| Dolutegravir Adult Qualification | | | |
|  | Clinical\* | Simulated Mean ± SD (%CV) | AAFE |
| AUC (mg.h/L) | 53.6 (27) | 54 ± 14.02 (26) | 1.311 |
| Cmax (mg/L) | 3.67 (20) | 2.8 ± 0.69 (25) | 1.007 |
| Ctrough (mg/L) | 1.11 (46) | 1.62 ± 0.43 (27) | 1.462 |
| CL (L/h) | 0.776 | 0.793 ± 0.17 | 1.022 |

Table 2 Comparison of dolutegravir PK in adults between simulated and observed values

Abbreviations: \*Geometric Mean (%CV); AUC, area under curve over 24 hours, Cmax, maximum plasma concentration, Ctrough, minimum plasma concentration, CL, clearance.

|  |  |  |  |
| --- | --- | --- | --- |
| Dolutegravir Infant Qualification | | | |
|  | Clinical\* | Simulated Mean ± SD (%CV) | AAFE |
| AUC (mg.h/L) | 61 (44) | 38.58 ± 15.93 (41) | 1.581 |
| Ctrough (mg/L) | 1.2 (55) | 1.25 ± 0.60 (48) | 1.040 |

Table 3 Comparison of dolutegravir PK in infants between simulated and observed values

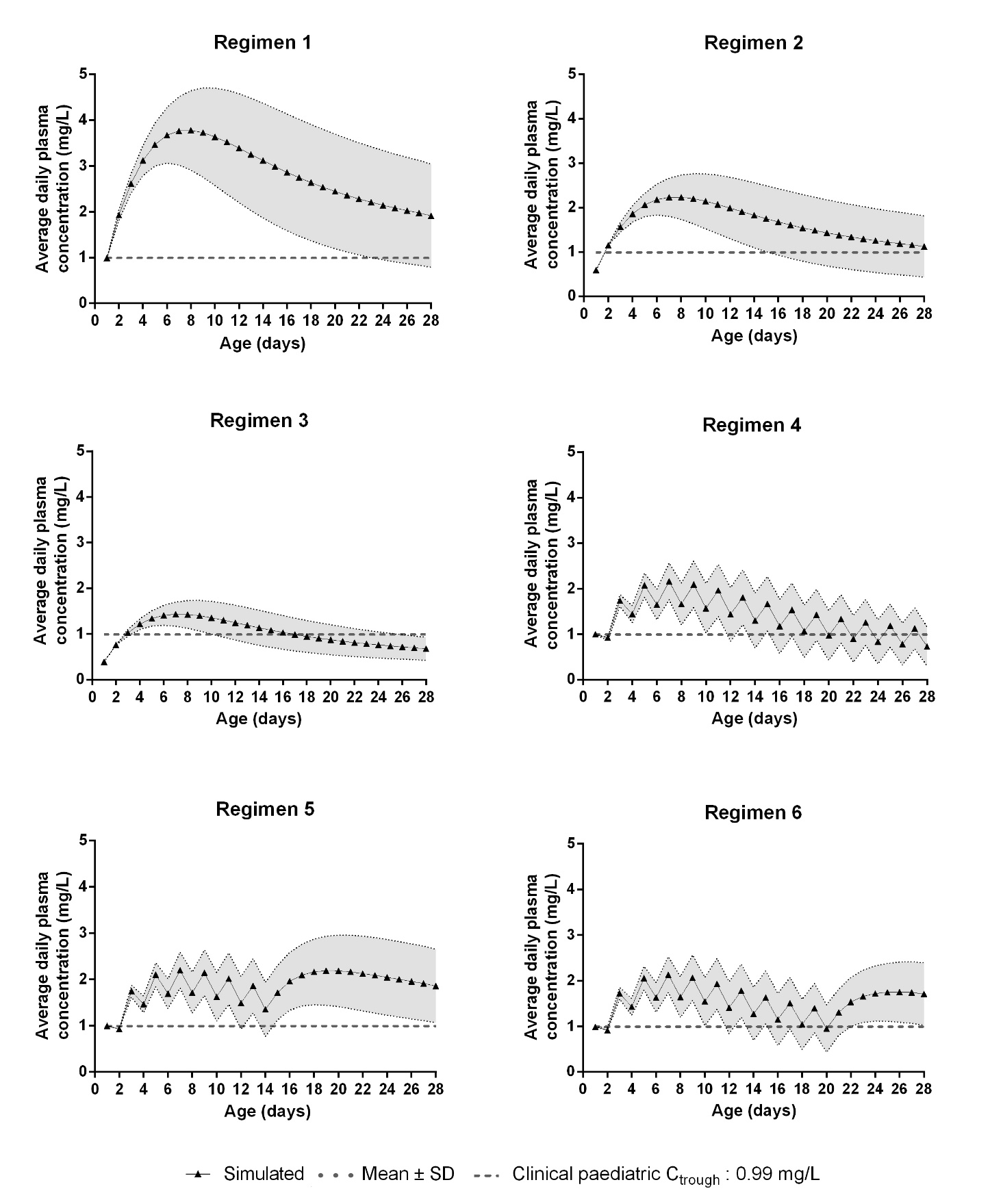
Abbreviations: \*Geometric Mean (%CV); AUC, area under curve over 24 hours, Ctrough, minimum plasma concentration.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Regimen** | **Total Dose** | **Dose\* (mg/kg)** | **Cmax1**  **(mg/L)** | **AUCav**  **(mg.h/L)** | **Cmax2**  **(mg/L)** | **AUC**  **(mg.h/L)** | **Ctrough**  **(mg/L)** | **T1/2**  **(h)** |
| 1 | 5 mg Q24h | 1.4  (1.7 - 1.1) | 4.0 ± 1.1 | 66.1 ± 22.9 | 2.3 ± 1.1 | 42.9 ± 18.9 | 1.6 ± 1.1 | 34.3 |
| 2 | 3 mg Q24h | 0.85  (1 - 0.7) | 2.4 ± 0.6 | 35.2 ± 13.4 | 1.3 ± 0.7 | 28.2 ± 19.3 | 0.9 ± 0.7 | 33.6 |
| 3 | 2 mg Q24h | 0.55  (0.7 - 0.4) | 1.6 ± 0.3 | 23.5 ± 6.6 | 0.8 ± 0.3 | 17.6 ± 8.1 | 0.5 ± 0.2 | 31.4 |
| 4 | 5 mg Q48h | 1.4  (1.7 - 1.1) | 2.5 ± 0.4 | 33.3 ± 10.7 | 1.4 ± 0.4 | 25.1 ± 17.0 | 0.6 ± 0.4 | 33.1 |
| 5 | Day 1-13 = 5 mg Q48h,  Day 14-28 = 5 mg Q24h | 1.4  (1.7 - 1.1) | 2.7 ± 0.7 | 44.4 ± 13.3 | 2.3 ± 0.8 | 42.6 ± 26.9 | 1.5 ± 0.8 | 36.4 |
| 6 | Day 1-20 = 5 mg Q48h,  Day 21-28 = 5 mg Q24h | 1.4  (1.7 - 1.1) | 2.5 ± 0.5 | 37.2 ± 11.3 | 2.1 ± 0.7 | 38.1 ± 14.3 | 1.3 ± 0.7 | 37.2 |

Table 4 Predicted PK of orally administered dolutegravir multiple dosing regimens in neonates

\*Median (Range), neonate weight range in the model is 3.0 - 4.5 kg. Cmax1, Average maximum plasma concentration over 28-day simulations; Cmax2, Maximum plasma concentration after final dose has been administered; AUCav, Average area under curve over 28-day simulations; AUC, Area under curve after final dose; Ctrough, Minimum plasma concentration after final dose; T1/2, Half-life.

**Figures**



**Figure 1 Average daily concentration-time profiles of dolutegravir multiple dosing regimens in neonates. Solid lines represent simulated data, dotted lines represent simulated mean ± standard deviation and dashed lines represent paediatric clinical Ctrough value.**