Title: Population Pharmacokinetic Modelling of Twice Daily 50mg Dolutegravir in Children with Tuberculosis and HIV during Rifampicin Co-administration

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Introduction: The World Health Organization (WHO) recommends a dolutegravir-based regimen for first-line antiretroviral treatment (ART), with ART initiated during tuberculosis treatment for children older than 4 weeks (1). Dolutegravir is primarily metabolised by hepatic uridine glucuronosyltransferase 1A1 (UGT1A1), with minor contribution of CYP3A4 (2). Treatment of drug-susceptible tuberculosis includes rifampicin, a potent inducer of UGT1A1, CYP3A4, and other metabolising enzymes, thus leading to drug-drug interactions with dolutegravir (3). Hence, when co-administered with rifampicin, the 50 mg once daily (QD) dolutegravir dose is increased to 50 mg twice daily (BID), to ensure therapeutic exposure, as per WHO recommendation, despite the limited pharmacokinetic and safety data in children to support this guidance. This analysis aims to describe the pharmacokinetic profile of dolutegravir in children with tuberculosis and HIV, with or without rifampicin co-treatment.

Methods: An ongoing prospective open-label, sequential non-randomised study recruited children weighing 20-35kg with tuberculosis and HIV (ORCHID, NCT04746547). Study participants received a rifampicin-based tuberculosis regimen with 50 mg dolutegravir BID for 6 months, followed by 50 mg dolutegravir QD beginning 2 weeks after stopping rifampicin. Both doses were given on an empty stomach and plasma samples for dolutegravir quantification were collected on week 8 after starting rifampicin, and 2 weeks after discontinuing rifampicin, at pre-dose and at 1, 2, 3, 4, 6, and 12 or 24 h post-dose. Plasma samples were assayed with a validated LC-MS/MS method. Population pharmacokinetic models were fitted using FOCE-I in NONMEM v7.5.0. We tested one- and two-compartment models with first-order elimination and absorption with and without lag in absorption or transit compartments. Either weight or fat-free mass (4) was used to allometrically scale clearance and volume of distribution with fixed exponent of 0.75 and 1, respectively. The effect of rifampicin on dolutegravir pharmacokinetics was tested on dolutegravir clearance, volume of distribution, and bioavailability.

Results: Data from 12 children were included in this preliminary analysis, contributing 12 profiles for dolutegravir with rifampicin and 2 profiles on dolutegravir alone. Study participants had a median

(range) age and weight of 10.0 (6.00–13.1) years and 24.9 (20.6–35.1) kg, respectively. 112 dolutegravir plasma concentrations were included. The data were best described using a one-compartment model, allometrically scaled with fat-free mass, and first-order absorption with lag. The typical 19.7 kg fat-free mass child was estimated to have a clearance of 0.557 L/h and a volume of distribution of 6.63 L. Between-subject variability (BSV) was included on clearance, while between-occasion variability was included on bioavailability, absorption rate constant, and lag time. Co-administration of rifampicin resulted in a 104% increase in clearance ($p < 0.001$).

Conclusion: In this preliminary analysis, we report a 104% increase in clearance, when on rifampicin. This is in line with a previous report by Kawuma et al. (3), who reported a 143% increase in dolutegravir clearance when on rifampicin in healthy adults. After adjusting for body size, our typical value of dolutegravir clearance without rifampicin, 0.577 L/h, was in line with 0.474 L/h from Kawuma et al. (3), 0.479 L/h from Parant et al. (5), 0.662 L/h from Barcelo et al. (6), and 0.573 L/h from Zhang et al. (7). These data support the use of dolutegravir 50 mg twice daily among children weighing 20-35 kg with HIV-associated tuberculosis. Our next step is to perform clinical trial simulations to inform on the dolutegravir exposure in younger and smaller children and subsequently study it in this vulnerable population.

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