Population pharmacokinetic and pharmacodynamic modelling to improve tuberculosis treatment

By

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“Where is the wisdom we have lost in knowledge?

Where is the knowledge we have lost in information?”

TS Eliot – The Rock

My mom, this is for you.

CONTRIBUTIONS TO THE FIELD

This thesis includes some of the following contributions to the field of pharmacometrics and clinical pharmacology:

Full length original articles

1. **Abdelwahab, M. T**., Leisegang, R., Dooley, K. E., Mathad, J. S., Wiesner, L., McIlleron, H., Martinson, N., Waja, Z., Letutu, M., Chaisson, R. E., & Denti, P. (2020). Population Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Pregnant South African Women with Tuberculosis and HIV. Antimicrobial Agents and Chemotherapy, 64(3), 1774–1780. https://doi.org/10.1128/AAC.01978-19

2. Ignatius, E. H., **Abdelwahab, M. T**., Hendricks, B., Gupte, N., Narunsky, K., Wiesner, L., Barnes, G., Dawson, R., Dooley, K. E., & Denti, P. (2020). Pretomanid Pharmacokinetics in the Presence of Rifamycins: interim Results from a Randomised Trial among Patients with Tuberculosis. Antimicrobial Agents and Chemotherapy, AAC.01196-20. https://doi.org/10.1128/AAC.01196-20

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5. **Abdelwahab, M. T**., Wasserman, S., Brust, J. C. M., Dheda, K., Wiesner, L., Maartens, G., & Denti, P. Linezolid population pharmacokinetics in South African patients with drug-resistant tuberculosis. *In manuscript format*

Scientific conference presentations

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2. Poster: **Abdelwahab, M. T**, Ignatius E, Denti P, Dooley KE, Gupte N, Dawson R, Barnes G, Narunsky K, Hendricks B. Effect of rifamycins on pretomanid exposure in patients with pulmonary TB. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI) conference, Boston, Massachusetts, 2020. Abstract 3688

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DECLARATION OF WORK

I, Mahmoud Tareq Abdelwahab, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. Chapters three, four, five, six and seven of the thesis have been published in an international journal and contents remain unchanged from the printed versions excepted where formatting was required to maintain consistency in the thesis. All co-authors gave their written consent to include the publications as part of a PhD.

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ABSTRACT

Population pharmacokinetic and pharmacodynamic modelling to improve tuberculosis treatment

Mahmoud Tareq Abdelwahab (2021)

Tuberculosis continues to claim millions of lives each year despite enormous efforts to control the epidemic over the past century. It remains the leading cause of death worldwide from a curable infectious disease. Tuberculosis is a significant cause of maternal mortality and morbidity, but little is known about the effect of pregnancy on anti-TB drugs concentrations. A critical challenge to the global efforts to control the tuberculosis epidemic is the spreading of drug resistance to first-line tuberculosis drugs. The treatment of drug-resistant tuberculosis relies on both new anti-tuberculosis agents such as bedaquiline, delamanid, and pretomanid and repurposed drugs, such as linezolid and clofazimine.

In this thesis, we employed nonlinear mixed-effects modelling to evaluate the pharmacokinetics of first-line tuberculosis drugs isoniazid, pyrazinamide, and ethambutol in pregnancy. We assessed the pharmacokinetics and pharmacodynamics of pretomanid, clofazimine, and linezolid in African tuberculosis patients.

Reassuringly, we found no significant pregnancy effect on the exposure of these anti-tuberculosis agents, thus confirming the suitability of current doses in pregnancy. For pretomanid, we found that in spite of exposure being reduced by 44% with rifampicin co-administration, the drug levels were within the efficacy range observed in previous trials, provided that pretomanid doses are administered with food. Clofazimine exposure was found to accumulate more slowly in women, an effect driven by sex-related differences in the proportion of body fat. We characterised the effect of clofazimine concentration on QT interval prolongation. We investigated alternative dosing regimen to optimise clofazimine treatment and suggested that a 2-week loading dose may support treatment shortening by safely enabling more rapid attainment of efficacy targets. For linezolid model, we characterised population pharmacokinetic parameters in African tuberculosis patients, assessed probability of target attainment and related toxicity following different doses administration. We showed that population modelling could maximize information from collected data, and have a significant impact on advancing patients care especially in places with limited resources.

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Abbreviations and acronyms

AcINH Acetyl-isoniazid

AIC Akaike Information Criterion

ALT Alanine Aminotransferase

ART Antiretroviral Therapy

AST Aspartate transaminase

$AUC_{0–24}$ 24-hour area under the concentration-time curve

BLQ Below the Limit of Quantification

BOV Between-Occasion Variability

CI Confidence Interval

CL Clearance

CLH Hepatic clearance

CLint Intrinsic clearance

CLint,max Maximum Intrinsic clearance

Cmax Maximum plasma concentration

Cmin Minimum plasma concentration

DR-TB Drug resistant tuberculosis

EH Hepatic extraction

F Oral bioavailability

FDC Fixed Dose Combination

FFM Fat-Free Mass

FOCE-I First-Order Conditional Estimation with eta-epsilon Interaction

Fprehep Prehepatic oral bioavailability

Fu Unbound fraction

GOF Goodness of Fit

HAART Highly Active Antiretroviral Therapy

HIV Human Immunodeficiency Virus

Ka Absorption rate constant

Km Michaelis-menten constant

K transit Absorption intercompartment transfer rate

LLOQ Lower Limit of Quantification

MTT Mean Transit Time

NCA Noncompartmental Analysis

NN Number of absorption transit compartments

OFV Objective Function Value

PD Pharmacodynamics

PK Pharmacokinetics

PK-PD Pharmacokinetics-pharmacodynamics

P-pg P-glycoprotein

PsN Perl-speaks-NONMEM

PXR Pregnane X receptor

PTA probability of target attainment

Q Intercompartmental clearance

QH Hepatic plasma flow

SIR Sampling Importance Resampling

TB Tuberculosis

TBW Total Body Weight

Tmax Time to maximum plasma concentration

V Volume of distribution

VC Volume of distribution of the central compartment

VH Volume of distribution of the liver

VP Volume of distribution of the peripheral compartment

VPC Visual Predictive Check

WHO World Health Organization

XDR-TB extensive Drug resistant tuberculosis

Chapter 1:Introduction and literature review

1.1 Global burden of tuberculosis

Tuberculosis continues to claim millions of lives each year despite the enormous efforts to control the disease over the past century. Tuberculosis is a disease of poverty and economic distress. Patients are often faced with stigma and marginalisation, especially in developing countries. In 2019, there was an estimated 10 million new tuberculosis cases and an estimated 1.2 million tuberculosis deaths in HIV negative patients with additional 208,000 tuberculosis death in HIV positive patients (World Health Organization, 2020a). Geographically, most tuberculosis cases in 2019 were in South-East Asia (44%), Africa (25%) and the Western Pacific (18%), with a smaller percentage scattered across the rest of the world (World Health Organization, 2020a). Furthermore, tuberculosis is the leading HIV-associated opportunistic infection and the main cause of death, particularly in resource-limited countries (Letang *et al.*, 2020).

1.2 Tuberculosis burden in pregnancy

Tuberculosis prevalence is high in developed and under-developed countries especially in young adults (Shiu *et al.*, 2020); women accounted for 32% of tuberculosis cases in 2019 (World Health Organization, 2020a). Tuberculosis is a significant cause of maternal mortality and among the leading causes of death in women of child-bearing age in settings with high tuberculosis burden (Loto *et al.*, 2012). It is estimated that the prevalence of active tuberculosis in pregnant women reaches up to 8% in high-burden countries (Mathad *et al.*, 2012). It was also reported that the prevalence of latent tuberculosis cases in pregnancy was up to 34% in India among HIV-negative pregnant women (Mathad *et al.*, 2012) and up to 49% in HIV-positive women in South Africa (Nachega *et al.*, 2003).

1.2.1 Physiological changes during pregnancy

Many physiologic changes during pregnancy could significantly affect drugs' pharmacokinetics.

1.2.1.1 Absorption

Some of the physiologic changes that could affect drug absorption include delayed gastric emptying and intestinal passage prolongation. Gastric acid secretion is reduced, and mucus secretion increases, resulting in a higher pH in the stomach (Anderson, 2005). Nausea and vomiting especially in the first trimester affect adherence and reduction in drug amount available for absorption (Chaphekar *et al.*, 2020; Hazenberg *et al.*, 2021).

1.2.1.2 Distribution

During pregnancy, the volume of total body fluid increases, plasma proteins including albumin and α-1 acid glycoprotein decrease, which could cause the volume of distribution of drugs to become larger. Additionally, there is also an elevated amount of fat, higher cardiac output and faster heart rate, all of which could affect drug distribution (Pavek *et al.*, 2009).

1.2.1.3 Metabolism

The activity of some cytochrome P450 metabolising enzymes (CYP3A4, CYP2D6, CYP2C9, and CYP2A6) and uridine diphosphate glucuronosyltransferase (UGT) isoenzymes (UGT1A4 and UGT2B7) is higher. On the other hand, the activity of some others, such as CYP1A2 and CYP2C19 are reduced. Lastly, Pregnancy has been associated with suppressed cell-mediated immunity. (Weinberg, 1984)

1.2.1.4 Elimination and Excretion

The hepatic blood flow is increased during pregnancy resulting in increased elimination of drugs with high hepatic extraction ratio.(Hazenberg *et al.*, 2021) There is also an increase in renal

blood flow (60 to 80%) and higher glomerular filtration rate (by 50%) causing increased elimination of renally excreted drugs. (Davison *et al.*, 1980)

1.3 Global MDR-TB burden

The occurrence of drug resistance to tuberculosis medications poses critical challenges to global efforts to manage and cure tuberculosis. Resistance to both rifampicin and isoniazid is defined as multidrug-resistance tuberculosis (MDR-TB) and additional resistance to any fluoroquinolone, and at least one additional Group A drug (bedaquiline and linezolid) is defined as extensively drug-resistant TB (XDR TB) (Lobue, 2009; World Health Organization, 2020b). Patients acquire drug-resistant TB either by infection with a drug-resistant strain (primary resistance) or by developing resistance throughout treatment (acquired resistance) due to subtherapeutic drug concentrations or non-adherence to medication regimens (Dheda *et al.*, 2017; Dousa *et al.*, 2020). Approximately 20% of tuberculosis isolates are reported to be resistant to at least one major first-line TB drug, group A or B (clofazimine, cycloserine/terizidone) of second-line TB drugs, and approximability 10% are resistant to isoniazid (Dheda *et al.*, 2017). In 2019, there were half a million people with rifampicin-resistant TB (RR-TB), 78% of which were multidrug-resistant TB (MDR-TB) (World Health Organization, 2020a). DR-TB is associated with high morbidity and mortality and accounts for 20% of the global tuberculosis mortality. The MDR-TB mortality rate is estimated to be at 40% and at 60% in the case of XDR-TB (Dheda *et al.*, 2017).

1.4 Tuberculosis pathogenesis

Tuberculosis is caused by infection with *Mycobacterium tuberculosis*, a member of *Mycobacterium tuberculosis* complex (MTBC), which is a group of genetically similar, slow-growing, non-spore-forming, aerobic, non-motile Gram-positive and acid-fast bacilli. MTBC contains *Mycobacterium tuberculosis, Mycobacterium canettii, Mycobacterium africanum,*

Mycobacterium microti, Mycobacterium bovis, Mycobacterium caprae and Mycobacterium pinnipedii (Kanabalan *et al.*, 2021). the MTCB is a member of the genus *Mycobacterium*, which is characterised by complex cell wall envelope responsible for their remarkable low permeability and the characteristic Ziehl-Neelsen acid-fast staining procedure (Forrellad *et al.*, 2013). Tuberculosis affects every organ in the human body but primarily resides in the lung, causing pulmonary tuberculosis, accounting for 80% of all tuberculosis cases (Loto *et al.*, 2012; Forrellad *et al.*, 2013). The infection starts with the inhalation of airborne particles containing bacilli-droplet nuclei of *M.tb*. Once inside the lung, it will pass through the alveoli. The human immune system utilises alveolar macrophages and other phagocytic immune cells to engulf the invading bacilli (Kanabalan *et al.*, 2021). While acting as a first-line of defence against the mycobacteria, this process provides a proliferating environment for the bacteria to replicate intracellularly (Dannenberg, 1989; Ahmad, 2011), mainly due to *M.tb*'s ability to inhibit autophagy, acquisition of cytosol access, and neutralisation of toxic components (Lerner *et al.*, 2015), which aids in initiating the early stage of tuberculosis infection (Kanabalan *et al.*, 2021). These bacteria-ridden macrophages can be transported to extrapulmonary tissues and neighbouring lymph nodes via blood and lymphatic circulation (Guirado *et al.*, 2013). As a response, the immune system develops an adaptive response (Van Crevel *et al.*, 2002) which relies on the interaction between different immune cells, namely dendric cells and $CD4^+$ T cells (de Martino *et al.*, 2019), which - if effective- will prevent further tubercle bacilli multiplication (Ahmad, 2011). The innate immune system response (macrophages) and activation of adaptive cell-mediated immune response will result in phagosome-lysosome fusion and production of various cytokines, which will enhance the antimicrobial response against the invading bacilli (Palucci *et al.*, 2018; Kanabalan *et al.*, 2021). However, it can result in a hyper-inflammatory response leading to lung

tissue damage indicating active tuberculosis infection (Zumla *et al.*, 2015). The hallmark of *M.tb* infection is granulomas (Kanabalan *et al.*, 2021). Granulomas are compact, organised immunological structures filled with infected macrophages and other immune cells (Kumar, 2016). These granulomas provide an additional protective mechanism against *M.tb*, as they restrict mycobacterial dissemination and limit tissue damage at the infection site (Saunders *et al.*, 1999; Ramakrishnan, 2012).

Mycobacterium tuberculosis has a rather unique and dynamic cell envelope capable of modulating host-immune response (Dulberger *et al.*, 2020). The outer membrane is composed of long-chain and branched fatty acids (Favrot *et al.*, 2012). Structurally, the mycobacterial cell envelope is composed of three macromolecules bonded covalently. These macromolecules or layers are called peptidoglycan, arabinogalactan and mycolic acid and are referred to as mycolyl-arabinogalactan- peptidoglycan complex (mAGP) (Alderwick *et al.*, 2015). Additionally, there are free glycolipids which are an important component of the cell wall as they interact with the mycoloyl moiety of mAGP and form a bilayer acting as a formidable permeation barrier, thus limiting drug penetration into the bacilli, in addition to the drug-efflux pump embedded in the cell wall that hinders drugs from reaching therapeutic concentration (Nikaido, 2001; Favrot *et al.*, 2012). Furthermore, *M.tb* is capable of developing resistance to various antimicrobial agents, either by acquiring resistance to specific agents (acquired antibiotic resistance) or by utilising its array of intrinsic resistance mechanisms (intrinsic resistance). Acquired resistance mainly occur due to chromosomal mutation caused by the selective pressure of antibiotic use (Smith *et al.*, 2013).

1.5 Tuberculosis treatment

The current recommended treatment regimen for drug-susceptible TB is a six-month regimen, with an intensive treatment phase for 2 months where rifampicin, isoniazid, pyrazinamide and ethambutol are administered as a fixed-dose combination, followed by 4 months of continuation phase where only rifampicin and isoniazid are administered. The four drugs are administered based on weight bands targeting the following mg/kg doses: rifampicin (8 to 12 mg/kg), isoniazid (4 to 6 mg/kg), pyrazinamide (20 to 30 mg/kg), and ethambutol (15 to 25 mg/kg) of total body weight (World Health Organization, 2017). In case of pregnancy, WHO, the British Thoracic Society, and International Union Against Tuberculosis and Lung Disease recommend the use of the same treatment regimen of first-line TB drugs as in non-pregnant women (Loto *et al.*, 2012).

In the case of drug-resistant tuberculosis, WHO recommends the use of a longer more complex treatment regimens (9 to 12 month and sometimes 18 to 20 months). These regimens consist of second-line TB drugs alone or in combination with first-line TB drugs based on drug-susceptibility testing and tuberculosis diagnosis (World Health Organization, 2019b, 2020b). Second-line TB drugs that are used include many anti-infective agents, but the main ones are bedaquiline and delamanid (novel new agents) and the repurposed drugs of linezolid, clofazimine, and carbapenems (Dousa *et al.*, 2020; World Health Organization, 2020b).

1.6 Safety of tuberculosis treatment

Tuberculosis treatment, especially for DR-TB, relies on a combination of multiple drugs in complex dosing regimens. However, limited information is available on the possible interactions and combined toxicity of these drugs (Akkerman *et al.*, 2019). The newly approved drugs against DR-TB, bedaquiline and delamanid, have been reported to affect cardiac electrophysiology via prolonging QT interval (Pontali *et al.*, 2017, 2018; Cohen *et al.*, 2019). The QT interval

represents cardiac depolarisation and repolarisation (contraction and relaxation) (Postema *et al.*, 2014) and for that reason, QT interval is usually monitored during routine cardiac safety procedures (Pontali *et al.*, 2017). Prolonged QT interval predisposes the patients to polymorphic ventricular tachycardia, known as *torsades de points* (TdP) (Dessertenne, 1966) which can degenerate to ventricular fibrillation resulting in sudden cardiac death (Del Rosario *et al.*, 2010). Dooley et al. (Dooley *et al.*, 2021). recently reported a modest effect of bedaquiline and delamanid on QT. However, due to the multidrug nature of tuberculosis treatment with other drugs with established QT-prolonging effects, there is an increased risk of adverse events and additive toxicity. Clofazimine and fluoroquinolones, drugs with a crucial role in drug-resistance tuberculosis treatment, have been linked to QT interval prolongation as well (Choudhri *et al.*, 1995; Amankwa *et al.*, 2004).

1.7 Pharmacology of tuberculosis drugs discussed in the thesis

1.7.1 Isoniazid

Isoniazid (isonicotinic acid hydrazide, INH; PubChem ID 3767) is a synthetic derivative of nicotinic acid. INH is a cornerstone of first-line TB drug.

Isoniazid is a prodrug that gets activated upon diffusion into *M.tb* by the action of KatG-encoded catalase-peroxidase enzyme into INH-NAD^+ adduct (Singh *et al.*, 2010). The transformed INH-NAD^+ competitively inhibit the inhA-encoded carrier protein reductase involved in the fatty acid synthesis, a critical step in cell wall production (Slayden *et al.*, 2000; Nguyen *et al.*, 2002; Jena *et al.*, 2014).

The daily oral dose is (4-6 mg/kg) for drug-sensitive TB (Erwin *et al.*, 2019). Food decreases INH absorption and bioavailability (Zent *et al.*, 1995; Kumar *et al.*, 2017) while antacids intake

was found to have a minimal effect on INH speed and extent of absorption (Hurwitz *et al.*, 1974). Peak plasma concentration usually occurs between 1 - 3 hours post-dose.

The drug is metabolised to acetyl-isoniazid by the action of N-acetyltransferases enzymes (mainly NAT2 isoenzyme) (Erwin *et al.*, 2019). NAT2 is a polymorphic enzyme found mainly in the liver and small intestine. Genetic variability and mutation in gene encoding NAT2 enzyme result in different isoniazid acetylation rate and drug levels (Perwitasari *et al.*, 2015). Depending on the INH acetylation rate, patients are generally characterised into three main NAT2 phenotypes: fast, intermediate and slow (Deguchi *et al.*, 1990; Parkin *et al.*, 1997). Rapid acetylators metabolise INH five to six times more rapidly than slow acetylators (Weber *et al.*, 1979). The polymorphisms in NAT2 account for the large variability observed in isoniazid clearance (Kinzig-Schippers *et al.*, 2005).

Approximately 80% of INH metabolites are excreted in the urine, less than 10% in faeces and to a lesser extent in breast milk (Holdiness, 1984; Tostmann *et al.*, 2008; Erwin *et al.*, 2019).

Hepatic metabolism of INH produces hydrazine derivatives which are involved in the pathogenesis of INH-induced hepatitis. INH administration has also been associated with peripheral neuropathy by interfering with the bioactivation pathway of pyridoxine(Vitamin B6), which is an important cofactor for many reactions.(Middlebrook, 1958)

1.7.2 Pyrazinamide

Pyrazinamide (PZA) has an integral role in tuberculosis treatment. The drug was first synthesised in 1932 (Zhang *et al.*, 2014). However, its activity against tuberculosis was discovered in 1952 following the experiments done against *M.tb* in mouse models on nicotinamide analogues (Yeager *et al.*, 1952).

Due to the higher rate of hepatotoxicity caused by high drug doses, it was mainly used against MDR-TB or relapsed tuberculosis treatment. The studies performed by McDermott and the British medical research council MRC (Fox *et al.*, 1999) found that PZA has high sterilising activity, almost as effective as rifampicin. These studies showed that tuberculosis treatment containing PZA could be shortened from 12 months to 6- 9 months. Currently, PZA forms with rifampicin and INH the basis for the short 6-months tuberculosis treatment (World Health Organization, 2017).

PZA is a prodrug activated by pyrazinidase/nicotinamidase enzyme in the *M.tb* to the pyrazinoic acid (Zhang *et al.*, 2014). Once activated, pyrazinoic acid will accumulate within the *M.tb* cell causing cytoplasmic acidification and inhibiting various essential enzymes within the *M.tb* cell. PZA is primarily active against non-growing persisters *M.tb* bacteria (Mitchison, 1985).

The drug is readily absorbed and reaches maximum concentration in less than an hour with a short distribution phase and a terminal half-life of 9 hours (Holdiness, 1984; Lacroix *et al.*, 1989). Food has minimal effect on the drug bioavailability; however, the absorption is delayed when given with a high-fat meal (Peloquin *et al.*, 1998).

The drug is metabolised to pyrazionic acid (POA) by the action of microsomal deamidase enzyme, then further metabolised by xanthine oxidase enzyme (Weiner *et al.*, 1972; Lacroix *et al.*, 1989). Only 4% of the drug is excreted unchanged via bile, and up to 30% excreted as pyrzionoic acid (Ellard, 1969).

The major adverse effect is hepatotoxicity which is pronounced with higher doses (>3.0 g) and prolonged administration (Zhang *et al.*, 2014).

1.7.3 Ethambutol

Ethambutol (EMB) is an ethylenediamine derivative discovered in 1961 (Thomas *et al.*, 1961). Ethambutol is the fourth drug of the recommended first-line TB drugs (Peloquin *et al.*, 1999).

Ethambutol has bacteriostatic activity against *Mycobacterium tuberculosis.* It interferes with the cell wall structure via inhibition of arabinogalactan synthesis (Alderwick *et al.*, 2015). The primary role of ethambutol as part of the first-line TB regimen is to minimise or reduce the risk of developing resistance against the companion tuberculosis drugs (Mitchison, 1985).

With the current recommended dose of (15 – 25 mg/kg), ethambutol reaches peak plasma concentrations of 5 mg/L between 2-4 hours and bioavailability of 80% regardless of food status (Bass *et al.*, 1994; Peloquin *et al.*, 1999; Saktiawati *et al.*, 2016).

The drug is extensivity distributed to body tissues with high accumulation in the lung tissues (Holdiness, 1984; Zimmerman *et al.*, 2017). Ethambutol is metabolised by alcohol dehydrogenase enzyme to aldehyde intermediate followed by oxidation to dicarboxylic metabolite (Peets *et al.*, 1965; Sundell *et al.*, 2020); however, up to 80% of the drug is excreted unchanged in the urine, with the remaining fraction excreted as inactivated metabolites (Peets *et al.*, 1965; Breda *et al.*, 1999).

The most common adverse effect is ocular toxicity and vision deterioration which is reversal upon treatment cession (Koul, 2015).

1.7.4 Pretomanid

Pretomanid is a novel chemical entity recently approved by the FDA in 2019 for the treatment of XDR-TB along with bedaquiline and linezolid based on the findings from the Nix-TB trial (Conradie *et al.*, 2020; Dousa *et al.*, 2020).

Pretomanid is a new nitroimidazole compound with potent activity against replicating and non-replicating *M.tb* with MIC ranging from 0.015 to 0.25 (Stover *et al.*, 2000; Lenaerts *et al.*, 2005). Pretomanid is a prodrug activated by *M.tb*-reductase enzyme to des-nitroimidazole. It interferes with cell wall biosynthesis by inhibiting the oxidation of hydroxy mycolate to ketomycolate (Stover *et al.*, 2000).

Currently, pretomanid is recommended by the WHO for treatment against XDR-TB as part of BPaL regimen (Bedaquiline, pretomanid and linezolid) (World Health Organization, 2020b). Additionally, pretomanid is being tested in an experimental four-drug regimen with bedaquiline, moxifloxacin and pyrazinamide in a phase 2c trial against DS- and MDR-TB (ClinicalTrials.gov Identifier: NCT03338621).

The current recommended dose is 200 mg daily. The drug is well absorbed following oral administration, time to reach the maximum concentration of 4.5 hours, C_{max} 1.7 mg/L, and half-life ($t_{1/2}$) 16.0 hours. Food increases bioavailability, and high-fat, high-calorie meal increases C_{max} of a 200 mg dose by 75% and AUC by 88% compared to the fasting state (TB Alliance, 2019).

The drug is extensively metabolised -less than 5% is recovered as parent drug in urine and faeces- to multiple metabolites. The drug is 20% metabolised by CYP3A4 isoenzyme (Dooley *et al.*, 2014) and primarily eliminated in the urine (53-65%) and feces (26-38%).

Abnormal liver function tests have been associated with repeated pretomanid administration in multiple drug-regimen. These abnormalities are usually asymptomatic, mild-to-moderate in severity. (*Pretomanid*, 2012)

1.7.5 Clofazimine

Clofazimine is a lipophilic riminophenazine antibiotic discovered in 1957 and used in clinical practice since 1962 to treat multibacillary leprosy (Browne *et al.*, 1962; Barry *et al.*, 1965).

Clofazimine is mainly indicated for the treatment of lepromatous leprosy and included in the current WHO model list of essential medicines against leprosy (Cholo *et al.*, 2012). Clofazimine has delayed antimicrobial activity against *Mycobacterium tuberculosis* in vitro and in vivo (Ammerman *et al.*, 2017; Riccardi *et al.*, 2020).

In 2010, clofazimine came under the spotlight following the findings of the so-called 'Bangladesh trials. They reported improved treatment outcomes in MDR-TB patients with a 9-month short-regimen containing clofazimine (Van Deun *et al.*, 2010). These findings have been replicated in other clinical trials (Xu *et al.*, 2012; Aung *et al.*, 2014; Trebucq *et al.*, 2018). Currently, WHO recommends clofazimine as group B for drugs used in the treatment of DR-TB (World Health Organization, 2020b).

Clofazimine is a prodrug that interferes with the respiratory chain and ion transporters of *M.tb*. Upon reduction by NADH-dehydrogenase-2 (NDH-2), it releases reactive oxygen species and competes with menaquinone, a compound involved in the electron transfer chain in *M.tb* (Cholo *et al.*, 2016; Riccardi *et al.*, 2020).

The current recommended dose is 100 mg daily. Clofazimine bioavailability is around 70% with variable absorption (Holdiness, 1989; Cholo *et al.*, 2012; Riccardi *et al.*, 2020). Food significantly affects the rate and extent of absorption. When administered with a high-fat meal, there was a 60% increase in AUC and a 30% increase in maximum concentration (Nix *et al.*, 2004). The time to peak concentration is around 5 to 7-hour post-dose. Clofazimine is

extensively distributed to body tissues. It undergoes duration-dependent accumulation in fatty tissues and reticuloendothelial system (Cholo *et al.*, 2017).

Clofazimine is metabolised into three metabolites via different hydrolytic reactions and is excreted mainly unchanged (Feng *et al.*, 1981; Holdiness, 1989). Clofazimine is characterised by an extremely long terminal half-life, up to months (Levy, 1974; Schaad-Lanyi *et al.*, 1987).

The major side effects of clofazimine are skin discolouration caused mainly by its affinity to crystallise and deposit in fatty tissues (Baik *et al.*, 2013; Swanson *et al.*, 2015), and QT prolongation (Diacon *et al.*, 2015; Cohen *et al.*, 2019); however, it is unknown how these toxicities relate to dose or plasma concentrations.

1.7.6 Linezolid

Linezolid (LZD) is the first member of oxazolidinones, a new class of anti-infective agents with potent activity against tuberculosis and is associated with improved treatment outcomes when added to the treatment regimen for drug-resistant TB (Wasserman *et al.*, 2019; Fermeli *et al.*, 2020). WHO recommends linezolid at a dose of 600 mg daily for most patients with rifampicin-resistant tuberculosis (World Health Organization, 2020b).

Linezolid inhibits *M.tb* microbial growth by interfering with bacterial protein biosynthesis via binding to the 23S rRNA peptidyl transferase centre (PTC) of the 50S subunit of the prokaryotic ribosome (Zhou *et al.*, 2002; Leach *et al.*, 2011; Wasserman *et al.*, 2016).

Linezolid is rapidly absorbed, and it reaches a maximum concentration of 10.3 to 14.7 mg/L within 2 hours following 600 mg oral dose. Linezolid has an oral bioavailability of 100% and a terminal half-life of 4 to 6 hours (Dryden, 2011; Wasserman *et al.*, 2016, 2019; Millard *et al.*, 2018).

The majority of the administered dose undergoes non-enzymatic oxidative metabolism (65%) to pharmacologically inactive metabolites (Tan *et al.*, 2008), and up to 80% of linezolid or its metabolites are excreted via the kidney (Tan *et al.*, 2008; Leach *et al.*, 2011).

Linezolid is associated with haematological and neurological adverse events. These adverse events are dose and duration-dependent; additionally, these adverse events occur due to structural similarity between linezolid target in *M.tb* and human mitochondria, resulting in inhibition of the respiratory chain leading to neuropathy and thrombocytopenia (Wasserman *et al.*, 2016).

1.8 Thesis justification

There is an urgent need for safe and effective tuberculosis treatment. With the current six months standard treatment regimen against drug-susceptible TB, the incidence rate and tuberculosis mortality is decreasing worldwide (World Health Organization, 2020a). However, tuberculosis remains a significant cause of maternal-child mortality. Moreover, resistance to standard tuberculosis regimens is a major public health issue and calls for an innovative, effective and safe dosing regimen.

Addressing the research gaps on the exposure of tuberculosis drugs in the neglected population, especially pregnant women living with tuberculosis and HIV, is a research priority. Denti et al. reported reassuring results on rifampicin exposure in pregnancy with no need for dose adjustment. (Denti, Martinson, *et al.*, 2015) However, evaluating the pharmacokinetic exposure of remaining first-line TB drugs (isoniazid, pyrazinamide, and ethambutol) in pregnant women with tuberculosis and whether a dose adjustment is needed remains an open research question.

Currently, pretomanid, a novel new tuberculosis drug used with bedaquiline and linezolid for XDR-TB treatment, is recommended not to be co-administered with rifampicin (a cornerstone

drug in the tuberculosis treatment regimen and is also known for its induction effect on metabolising enzymes). There is increased interest in pretomanid and its promising role in possible treatment shortening when combined with first-line TB drugs. However, there are no reports available evaluating pretomanid exposures when co-administered with rifampicin in tuberculosis patients and whether it will achieve effective drug exposures.

Clofazimine has been used in clinical practice for decades, mainly to manage leprosy infections. Currently, clofazimine has been repurposed to be included in the treatment of DR-TB, and it showed promising results with improved treatment outcomes (Van Deun *et al.*, 2010; World Health Organization, 2020b). The pharmacokinetic reports on clofazimine exposure are scarce, particularly in tuberculosis patients. Moreover, there is no information on the efficacy and safety of the established dose used in clinical practice and whether therapeutic and safe drug levels are achieved.

Lastly, linezolid has been used off-label to treat drug-resistant TB. Linezolid is a potent anti-infective drug with a narrow therapeutic window. There are numerous efforts to develop a safe and effective dosing regimen of linezolid in tuberculosis patients. The available reports on linezolid pharmacokinetics show high variability among different populations (Millard *et al.*, 2018), and no information is available on the drug exposure in the African population.

Applying population pharmacokinetic/pharmacodynamic modelling will assist answering these open questions. PopPK/PD has been proven to be extremely efficient in analysing data from sparse, unbalanced studies and in pooling dataset from different studies. (Ette *et al.*, 2006) It also helps with identifying different sources of variability in the population parameters and explore the effect of demographic factors and/or disease status. Finally, popPK/PD is a useful prediction

tool that can used to explore alternative dosing regimens and optimize individual dose selection to maximise efficacy and safety. (Owen *et al.*, 2014c; Upton *et al.*, 2014)

1.9 Aims

The general aim of this thesis was to improve tuberculosis treatment by applying population pharmacokinetic and pharmacodynamic modelling to data from studies in tuberculosis patients:

- Characterise the population pharmacokinetics of first-line TB drugs in pregnant women and investigate the effect of pregnancy on the exposure of these anti-infective agents.
- Describe the exposure and pharmacokinetics of the novel anti-TB drug pretomanid in tuberculosis patients when co-administered with rifamycin (Rifampicin or rifabutin) in tuberculosis patients.
- To describe pharmacokinetics of the repurposed drug clofazimine in tuberculosis patients and evaluate alternative dosing regimen to optimise drug exposure and evaluate the exposure-safety relationship between clofazimine and QT interval following standard and alternative dosing regimen.
- Evaluate the probability of target attainment and characterise linezolid population pharmacokinetics in patients with drug-resistant TB.

Chapter 2:Methodology

2.1 Study designs and data description

2.1.1 Tshepiso: pharmacokinetic of isoniazid, pyrazinamide, and ethambutol in pregnant women with tuberculosis.

The data was generated from Tshepiso, a prospective cohort study evaluating the effects of tuberculosis infection on maternal and infant outcomes in pregnant women with HIV co-infection. The study was conducted in Soweto, South Africa, from 2011 to 2014 (Salazar-Austin *et al.*, 2018). The study enrolled HIV-infected pregnant women with tuberculosis (case patients) or without tuberculosis (control patients). The case-patients were HIV-infected pregnant women with gestational age > 13 weeks and older than 18 years diagnosed with pulmonary or extrapulmonary tuberculosis (Salazar-Austin *et al.*, 2018). All case-patients were matched with two control patients based on gestational age (within two weeks), maternal age (within five years), date of enrollment and site of planned delivery.(Dooley *et al.*, 2015) This was a noninterventional study; enrolled patients received antiretroviral and tuberculosis treatment according to South African ARV and tuberculosis treatment guidelines. Efavirenz was given at a dose of 600 mg once daily at bedtime. Tuberculosis drugs were administered using weight banded-based doses using fixed-dose combination tablets, Rifafour (Rifampicin 150mg, Isoniazid 75 mg, Pyrazinamide 400 mg, Ethambutol 275 mg) in case of intensive phase or Rifinah (Rifampicin 300 or 150 mg, Isoniazid 150 or 75 mg) in case of continuation phase. The number of tablets depended on patient weight (**Table 2.1)**. The patients receiving tuberculosis treatment participated in a pharmacokinetic substudy and underwent pharmacokinetic sampling at either 36 weeks of gestation or at delivery, and then again at six weeks postpartum. The plasma samples were collected predose and then 2, 4, and 6 to 8 h post-dose. In all patients, the timing of any doses before presentation to the clinic was recorded based on self report. In the

parent study, they enrolled 80 case-patients matched with 155 controls. The study participants provided written informed consent. The study was approved by the institutional review board of John Hopkins Medicine, University of the Witwatersrand, and University of Cape Town.

Table 2.1: Summary of weight band-based doses in Tshepiso Study

Pre-treatment body weight	**Intensive Phase 7 days a week for 2 months**	**Continuation phase 7 days a week for 4 months**	
	RHZE (150,75,400,275)	RH (150,75)	RH (300,150)
30-37 Kg	2 tablets	2 tablets	
38-54 Kg	3 tablets	3 tablets	
55-70 Kg	4 tablets		2 tablets
> 70 Kg	5 tablets		2 tablets

R: Rifampicin, H: Isoniazid, Z: Pyrazinamide, E: Ethambutol

2.1.2 Assessing pretomanid for Tuberculosis (APT study)

Assessing pretomanid for tuberculosis (APT Trial) was a Phase IIB, 12-week, open-label, single-site, randomised clinical trial with three treatment groups. Arm 1 participants received pretomanid 200 mg daily and rifampin 600 mg daily for 12 weeks. Arm 2 participants received pretomanid 200 mg daily and rifabutin 300 mg daily for 12 weeks. Arm 3 participants (control group) received rifampin for 12 weeks and ethambutol for 8 weeks. A total of 183 adult patient newly diagnosed with pulmonary tuberculosis aged 18 years or older were recruited from the University of Cape Town inpatient wards and outpatient clinics between 2014 to 2019. The inclusion criteria included: weight ≥ 40 kg and ≤ 80 kg, Karnofsky score of at least 50, HIV negative or HIV positive with CD4 ≥350 cells/mm^3 without plans to start antiretroviral therapy during the experimental phase of the trial and had acid-fast bacilli on a stained smear from

expectorated sputum (ClinicalTrials.gov Identifier: NCT02256696). Women of child-bearing potential were required to use two methods of contraception for 1 week after the last dose of study medication. Male participants were required to use similar methods with their female partners to prevent pregnancy. The patients were excluded if they were pregnant or breastfeeding, history of neuropathy or epilepsy, QTcF > 450 ms, resistance to first-line TB drugs, alanine aminotransferase (ALT) activity > 3 times upper normal limit and Platelet count less than 100,000/mm^3. The study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine and the University of Cape Town's Human Research Ethics Committee and registered with clinicaltrials.gov (NCT02256696). The overall study scheme is depicted in **Figure 2.1**. In short, Patients were screened within 1 week of tuberculosis diagnosis and randomised to 1:1:1 to receive 12 weeks of study treatments, as shown in **Table 2.2**. Patients returned for follow-up visits at 4, 12, and 36 weeks after study treatment completion.

The primary objectives of the study were comparing the efficacy of the test regimens (ARM 1 and 2), using the endpoint of time to culture conversion on liquid medium, to the efficacy of standard treatment and comparing the safety and tolerability of each test regimen to the safety and tolerability of standard treatment.

Table 2.2 Study drugs and treatment arms in the APT trial

Arm	Weeks 0-8	Weeks 9-12	Weeks 13-24*
1	**Pa**HRZ	**Pa**HR	HR
2	**Pa**HRbZ	PaHRb	HR
3 (standard Rx)	**E**HRZ	HR	HR
PA-824 (Pa):		200 mg once daily (7/7)	
Rifampin (R):		600 mg once daily (7/7)	
Rifabutin (Rb):		300 mg once daily (7/7)	
Isoniazid (H):		300 mg once daily (7/7)	

Ethambutol (E) and Pyrazinamide (Z) was given at standard doses, according to weight bands
*Note: During Weeks 13-24, patients will receive standard TB treatment through local TB programs.

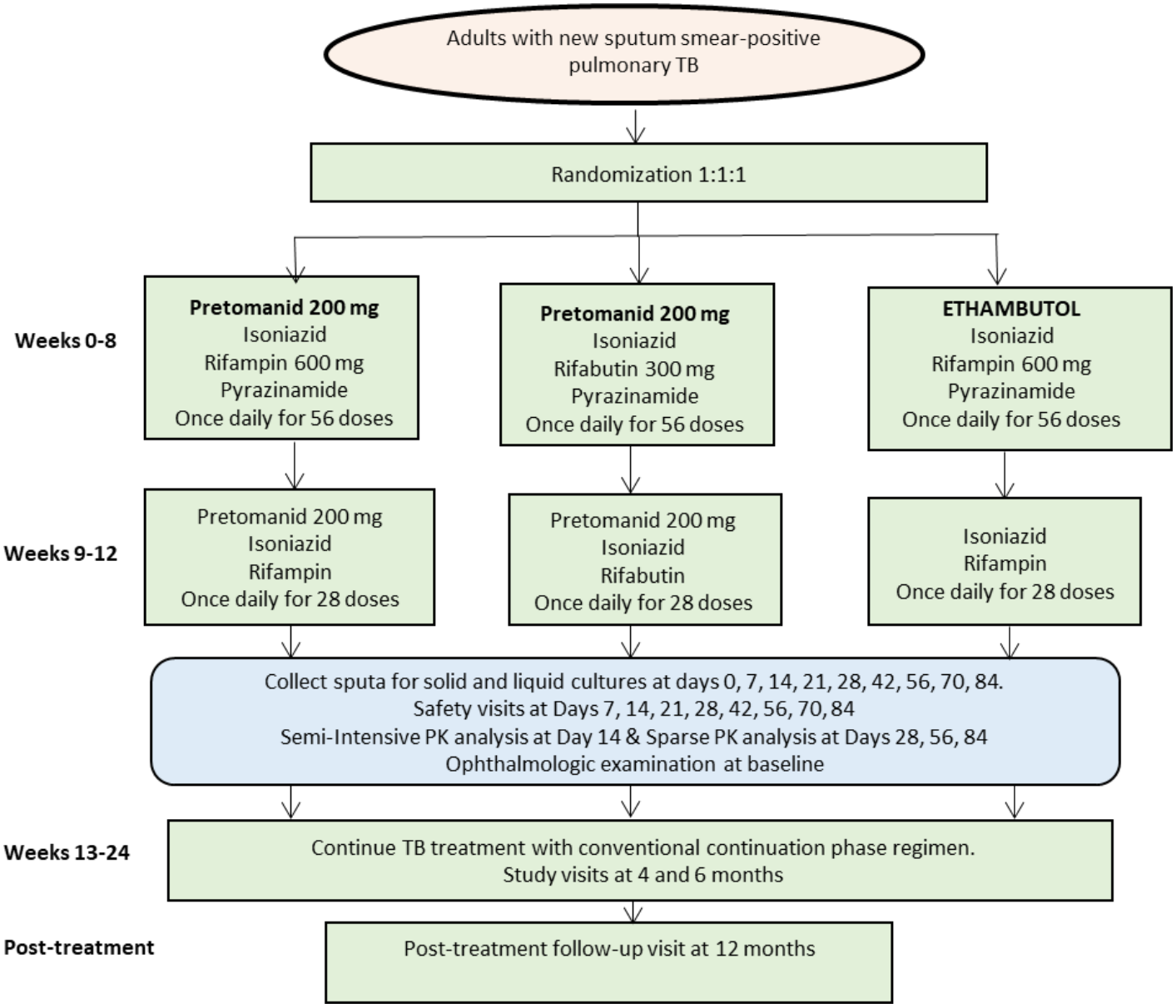

Figure 2.1 Schematic representation of study and samples collections in the APT trial

2.1.3 A5306 trial: Safety, Pharmacokinetics, and Pharmacogenetics Study of the Antituberculosis Drug pretomanid with Concomitant Lopinavir-Ritonavir, Efavirenz, or Rifampin

A5306 was a phase I study entitled "Safety, Pharmacokinetics, and Pharmacogenetics Study of the Antituberculosis Drug pretomanid with Concomitant Lopinavir-Ritonavir, Efavirenz, or Rifampin."

Eligible participants had negative HIV, normal liver functions tests, creatine clearance > 50 ml/min. Participants were excluded if they were anaemic (≤10.0 g/dl (females and ≤12.0 g/dl (males)), QTc > 450 or active tuberculosis. All participants provided written informed consent. ACTG study A5306 was registered at ClinicalTrials.gov under registration number (NCT01571414). The study included fifty-two healthy, HIV-uninfected volunteers without tuberculosis disease. Participants were sequentially allocated to study arm 1(efavirenz), arm 2 (lopinavir/r), or arm 3 (rifampin). A schematic representation of the dosing regimen and study arms is depicted in **Figure 2.2**. Arm 1 (efavirenz), participants were randomised to sequence A, consisting of pretomanid 200 mg dosing once daily for 7 days, a 2-week washout period, efavirenz dosed 600 mg once daily at evening for 14 days, and then efavirenz with pretomanid for 7 days, or sequence B, consisting of efavirenz for 14 days, efavirenz with pretomanid for 7 days, a 2-week washout period, and then pretomanid alone for 7 days. Arm 2 participants (lopinavir/r) were randomised to two sequences as follows: sequence A, consisting of pretomanid for 7 days, a 2-week washout period, lopinavir/r dosed 400/100 mg every 12 hours for 14 days, and then lopinavir/r with pretomanid for 7 days, or sequence B, consisting of lopinavir/r for 14 days, lopinavir/r with pretomanid for 7 days, a two-week washout period, and pretomanid alone for 7 days. In arm 3 (rifampin), participants received pretomanid for 7 days, rifampicin dosed 600 mg in the morning for 7 days and then pretomanid with rifampicin for 7

days. Serial plasma sampling was performed at the end of each dosing period for pretomanid, efavirenz, and lopinavir. For pretomanid, plasma was obtained predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h post-dose. The primary objective of the study was to evaluate drug-drug interactions and safety in healthy volunteers of these drug combinations and the effect on

pretomanid exposure. (Dooley *et al.*, 2014).

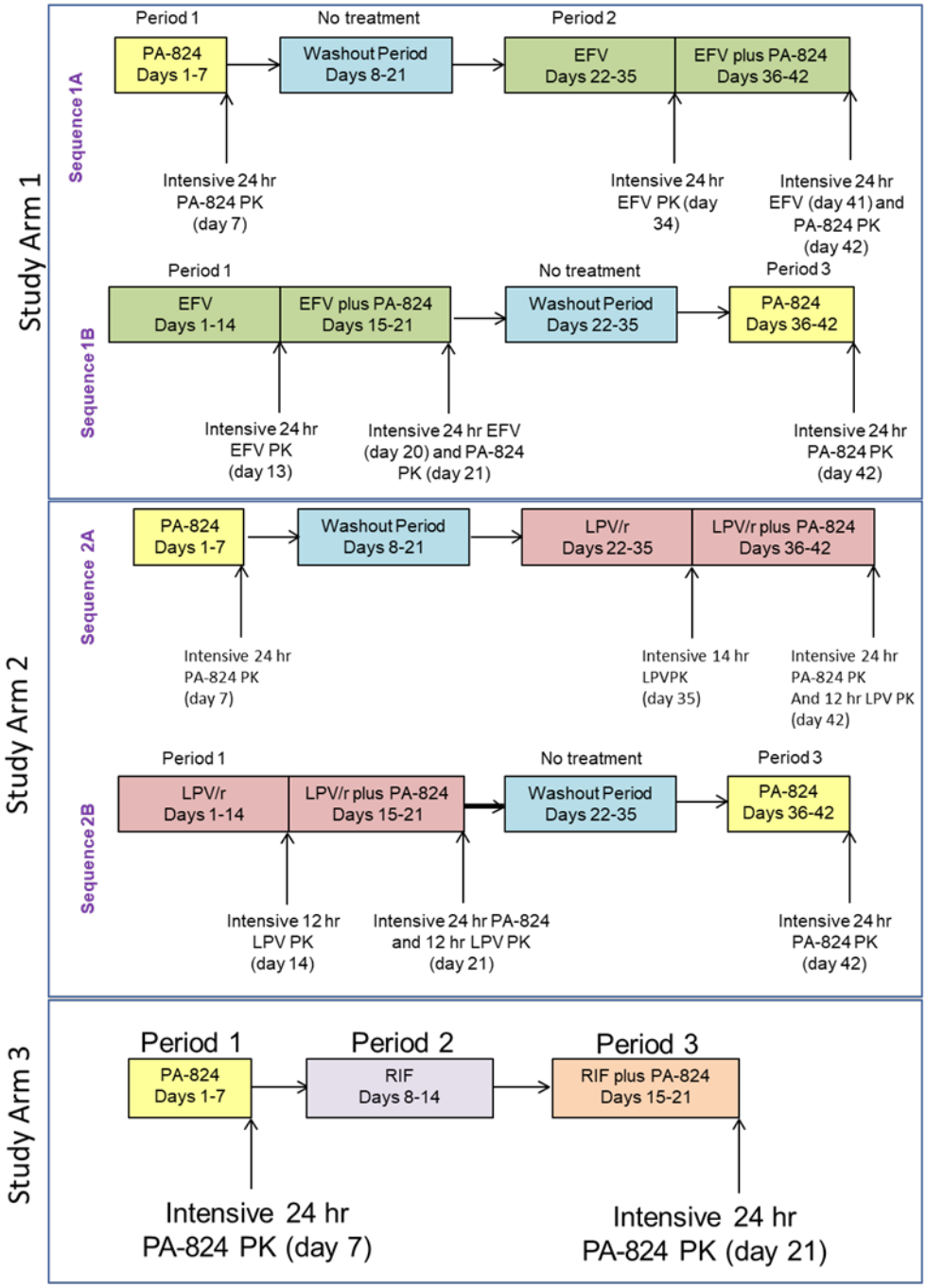

Figure 2.2 Schematic of the dosing regimen and pharmacokinetic sample collection in A5306 study

*Arm 1, PA-824 with efavirenz (EFV) (A); arm 2, PA-824 with lopinavir/ritonavir (LPV/r) (B); arm 3, PA-824 with rifampin (RIF) (C)

For the analysis performed in this thesis, only data from period 1 in study sequences 1A and 2A plus data from study arm 3 period 1 and 2.

2.1.4 PROBeX: Pharmacokinetics, Resistance, and Outcomes of Bedaquiline in MDR and XDR-TB

PROBeX was a prospective, observational cohort study of patients with pulmonary XDR and pre-XDR TB with or without HIV co-infection treated with a regimen containing bedaquiline, linezolid and clofazimine. The study included 195 adult patients aged ≥ 18 years old, with confirmed diagnosis of XDR, pre-XDR and MDR TB and known HIV status. The patients were excluded if they had extrapulmonary tuberculosis, serum creatinine > 2.5x upper limit of normal value (ULN), AST or ATL ≥ 5.0x ULN, and patients with QTcF > 450 ms. The patients were recruited from three TB referral sites in South Africa, Durban, Brooklyn Chest Hospital/Khayelitsha and Jose Pearson hospital. The primary objectives of the main study were to determine the molecular mechanism of bedaquiline resistance using whole-genome sequencing of *M. tuberculosis* isolates and define the pharmacokinetic and pharmacodynamic properties of bedaquiline when administered with an antiretroviral regimen containing lopinavir/ritonavir. Secondary objectives included developing population pharmacokinetic models of clofazimine and linezolid for where there is limited data in the African population. Sparse plasma pharmacokinetic samples were collected at month 1, 2 and 6 from study initiation. Additional 40 patients were invited to participate in an intensive pharmacokinetic sub-study. The pharmacokinetic sampling schedule is depicted in **Figure *2.3***.

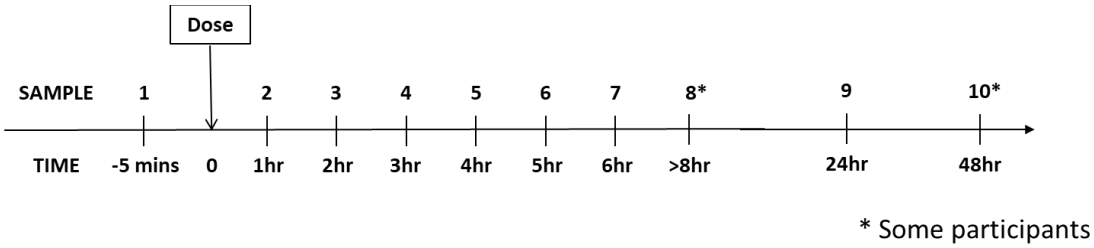

Figure 2.3 Schedule for Intensive pharmacokinetic sampling at months 2 in PROBeX

2.1.5 Phase 2A-EBA NC-003-(C-J-Pa-Z)

The study was a phase 2 trial to evaluate the early bactericidal activity, safety and tolerability of bedaquiline (B), pretomanid (Pa), pyrazinamide (P) and clofazimine (C) given in combination or alone in adult patients with newly diagnosed, smear-positive pulmonary tuberculosis. Eligible patients were consenting adults from outpatient clinics in Cape Town with a body weight of 40-90 kg, aged 18 to 65 years and of non-childbearing potential or using effective methods of contraceptive. Patients were hospitalised at the Task Clinical Research Centre, Bellville, or the Centre for Tuberculosis Research Innovation, University of Cape Town Lung Institute, for the duration of study treatment. The study was a multicenter, open-labelled, randomised clinical trial that included 105 adult patients randomised into seven different treatment arms (each of 15 patient). Study treatments were administered orally once daily for 2 weeks according to the following schemes in **Table 2.3** Triplicate 12-lead ECGs measurement were performed before treatment and on days 1, 2, 3,8 and 14 after treatment initiation. All ECGs were read by a central cardiology service, and the QT intervals were corrected for the effect of heart rate by both the methods of Fridericia (QTcF) and of Bazett (QTcB). Pharmacokinetic plasma samples were obtained on day 1, 2, 3, 8 and 14. **Table 2.4** shows ECG and pharmacokinetic sampling schedule

Table 2.3 Study drugs and randomisation in NC-003-(C-J-Pa-Z)

Arm 1 (B-Pa-P-C)	**Bedaquiline 400 mg Day 1, 300 mg Day 2 and 200 mg Days 3-14; pretomanid 200mg Days 1-14; pyrazinamide 1500mg Days 1-14; Clofazimine 300mg Days 1-3 and Clofazimine 100mg Days 4-14.**
Arm 2 (B-Pa-P)	Bedaquiline 400 mg Day 1, 300 mg Day 2 and 200 mg Days 3-14; pretomanid 200mg Days 1-14; pyrazinamide 1500mg Days 1-14
Arm 3 (B-Pa-C)	Bedaquiline 400 mg Day 1, 300 mg Day 2 and 200 mg Days 3-14; pretomanid 200mg Days 1-14; Clofazimine 300mg Days 1-3 and Clofazimine 100mg Days 4-14.
Arm 4 (B-P-C)	Bedaquiline 400 mg Day 1, 300 mg Day 2 and 200 mg Days 3-14; pyrazinamide 1500mg Days 1-14; Clofazimine 300mg Days 1-3 and Clofazimine 100mg Days 4-14.
Arm 5 (P)	Pyrazinamide 1500mg Days 1-14;
Arm 6 (C)	Clofazimine 300mg Days 1-3 and Clofazimine 100mg Days 4-14.
Arm 7 (Control) HRZE	Rifafour e-275® supplied as tablets and administered orally once daily for 14 days as per South African National TB Treatment Guidelines. The daily dose was dependent on the participants' weight.

Table 2.4 ECG and pharmacokinetic sampling points schedule in NC-003-(C-J-Pa-Z)

STUDY VISIT »	1	3			4, 5, 6 and 11			17								18	EWD	19
STUDY DAY»	-9 to -3	-1			1, 2, 3 and 8			14								15		28
STUDY HOUR »	0	0	5	10	0	5	10	0	1	2	3	4	5	10	16	0		0
EVENT																		
Dose					X			X										
Triplicate ECGs	X	X	X	X	X	X	X	X					X	X			X	X
Plasma for Pharmacokinetics					X	X	X	X	X	X	X	X	X	X	X	X	X	X

2.1.6 NExT: New Treatment Regimen for Patients With Multi-drug Resistant Tuberculosis

The study was an open-label RCT to evaluate new treatment regimen for patients with multi-drug resistant tuberculosis. The general aim of the study was to evaluate the impact of a new injection-free six-to-nine months treatment regimen of linezolid, bedaquiline, levofloxacin, pyrazinamide (PZA) and ethionamide/high dose isoniazid (INH) (intervention arm) compared to the conventional empiric injection-based regimen (conventional arm). The secondary aim was to determine if other treatment-related outcomes, including adverse events, adherence to treatment, culture conversion, and cure/completion, are significantly different in the intervention and conventional arms. In the conventional arm, patients received a 6-8-months intensive phase of: Kanamycin IM 500-750mg (40-50kg) or 1000mg (51-90kg) daily, Moxifloxacin 400mg daily, Pyrazinamide 1000-1750mg (40-50kg) or 1750-2000mg (51-70kg) or 2000-2500mg (71-90kg) daily, Ethionamide 500mg (40-50kg) or 750mg (51-70kg) or 750-1000mg (71-90kg) daily, Terizidone 750mg (40-70kg) or 750-1000mg (71-90kg) daily. For the intervention arm, patients received six to nine months of oral of linezolid 600 mg daily (reduced to 300mg if toxicity occurs), bedaquiline 400 mg for 2 weeks, followed by 200 mg three times per week, levofloxacin 750 mg (<50 kg) or 1000 mg (>50 kg) daily, PZA 1000-1750 mg (40-50 kg) or 1750-2000 mg (51-70 kg) or 2000-2500 mg (71-90 kg) daily, ethionamide 15 mg/kg (max 900 mg) daily, or high-dose isoniazid 500 mg (40-50kg) or 750 mg (51-70kg) or 750-1000mg (71-90kg) daily, or terizidone 750mg (40-70kg) or 750-1000mg (71-90kg) daily. Nested within the main study, an intensive pharmacokinetic sub-study that involved 30 patients with MDR-TB in the intervention arm. Eligible patients were adult (≥ 18 years old) diagnosed with rifampicin-resistant tuberculosis. Additional inclusion criteria for the pharmacokinetic sub-study included study participants that received 2 weeks of study drugs. The aim of the pharmacokinetic sub-study was

to describe the pharmacokinetic of linezolid, bedaquiline, levofloxacin, pyrazinamide, and ethionamide or isoniazid in participants with MDR-TB assigned to the intervention arm of the NExT study. Approximately 4 mL of blood was drawn prior to dosing, then at 1, 2, 3, 4, 5, 6, and 24 hours after the observed dose. The study was approved by the ethics committees at the University of Cape Town (ref 661/2014, ClinicalTrials.gov NCT02454205). In this thesis, only data from the intensive pharmacokinetic-sub-study was used to develop population pharmacokinetics of linezolid in MDR-TB patients.

2.2 Pharmacometrics

Pharmacometrics is the science of developing and applying mathematical and statistical methods to characterise, understand, and predict a drug's pharmacokinetics, pharmacodynamic and biomarker-outcomes behaviour (Ette *et al.*, 2006). One of the major advantages of pharmacometrics is the ability to pool data from different trials into a single analysis dataset which enrich the data for analysis beyond that which is attained from any single trial (Owen *et al.*, 2014b). Pharmacometrics allows us to quantify the uncertainty around model behaviour and rationalise knowledge-driven decision making in the drug development process (Ette *et al.*, 2006).

2.2.1 Nonlinear mixed-effects modelling.

Population models are comprised of several components, structural models, stochastic or statistical models and covariates models. The structural model usually describes the typical behaviour or fixed effects which is represented by algebraic or differential equations. Statistical models are used to describe random effects or variances in the observed data, usually attributed to between subjected variability (BSV) or within-subject variability (BOV) and random residual unexplained

variability (RUV). Covariate models are used to explain the between-subject variability and describe the effect of serval factors such as age, weight, and renal function (Mould *et al.*, 2013; Owen *et al.*, 2014b).

For continuous dependent variable y, the i^{th}observation in the j^{th} subject y_{ij} can be described using the following general nonlinear model:

$$y_{ij} = f(x_{ij}, \theta_i) + \varepsilon_{ij} \qquad 2.2.1.1$$

Where f is the function describing individual prediction based on the individual parameter θ_i and independent variables x_{ij} describing time, dose, and covariates and ε_{ij} the random effect describing the unexplained residual variability assuming normal distribution with mean zero and variance σ^2. The individual parameter θ_i can be derived from the following equation assuming lognormal distribution as most of the pharmacokinetic parameters are positive and skewed to the right (clearance and volume of distribution, for example).

$$\theta_i = \theta_p \cdot e^{\eta_i} \qquad 2.2.1.2$$

Where $\theta_p$is the population parameter value and $\eta_i$is the random effect describing the deviation of θ_i from the population value of a parameter θ_p assuming lognormal distribution with mean zero and variance ω_i^2. Moreover, individual model parameters can vary between sampling visits (occasions). Between-occasion variability (Karlsson *et al.*, 1993) can be described using the following equation:

$$\theta_i = \theta_p \cdot e^{\eta_i + k_{ik}} \qquad 2.2.1.3$$

where k_{ik} describes the inter-occasion variability for i^{th} individual and k^{th} occasion.

2.2.2 Covariate modelling

Covariates could be described as the characteristics of an individual such as sex, race, age, weight, or other factors affecting the outcome. The covariate could be time-invariant or constant within an individual, such as sex, race or it could be time-variant such as weight or age. Covariate analysis aims to attribute and describe the possible sources of between- and within-subjects variability in PK/PD population modelling. Including a covariate effect in population modelling is expected to reduce unexplained variability in the parameter directly affected by the covariate. It also provides an opportunity for dose individualisation and improves predictive performance of the population models. (Ette *et al.*, 2006; Owen *et al.*, 2014a)

Covariates could be classified as continuous covariates such as age, weight or categorical such as sex or race. Categorical covariates can take on two or more discrete values. The parameter-covariate relationship is usually described relative to a reference covariate level. The effect of continuous covariate is often expressed relative to its median value in a relevant patient population. The parameter-covariate relationship is often described using linear, power, or exponential function.

A notable covariate effect on pharmacokinetics is that of body size, a theory that goes under the name of allometris scaling. Allometry describes the relationship between the basal metabolic rate and the body size of species (Holford *et al.*, 2017). The relationship between body size and population PK parameters, especially disposition parameters, is nonlinear:

$$\theta_i = \theta_p \cdot \left(\frac{W_i}{W_p}\right)^{\alpha} \qquad 2.2.2.4$$

Where θ_i is the individual PK parameter of body mass W_i and θ_p is the standardized individual with body mass W_p and α is an empirically derived constant which is set to ¾ in case of flow parameters and 1 in case of volumes parameters. (Anderson *et al.*, 2008)

2.2.3 Model Evaluation

Model evaluation is a critical step in any population PK/PD analysis, and it should be conducted to examine whether the model can adequately describe the observed data and generate reliable modelling and simulation results. (US Food and Drug Administration, 2019) The goal of model evaluation is to objectively assess the predictive ability of the developed model for a domain-specific quantities of interest or to determine whether model deficiencies have noticeable effect on substantive inferences. (Yano *et al.*, 2001) There are several methods to deal with model evaluation and validation. No single method is generally sufficient to evaluate all component of modelling exercise, thus serval methods are needed so that the relative strengths and weaknesses of each method can complement each other. In general, models need to describe the data with an acceptable level of bias and an acceptable degree of precision. An appropriate model should be biologically plausible, consistent with current knowledge, and have mathematically identifiable parameters.(US Food and Drug Administration, 2019)

Methods to evaluate model performance include internal validation, where a portion of the analysis dataset is randomly selected and set aside prior to model development. Once final model is developed, the model is used to predict the observations in the validation dataset. Similarly, in external validation, model performance is assessed by predicting separate dataset, however, the validation datasets are usually from studies that are separate from the ones used to generate datasets incorporated in model development.

Additionally, basic goodness-of-fit plots show how well the model describe the observed data, they also used to evaluate model assumptions. Some of these plots that are considered informative include: dependent variable vs. individual or population predictions, conditional weighted residual vs. individual prediction or time, or correlation between random effects. Simulation-based diagnostic plots can also be used to evaluate model performance especially with sparse data. These diagnostic imply performing simulations relying on the stochastic component of the model and then compare the statistical properties of the simulations with the observed data. These diagnostics include the visual and numerical predictive checks. (Bergstrand *et al.*, 2011)

2.2.4 Handling censored data

For some data, the observed value is not available for analysis because above or below a quantification threshold. An example of this are the concentration of drug in PK samples whose assay results are below the quantification limit (BQL). For such values, only the information that the value was below a certain threshold is available, and this is referred to as data censoring. There are several methods in literature detailing how to handle such data. (Beal, 2001; Keizer *et al.*, 2015)

- "Discard": all BLOQ data are discarded.
- "LLOQ/2": all BLOQ data in the absorption phase are substituted with LLOQ/2, while in the elimination phase only the first data point under the LLOQ is substituted with LLOQ/2 and subsequent points are discarded.
- Likelihood-based methods: enables simultaneously modeling of the continuous data above the LLOQ and maximizing the likelihood of the BLOQ data being below the LLOQ is maximized with respect to the model parameters.

If not handled correctly, BQL data can introduce bias in parameter estimates. (Beal, 2001)

2.2.5 QT correction and PK-QT analysis.

An electrocardiogram (ECG) **Figure 2.4** is a recording of the electric activity during cardiac muscle activity. The QT interval represents the time of ventricular depolarisation and repolarisation (relaxation and contraction), while the RR interval represents the time duration between two consecutive R waves on the ECG (Lanfranchi *et al.*, 2010). The RR interval and heart rate are related as follow:

$$Heart\ rate\ (HR)[bpm] = \frac{60}{RR\ interval\ [sec]} \qquad 2.2.5.1$$

QT intervals adapt to changes in heart rate, thus makes it difficult to compare QT intervals recorded at different heart rates (Wang *et al.*, 2016). The heart rate corrected QT interval (QTc) accounts for such correlation or adaptation by normalising the QT interval as if it would have been measured at a standard rate of 60 beats per minute or RR interval of 1 sec (Malik *et al.*, 2002). There are several formulas that deal with this correction. The most famous and widely used one is the Bazett formula (Bazett, 1920).

$$QT_cB = \frac{QT}{\sqrt{RR}} \qquad 2.2.5.2$$

Another widely used formula and usually favoured by clinicians is the Fridericia correction formula (Fridericia, 1920):

$$QT_cF = \frac{QT}{\sqrt[3]{RR}} \qquad 2.2.5.3$$

Additionally, a population-specific correction factor can be estimated instead of a predefined value using non-drug ECG data (Malik *et al.*, 2001; Benatar *et al.*, 2015; Li *et al.*, 2019):

$$QT_CN = \frac{QT}{RR^{\beta}} \quad 2.2.5.4$$

Where β, the correction factor, is derived from the following log-linear regression model with slope β and intercept QT_cN :

$$\log(QT) = \log(QT_cN) + \beta \log(RR) \quad 2.2.5.5$$

Variability in QT interval has been attributed to several factors that need to be considered when analysing QT data. For example, sex, females tend to have a longer QT interval than males (Stramba-Badiale *et al.*, 1997). Obesity, a 10 kg increase in fat-mass, was linked to a more than 5 ms increase in QT (Carella *et al.*, 1996; Kumar *et al.*, 2019). Additionally, QT interval tends to vary throughout the day (diurnal variation), which can be described using cosin or circadian analysis (Piotrovsky, 2005; Cheung *et al.*, 2018).

In 2015, The International Council for Harmonisation (ICH) E14 Questions and Answers document was revised to allow for concentration-QTc (C-QTc) modelling to be used as the primary analysis for assessing the QTc interval prolongation risk of new drugs (Garnett 2018, Cheung2018). Generally, the recommended approach to analyse concentration-QT data is to use a pre-specified linear mixed-effects model (Garnett *et al.*, 2018). The default dependent variable is the baseline adjusted QTc or ΔQTc:

$$\Delta QT_{C_{ijk}} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_3 TIME_j + \theta_4 \left(QT_{C_{i,j=0}} - \overline{QT_{C_0}}\right) + \varepsilon \quad 2.2.5.6$$

Where θ_0 is the population mean intercept associated with normally distributed random effect η_0; θ_1 is the fixed effect associated with treatment TRT_j (0 = placebo, 1 = active drug); θ_2 is the population mean slope of the assumed linear association between concentration and $\Delta QT_{C_{ijk}}$ associated with normally distributed random effect η_2; C_{ijk} is the concentration for subject *i* in

treatment j and time k; θ_3 is the fixed effect associated with time, to account for diurnal variation in ΔQT_c ; and θ_4 is the fixed effect associated with individual baseline $QT_{c_{i,j=0}}$; $\overline{QT_{c_0}}$ is overall mean of $QT_{c_{i,j=0}}$, i.e., the mean of all the baseline (= time 0) QTc values; ε account for residuals, which are normally distributed with mean 0 and variance R (Garnett *et al.*, 2018).

Another approach is to use the absolute QTc measurements as the dependent variable and estimation of diurnal variation using cosine functions and evaluate the drug effect via different relationships (linear slope, maximal efficacy (E_{max} and sigmoidal E_{max}) (Garnett *et al.*, 2018; Jolling *et al.*, 2019).

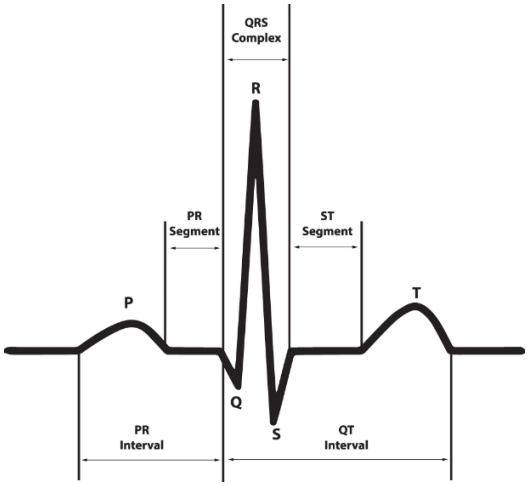

Figure 2.4 The ECG waveform and segments in lead II that presents a normal cardiac cycle.

(Zheng *et al.*, 2020)[1]

2.2.6 Software

Pharmacokinetic analyses were performed in NONMEM 7.4/7.5, using the first-order conditional inference with eta-epsilon interaction (FOCE-I) or stochastic approximation expectation maximisation (SAEM) followed by important sampling. Pirana (Certara, Princeton, NJ, USA), Perl-speaks-NONMEM (versions 4.9.0/ 5.0.0) (Lindbom *et al.*, 2004) and Xpose4 (Keizer *et al.*, 2013) were used for NONMEM execution and post-processing results. Data

management, post modelling processing of data and graphical analysis were done in R via RStudio interface (R Core Team, 2020; RStudio, 2020).

2.2.7 Pharmacokinetic modelling approach

Generally, the pharmacokinetic modelling was started by testing several disposition kinetics (one or two or three and four compartment) with linear and nonlinear elimination. The absorption model was developed by testing first-order absorption with and without lag, saturable absorption, and transit compartments absorption. Random variables included in the pharmacokinetic model were assumed to follow a lognormal distribution to account for inter- and intra- subject variability. Additive, proportional, and combined error models were tested to describe the residual unexplained variability. Allometric scaling was tested on all disposition parameters to account for the effect of body size with total body weight (TBW), fat-mass and fat free-mass as body size descriptors. Priors were also used when modelling sparse data to stabilise model parameters. Model development and inclusion of covariates followed a stepwise approach depending on physiological plausibility and improvement in model diagnostics. Model diagnostics included inspection of visual predictive checks (VPC) and the difference in the model objective function (ΔOFV), which was assumed to follow a chi-square distribution (χ^2) with a degree of freedom corresponding to the difference in the number of parameters between two nested models.

2.2.8 PK-QT modelling approach

The modelling procedure was done in a sequential approach. The population pharmacokinetic parameters were first characterised using plasma concentration-time data. The developed model was then used to predict concentrations at each ECG time point. Pre-treatment ECG measurements were used to evaluate different correction methods between heart rate (HR) and

raw QT interval. Also, covariates screening was tested first on the pre-treatment data. Once the "pre-treatment" model was developed, different relationships were tested to describe the effect of pharmacokinetic exposure on ECG measurement. We tested linear, Emax and sigmoidal Emax models. The model comparison and choice were guided by the drop in objective function in case of nested models or models with the lowest AIC and improved visual predictive checks.

Chapter 3:Population Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in South African Pregnant Women with Tuberculosis and HIV

3.1 Abstract

Tuberculosis is an important cause of maternal morbidity, but little is known about the effects of pregnancy on anti-tuberculosis drug concentrations. We developed population pharmacokinetic models to describe drug disposition of isoniazid, pyrazinamide, and ethambutol in pregnant women with tuberculosis and HIV.

HIV-positive pregnant women with tuberculosis receiving standard first-line tuberculosis treatment and participating in Tshepiso, a prospective cohort study in Soweto, South Africa, underwent sparse pharmacokinetic sampling at >36 weeks gestation and 7 weeks postpartum. The effects of pregnancy on the pharmacokinetics of isoniazid, pyrazinamide, and ethambutol were investigated via population pharmacokinetic modelling.

Isoniazid, pyrazinamide, and ethambutol concentrations were available for 29, 18, and 18 women respectively. Median weight was 66 kg while pregnant and 64 kg postpartum. No significant differences were observed in drug clearance, volume of distribution, or bioavailability during pregnancy and postpartum. The model-estimated isoniazid, pyrazinamide and ethambutol AUC_{0-24} medians during pregnancy were 6.88, 419 and 16.5 mg·h/L versus 5.01, 407 and 19.0 mg·h/L postpartum, respectively. The model-estimated C_{max} medians during pregnancy were 1.39, 35.9 and 1.82 mg/L versus 1.43, 34.5 and 2.11 mg/L postpartum for isoniazid, pyrazinamide and ethambutol, respectively.

A posteriori power calculations determined that our analysis was powered 91.8 %, 59.2%, and 90.1 % at $p < 0.01$, to detect a 40% decrease in AUC of isoniazid, pyrazinamide, and ethambutol, respectively.

Pregnancy does not appear to cause relevant changes in the exposure to isoniazid, pyrazinamide and ethambutol. Additional studies of anti-tuberculosis drugs in pregnancy are needed

3.2 Introduction

Tuberculosis is an important cause of maternal mortality and morbidity globally; the immune changes of pregnancy increase the risk of progressing from latent tuberculosis infection to active tuberculosis disease (Mathad *et al.*, 2012; Hoffmann *et al.*, 2013). Furthermore, tuberculosis in pregnancy carries high risk for the mother and the fetus, especially for those living with HIV who have a 37-fold increased risk of dying from tuberculosis and increased rates of obstetric complications. (Khan *et al.*, 2001; Pillay *et al.*, 2004; Mofenson *et al.*, 2007; Salazar-Austin *et al.*, 2018). Similarly, infants born to women with HIV and tuberculosis have a significant risk of low birth weight, tuberculosis , and early mortality (Salazar-Austin *et al.*, 2018). Thus, optimizing care of pregnant women with HIV-associated tuberculosis is critically important. Physiological changes during pregnancy may alter pharmacokinetic parameters and therefore impact drug exposure, thus complicating dosing for many medications. These changes include: reduced gastrointestinal motility and altered stomach pH, which impact the absorption and bioavailability of a drug. Additionally, reduced serum albumin may increase the unbound fraction of highly-protein bound drugs, thus increasing both volume of distribution and total clearance, while maintaining comparable levels of unbound drug concentrations. Finally, the altered activity of metabolizing isoenzymes (e.g. from CYP450 and UGT family), together with altered total and renal blood flow, also affect drug clearance. How all of these changes independently and synergistically affect drug concentration is highly dependent on the physicochemical and metabolic characteristics of the drug. Predictions are not always straightforward (Wadelius *et al.*, 1997; Anderson, 2005).

Current World Health Organization tuberculosis treatment guidelines recommend the use of the same regimens and dosages for pregnant and non-pregnant woman: an intensive phase of rifampicin (8-12 mg/kg), isoniazid (4-6 mg/kg), pyrazinamide (20-30 mg/kg), and ethambutol (15-25 mg/kg) daily for two months followed by a continuation phase of four months with rifampicin (8-12 mg/kg) and isoniazid (4-6 mg/kg) although some guidelines recommend that pyrazinamide to be withheld in pregnancy (American Thoracic Society, CDC, 2003) Previously, we reported, that rifampicin exposure was only marginally increased during pregnancy , supporting the use of standard doses (Denti, Martinson, *et al.*, 2015). However, there are no published pharmacokinetics data for the other first-line tuberculosis drugs.

The aim of this study was to evaluate the changes in pharmacokinetics of isoniazid, pyrazinamide and ethambutol among tuberculosis infected women treated with standard tuberculosis treatment regimens, from pregnancy through the postpartum period.

3.3 Materials and Methods

3.3.1 Study Population

The patients included in this analysis were enrolled in Tshepiso, a prospective cohort study evaluating the effects of tuberculosis on maternal and infant outcomes in women with HIV infection. The clinical outcomes and pharmacokinetic analysis of rifampicin and efavirenz have been published previously (Denti, Martinson, *et al.*, 2015; Dooley *et al.*, 2015), as have the main study results (Salazar-Austin *et al.*, 2018). The participants included in the current analysis were enrolled in Tshepiso's pharmacokinetic sub-study(Denti, Martinson, *et al.*, 2015).

Briefly, the participants were recruited from antenatal clinics and obstetrics wards at Chris Hani Baragwanath Hospital, Soweto, South Africa, between January 2011 and January 2013; they were pregnant women aged ≥18 years, (gestational age of > 13 weeks at the time of enrolment),

and HIV positive. Cases had tuberculosis, and matched controls did not. Antiretroviral and tuberculosis treatment were dispensed by local public-sector clinics in accordance with the South African national guidelines, and all treatment was self-administered.

Fixed-dose combination tablets provided by the national tuberculosis program were used in weight band-based doses, the number of tablets depended on patient weight (**Table 3.1**). For the intensive phase Rifafour® (Sanofi Aventis) tablets (150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol) were administered and for the continuation phase Rifinah-150/75 or Rifinah-300/150 ® (Sanofi Aventis) were administered (each tablet contains: 150 or 300 mg rifampicin and 75 or 150 mg isoniazid). This study was approved by the institutional review boards of Johns Hopkins School of Medicine, the universities of the Witwatersrand, and Cape Town. Participants provided written informed consent.

Table 3.1: Summary of weight-band based doses

Pre-treatment body weight	**Intensive Phase 7 days a week for 2 months**	**Continuation phase 7 days a week for 4 months**	
	RHZE (150,75,400,275)	RH (150,75)	RH (300,150)
30-37 Kg	2 tablets	2 tablets	
38-54 Kg	3 tablets	3 tablets	
55-70 Kg	4 tablets		2 tablets
> 70 Kg	5 tablets		2 tablets
R: Rifampicin, H : Isoniazid, Z : Pyrazinamide, E : Ethambutol			

3.3.2 Study Protocol

Women receiving standard first-line tuberculosis treatment underwent pharmacokinetic sampling at either 36 weeks of gestation or at delivery, and then again at 6 weeks postpartum. Samples were collected pre-dose and then 2, 4, and 6 to 8 h post-dose. In women taking their medications prior to arrival in the clinic or in the evening, and for women presenting in labour, opportunistic sampling was performed. In the latter group, samples were collected at 3-h intervals from presentation until delivery (maximum of four samples). In all patients, the timing of any doses prior to presentation to the clinic was recorded based on self-report.

We previously reported the methods used to determine N-acetyltransferase 2 (NAT2) genotype using known functional polymorphisms (Dooley *et al.*, 2015); 191G→A (rs1801279, *14), 341 T→C (rs1801280, *5), 590G→A (rs1799930, *6), and 857G→A (rs1799931, *7). NAT2 genotypes were assigned as follows: rapid (no variant allele), intermediate (1 variant allele), and slow (heterozygous for 2 different polymorphism or homozygous for 1 polymorphism)

3.3.3 Drug concentration analysis

Drug plasma concentrations were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS) performed in the Division of Clinical Pharmacology, University of Cape Town. For isoniazid, the calibration range was 0.195 (the lower limit of quantification [LLOQ]) to 25.0 mg/L. The inter-day accuracy of the isoniazid assay ranged from 99.1% to 101.5%, and the coefficient of variation (%CV) of the precision ranged from 2.6% to 3.2%. For pyrazinamide, the calibration range was 0.200 [LLOQ] to 80.0 mg/L. The inter-day accuracy of the pyrazinamide assay ranged from 99.7% to 102.3%, and the coefficient of variation (%CV) of the precision ranged from 0.7% to 2.8%. For ethambutol, the calibration range was 0.084

[LLOQ] to 5.40 mg/L. The inter-day accuracy of the ethambutol assay ranged from 103.3% to 105.8%, and the coefficient of variation (%CV) of the precision ranged from 4.0% to 8.1%.

3.3.4 Pharmacokinetic analyses

Population pharmacokinetics models of the drug concentration data for isoniazid, pyrazinamide, and ethambutol were analyzed using nonlinear mixed-effects model in NONMEM version 7.4.2 with first-order conditional estimation with eta-epsilon interaction (Beal, 2001). Pirana, Perl-speaks-NONMEM (PsN) version 4.9.0, and Xpose4 were used to aid the modelling process and to prepare model diagnostics (Keizer *et al.*, 2013). One- and two-compartment disposition models with first-order elimination and first-order absorption (with or without lag time or transit compartments (Radojka M. Savic *et al.*, 2007)) were tested. Between -subject and -occasion random effects were included on the pharmacokinetic parameters assuming log-normal distribution; a combined additive and proportional structure described the residual unexplained variability, with the additive component of the error constrained to be least 20% of lowest level of quantification (LLOQ). Values below the LLOQ were imputed to LLOQ/2, except for consecutive values during the elimination phase of the pharmacokinetics profiles which were excluded from the model fit, following the M6 method (Beal, 2001), but included in diagnostic plots. Allometric scaling (Anderson *et al.*, 2008) was used to adjust for the effect of body size on the disposition parameters, testing both total body weight and fat-free mass as body size descriptors. The allometric exponents were fixed to 0.75 and 1 for clearance and volume parameters, respectively. After the inclusion of allometric scaling, the following covariates effects were tested on the pharmacokinetics parameters: pregnancy, age, efavirenz vs. lopinavir/ritonavir-based antiretroviral treatment, and, for isoniazid, formulation/phase of

treatment (Rifafour® in intensive phase vs. Rifinah® during the continuation phase) and NAT2 acetylator genotype.

Missing NAT2 acetylator genotype was imputed using a mixture model based on the observed concentrations and a fixed relative proportion of each genotype in overall population based on the parent Tshepiso study (rapid NAT2 metabolizer constituted 13 % of the population, 44 % classified as intermediate and 43 % classified as slow metabolizer), as described in (Keizer *et al.*, 2012) .

The development of the model and the inclusion of covariates were based on physiological plausibility, inspection of diagnostic plots including visual predictive checks (Holford, 2005), and decreases in the objective function value (OFV), which was assumed to follow a chi-square (χ^2) distribution. The statistically significance cut-off for an additional degree of freedom (inclusion of one additional parameter) was an OFV drop of at least 3.84 points, corresponding to $p<0.05$. Covariates were added in a step-wise fashion in order of importance determined by the largest significant drop in OFV. Weakly informative priors (Gisleskog *et al.*, 2002) were added as needed to stabilize the model and improve parameters estimates for the three drugs with ~50% uncertainty. The typical values were obtained from previously published models for the three drugs in non-pregnant women with tuberculosis (Denti, Jeremiah, *et al.*, 2015) after allometrically scaling the values to adjust for different body size between the two populations. Sampling importance resampling (SIR) (Dosne *et al.*, 2017) was used to assess the robustness of the final parameter estimates and to obtain the 95 % CI.

A posthoc power analysis was performed on the final models to estimate the power to detect a clinically significant effect that was brought on by pregnancy using stochastic simulation and estimation (SSE), a feature of PsN (Lindbom *et al.*, 2004) based on the algorithm published by

(Ueckert *et al.*, 2016). For the three drugs, we simulated 70% clearance increase in pregnancy (-40% AUC). The simulated datasets (n = 200) were fitted with the full model (pregnancy effect being estimated) and reduced model (no effect of pregnancy) then generated power curves using chi-square significant level of 0.01.

3.4 Results

3.4.1 Study data

Data were available for 29 women taking isoniazid, 18 of whom also had concentrations for pyrazinamide and ethambutol. These patients underwent pharmacokinetic sampling for the drugs at a median (inter-quartile range) of 2.71 (1.29 - 3.57) weeks before delivery (18 were sampled during pregnancy and 3 were sampled during labour), and then 8 patients were sampled postpartum 6.64 (4.96 -7.18) weeks after delivery. For pyrazinamide and ethambutol, 13 patients were sampled during pregnancy, 2 were sampled during labour, and 3 sampled postpartum. The median weight was 66 kg during pregnancy and 63.5 kg postpartum. The demographics of the study participants are summarized in **Table *3.2***.

Table 3.2: Demographics for patients included in the population pharmacokinetics analyses for each of the drugs

Characteristics	Isoniazid (n = 29)	Pyrazinamide & Ethambutol (n = 18)
Age (yr)	28.1 (25.2-29.9)	26.7 (24.8-29.5)
Weight (kg)		
Prepartum	66.0 (60.0-80.0)	66 (58-77)
Postpartum	63.5(57.3 - 72.8)	66 (59 -72)
Fat free mass (kg)		
Prepartum*	41.4 (37.4 - 46.2)	41.4 (36.8 - 45.1)
Postpartum*	40.0 (36.9 – 44.6)	40.8 (39.2 – 45.1)
EFV- based HAART	24 (83)	13 (72)
LPV/r-based HAART	1 (3)	1 (6)
No ART	1 (3)	1 (6)
NAT2 metabolizer status		
Slow	11 (38)	
Intermediate	10 (34)	
Rapid	3 (10)	
Unknown	5 (17)	

Data are given as median (interquartile range) or no. (%) of subjects
ART, antiretroviral therapy; EFV, efavirenz; HAART, highly active antiretroviral therapy; LPV/r, lopinavir-ritonavir, NAT, N-acetyltransferase 2.
*N prepartum isoniazid is 21 and 8 postpartum for pyrazinamide and ethambutol 15 and 3 respectively.

Three patients had undetectable pre-dose concentrations for all measured drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol), but the concentrations following the observed dose in the clinic were in line with all the other subjects, so this was considered as non-adherence and the dosing records from the previous days were disregarded.

The final data for isoniazid included a total of 37 pharmacokinetic profiles from 29 patients (8 paired), based on 141 plasma concentration measurements (77 during pregnancy and 64 postpartum). For isoniazid, 46 samples were below the limit of quantification (BLQ), mostly pre-dose samples. For pyrazinamide and ethambutol, 19 pharmacokinetic profiles were obtained from 18 patients (1 paired), based on 66 plasma concentration measurements (54 during pregnancy and 12 postpartum) and no data below BLQ.

3.4.2 Isoniazid pharmacokinetics

The pharmacokinetics of isoniazid was best described by a two-compartment disposition model with first-order elimination and transit compartments absorption. The model structure is depicted in **Figure 3.1**. The model supported estimation of between-subject variability in clearance and between-occasion variability in mean transit time (MTT) and absorption rate constant (Ka). NAT2 acetylator status was a significant covariate on clearance (delta OFV= -29.9 points, 2 degrees of freedom, $p< 0.001$) and the estimated typical value of clearance was 97.1, 75.7 and 29.0 L/h, in fast, intermediate and slow metabolizers, respectively. Finally, the effects of pregnancy and concomitant use of efavirenz were explored on exposure parameters (clearance and bioavailability) and no statistically significant difference was observed.

The impact of the chosen method to handle BLQ values (M6 method) on the parameters estimates was tested by repeating the analysis after excluding these points, and no significant change was observed. Final parameter estimates are summarized in **Table 3.3**. A visual predictive check showing adequate fit is displayed in **Figure 3.3**. Model-estimated secondary pharmacokinetic parameters are summarized in **Table 3.4** and **Figure 3.2**.

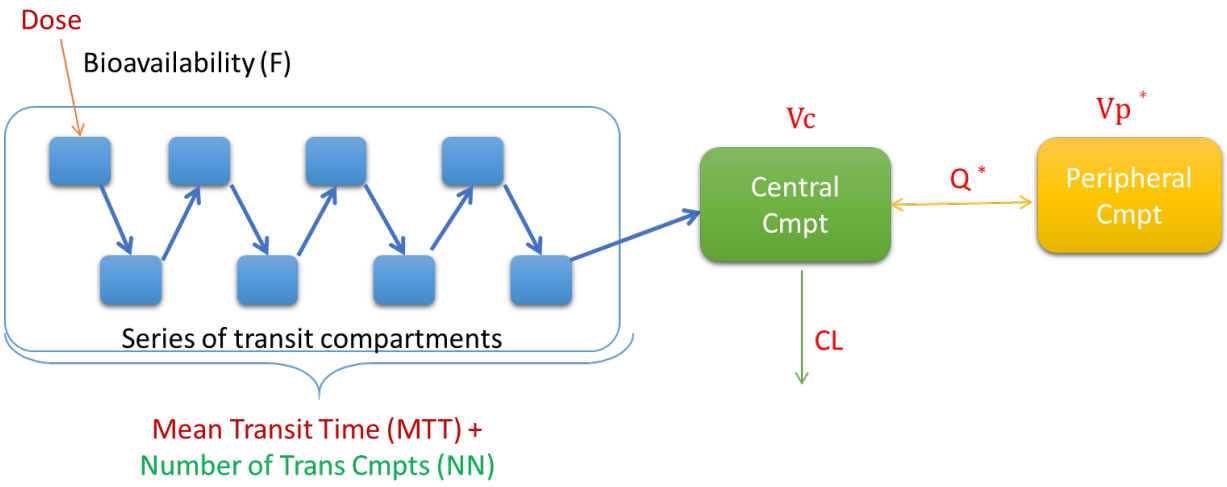

Figure 3.1: Structural model for isoniazid, pyrazinamide, and ethambutol.

The dose of each drug is assumed to go through a series of transit compartments before being absorbed into the central compartment. It is then eliminated from the central compartment with first-order kinetics. The asterisk (*) indicates the peripheral compartment which only applies to isoniazid and ethambutol. Vc; central volume of distribution, Vp; peripheral volume of distribution, Q; inter-compartmental clearance and CL; central clearance.

Table 3.3 Final population pharmacokinetic model parameter estimates for isoniazid, pyrazinamide and ethambutol.

Parameter description	Typical Value (95 % CI)[a]		
	Isoniazid	Pyrazinamide	Ethambutol
Clearance for Rapid NAT2 acetylator (L/h)[b]	97.1 (68.6-144)		
Clearance for Intermediate NAT2 acetylator (L/h)[b]	75.7 (59.4 - 95.8)	3.39 (2.96 - 3.87)	60.2 (53.7 - 68.5)
Clearance for Slow NAT2 acetylator (L/h)[b]	29.0 (24.3 - 34.8)		
Central volume of distribution Vc(L)[b, c]	130 (106-162)	43.8 (39.7 - 47.2)	268 (154 - 419)
Inter-compartmental clearance Q (L/h)[b, c]	12.4 (5.64 - 31.3)	-	174 (71.7 - 385)
Peripheral volume of distribution Vp (L)[b, c]	28.5 (10.8 - 50.1)	-	334 (217 - 490)
Absorption mean transit time (h)[c]	1.21 (0.953 - 1.51)	0.934 (0.565 - 1.17)	2.15 (1.84 - 2.51)
Number of transit compartment (NN)[c]	8.01 (3.95 - 14.9)	3.78 (2.24 - 7.71)	6.23 (3.21 - 11.6)
Bioavailability (F)	1 FIXED	1 FIXED	1 FIXED
Proportional error (%)	22.2 (15.2 - 30.4)	9.19 (6.99 - 14.4)	23.3 (17.8 - 33)
Additive Error (mg/L)	0.045 (0.035 - 0.062)	0.011 (0.002 - 0.019)	0.03[e] FIXED
BSV of clearance (%CV)[d]	12.7 (1.37 - 30.8)	25.4 (17.1 - 40.3)	4.69 (0.379 - 20.4)
BOV of mean transit time (%CV)[d]	56.7 (43.3 - 78.0)	71.9 (41.2 - 125)	24.1 (15.9 – 36.0)
BOV of bioavailability (%CV)[d]	36.7 (27.0 - 48.7)	13.6 (5.81 - 18.7)	20.1 (10.6 - 32.2)

[a] 95 % confidence intervals obtained with sampling importance resampling technique using PsN software

[b] Allometric scaling used for CL(FFM), Q, Vc and Vp (WT), typical values reported for the median FFM and median WT as reported in demographics table

[c] Priors[uncertainty] added to the parameter estimates; isoniazid: Q (16.1 L/h [50%]), Vp (16.5 L [50 %]), MTT (0.924 h [50%]) and NN (2.73 [50%]). pyrazinamide: MTT (0.84 h [30%]) and NN (2.6 [50%]). ethambutol: Vc (266 L [50%]), Vp (687 L [50%]), Q (109 L/h [50 %]), MTT (2.54 h [50%]) and NN (11.1[50%])

[d] Between subject variability (BSV) and between occasion variability (BOV) are assumed to be log-normally distributed and reported as approximate %CV

[e] Estimate of the additive error wasn't statistically significant from its lower bound (LLOQ/2), thus was fixed to that value

Table 3.4 : model-estimated secondary pharmacokinetic parameters

		Prepartum	Postpartum
C_{max} (mg/L)	**Isoniazid**	1.39(1.13 - 1.60)	1.43 (1.09 - 1.86)
	Pyrazinamide	35.9 (32.7 - 38.1)	34.5 (29.9 - 41.3)
	Ethambutol	1.82 (1.61 - 2.14)	2.11 (1.85 - 2.46)
AUC_{0-24} (mg·h/L)	**Isoniazid**	6.88 (3.63 - 10.40)	5.01 (2.89 -8.03)
	Pyrazinamide	419 (370 - 541)	407 (336 - 514)
	Ethambutol	16.5 (14.3 - 20.6)	19.0 (16.5 - 21.6)

Data are given as median (interquartile range)

N: for INH; 21(3 at birth) prepartum 16 postpartum, for PZA and EMB: 15 (2 at birth) prepartum and 4 postpartum

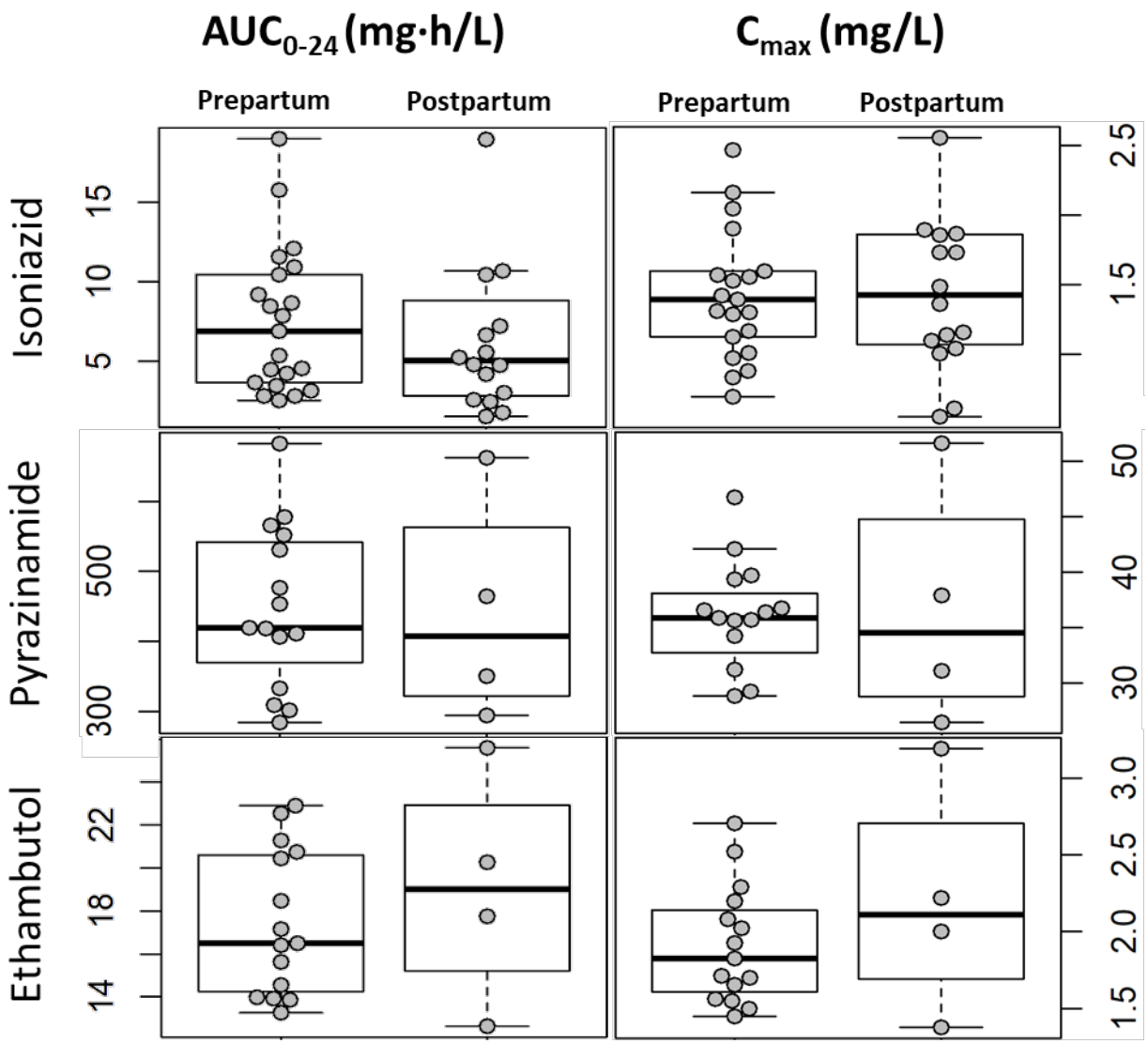

Figure 3.2. Box and whisker plots showing the three drugs $AUC_{0\text{-}24h}$ and C_{max} stratified by pre/postpartum.

The dots represent individual values, Whiskers showing 2.5th and 97.5th percentiles

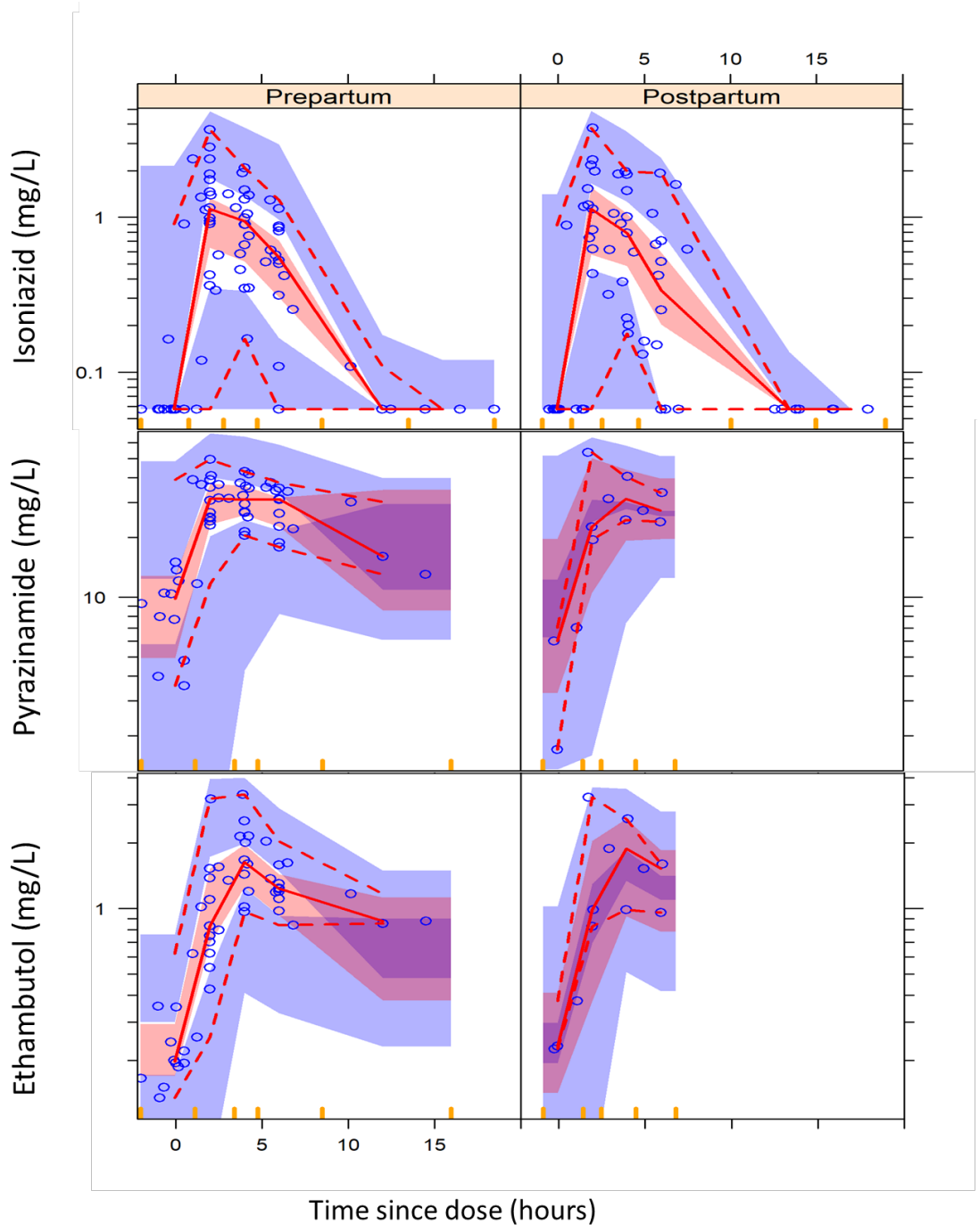

Figure 3.3: Visual predictive check (VPC) for isoniazid, pyrazinamide and ethambutol concentration versus time (time since dose), stratified by pregnancy.

The circles represent the original data, the dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

3.4.3 Pyrazinamide pharmacokinetics

The data was best fitted by one-compartment disposition model with first-order elimination and transit compartments absorption, the structural model shown in **Figure 3.1**, final parameter estimates are summarized in **Table 3.3** and visual predictive check in **Figure 3.3**. The model estimated a clearance value of 3.39 L/h for the typical patient. The effects of pregnancy and efavirenz were investigated on the exposure of the drug and the model didn't detect statistically significant effects.

3.4.4 Ethambutol pharmacokinetics

The chosen structural model was a two-compartment disposition model with transit compartments absorption as it gave best fit of our data and is depicted in **Figure 3.1**. Pregnancy and efavirenz effects were investigated on clearance and bioavailability and no statistically significant effects were detected. The typical value for clearance was 60.2 L/h.

3.4.5 A posteriori parametric power estimation and design evaluation

The stochastic simulation/re-estimation procedure revealed that our study data and design (same dosing and sampling times, patient covariates and variability in our study) had 91.8%, 59.2 %, and 90.1 % power (at significance $p < 0.01$) to detect a simulated 40% exposure difference for isoniazid, pyrazinamide, and ethambutol, respectively. The large difference in power between pyrazinamide and ethambutol, in spite of both drugs only having very few samples points in the postpartum arm, is owing to the low between-subject variability in clearance for ethambutol compared to pyrazinamide.

3.5 Discussion

In general, pharmacokinetic data on the impact of pregnancy on drug exposures are scarce (McCormack *et al.*, 2014). Our findings suggest that there is no clinically significant pregnancy

effect on the exposure for the three drugs. Although the study design and sample size were limited and prevented robust estimation of all pharmacokinetics parameters without relying on prior information, the posteriori power estimation suggests that if a large pregnancy effect (>40% reduction of exposure) were present between the 3rd trimester and postpartum, our analysis would have been powered to detect it at $p < 0.01$ with power 91.8%, 59.2%, and 90.1% for isoniazid, pyrazinamide, and ethambutol, respectively.

The observed exposure values in our cohort for isoniazid were low when compared with two conference proceedings on the pharmacokinetics of isoniazid in pregnancy.

The first one, (Schalkwyk *et al.*, 2017), reported median C_{max} of 4.1 and 4.0 mg/L for the 3rd trimester and postpartum, respectively, while the observed median C_{max} in our cohort in the 3rd trimester was 1.39 and 1.43 mg/L postpartum.

The second one, (Gausi *et al.*, 2019) reported among pregnant women with HIV co-infection, isoniazid clearance values of 72.3, 38.5, and 14.5 L/h for fast, intermediate, and slow NAT2 acetylator, respectively. Median C_{max} during pregnancy and postpartum were 2.89 vs. 3.69 mg/L, respectively, and AUC_{0-24} during pregnancy was 8.05 vs 11.1 mg·h/L postpartum. In our cohort, the observed clearance values were 97.1, 75.7, and 29.0 L/h for fast, intermediate, and slow metabolizers, with observed median AUC_{0-24} of 6.88 during pregnancy and 5.01 mg·h/L postpartum.

When compared to previous reports in non-pregnant population (Daskapan *et al.*, 2019), our exposure values for isoniazid are low. Median C_{max} is reported to range from 3.0 to 6.5 mg/L (Choudhri *et al.*, 1997; Taylor *et al.*, 1998; McIlleron *et al.*, 2006; Chideya *et al.*, 2009; Denti, Martinson, *et al.*, 2015; van Oosterhout *et al.*, 2015; Rockwood *et al.*, 2016), while the median values observed in our study were 1.39 and 1.43 mg/L for prepartum and postpartum

respectively. For $AUC_{0\text{-}24h}$, the median reported values are between 10.0 and 22.5 mg·h/L while ours was 6.88 mg·h/L prepartum and 5.01 mg·h/L postpartum. These large discrepancies between our values and the literature on non-pregnant individuals could be attributed to several factors, including different distribution of NAT2 genotype in different populations (Sabbagh *et al.*, 2011) (which was not accounted for in some of the reported values), and large variability in exposures possibly caused by sample handling and instability of isoniazid at room temperature (Poole *et al.*, 1960). On the other hand, it could be that isoniazid concentrations are lower both during pregnancy and early postpartum, with the pregnancy effect disappearing only a few months after delivery. So the lack of a "pregnancy" effect in our analysis could be explained by the choice of postpartum as comparator as pointed out in (Salman *et al.*, 2017). It will be important in future studies to evaluate this further given that isoniazid C_{max} values less than 3 mg/L are considered to be subtherapeutic.

The observed pyrazinamide exposure in our cohort is in line with previously reported values in literature in HIV-positive tuberculosis-infected patients. The reported median C_{max} (Choudhri *et al.*, 1997; Taylor *et al.*, 1998; McIlleron *et al.*, 2006; Chideya *et al.*, 2009; Denti, Jeremiah, *et al.*, 2015; van Oosterhout *et al.*, 2015; Rockwood *et al.*, 2016) ranged from 30 to 55 mg/L compared to a median value in our cohort of 35.9 mg/L for prepartum and 34.5 mg/L for postpartum. Reported $AUC_{0\text{-}24}$ (Denti, Jeremiah, *et al.*, 2015; van Oosterhout *et al.*, 2015; Rockwood *et al.*, 2016) ranges between 344 to 420 mg·h/L and median value observed in our cohort was 419 and 407 mg·h/L for prepartum and postpartum, respectively. This is reassuring: even if our analysis was poorly powered to detect a pregnancy effect for pyrazinamide, the values are very well aligned with a non-pregnancy population, so pregnant women are not at risk of over or under exposure to this anti-infective agent.

Ethambutol exposure values in our study were slightly lower than the reported results. Historical median C_{max} range from 2.11 to 5.0 mg/L (Tappero *et al.*, 2005; McIlleron *et al.*, 2006; Chideya *et al.*, 2009; Tostmann *et al.*, 2013; Denti, Jeremiah, *et al.*, 2015; van Oosterhout *et al.*, 2015) and $AUC_{0\text{-}24h}$ between 20.0 and 23.0 mg·h/L (Tappero *et al.*, 2005; Tostmann *et al.*, 2013; Denti, Jeremiah, *et al.*, 2015; van Oosterhout *et al.*, 2015);our median values for C_{max} were 1.82 mg/L for prepartum and 2.1 mg/L postpartum and $AUC_{0\text{-}24}$ were 16.5 prepartum and 19.0 mg·h/L postpartum. The lower concentrations in our study could once again be due to the choice of postpartum as the comparator, but the overall difference compared with historical non-pregnant values is very moderate, so our findings are reassuring that for ethambutol as well, pregnant women are not at risk of inadequate exposure.

Our study has several limitations. First, the timing of the doses and adherence was not always accurately captured, as this was an opportunistic sub-study within Tshepiso among women who had study visits late in pregnancy or during labour, and postpartum. Second, no HIV-negative women were included in the analysis, so we could not assess the effects of HIV co-infection with antiretroviral treatment on the pharmacology of tuberculosis drugs in the participants. Another limitation of the study is represented by the very few pharmacokinetic profiles and sample points of pyrazinamide and ethambutol available postpartum, since a majority of the patients were already in the continuation phase of their tuberculosis treatment at the time of pharmacokinetics sampling.

While this study was small, it is nevertheless unique, and the results are reassuring: pregnancy did not appear to meaningfully affect isoniazid, pyrazinamide, and ethambutol concentrations in women with HIV and tuberculosis, as previously reported for rifampicin (Denti, Martinson, *et al.*, 2015). The results of this study support the use of standard treatment without dose

adjustment for tuberculosis treatment in pregnancy . Pregnant women are at high risk of progression from latent tuberculosis infection to active tuberculosis disease and to suffer adverse maternal and foetal outcomes related to tuberculosis. It is therefore imperative to provide data-supported rational dosing for both prophylaxis and treatment of tuberculosis in this vulnerable population. Additional studies are needed across different geographic populations and with both first- and second-line anti-TB drugs.

Chapter 4:Pretomanid pharmacokinetics in the presence of rifamycins: interim results from a randomized trial among patients with tuberculosis

4.1 Abstract

Shorter, more potent regimens are needed for tuberculosis. The nitroimidazole pretomanid was recently approved for extensively drug-resistant tuberculosis in combination with bedaquiline and linezolid. Pretomanid may also have benefit as a treatment-shortening agent for drug-sensitive tuberculosis. It is unclear how and if it can be used together with rifamycins, key sterilizing first-line drugs.

In this analysis, data were pooled from two studies: the Assessing Pretomanid for Tuberculosis (APT) trial, in which patients with drug-sensitive pulmonary TB received pretomanid, isoniazid, pyrazinamide, plus either rifampicin or rifabutin vs. standard of care under fed conditions and the AIDS Clinical Trials Group (ACTG) 5306 trial, a phase I study in healthy volunteers receiving pretomanid alone or in combination with rifampicin under fasting conditions.

In our population pharmacokinetics model, participants taking rifampicin had 44.4 and 59.3% reduction in pretomanid AUC compared to rifabutin or pretomanid alone (due to 80 or 146% faster clearance) in APT and A5306, respectively. Median C_{max} in the rifampicin and rifabutin arms were 2.14 and 3.35 mg/L, while median $AUC_{0\text{-}24h}$ were 30.1 and 59.5 mg·h/L, respectively. Though pretomanid exposure in APT was significantly reduced with rifampicin, $AUC_{0\text{-}24}$ values were similar to those associated with effective treatment in registrational trials, likely because APT participants were fed with dosing, enhancing pretomanid relative bioavailability and exposures. Pretomanid concentrations with rifabutin were high, but in range with prior observations. Whilst pretomanid exposures with rifampicin are unlikely to impair efficacy, our data suggest that pretomanid should be taken with food if prescribed with rifampicin.

4.2 Introduction

In 2018, over 10 million people had incident tuberculosis (TB) and 1.4 million died(World Health Organization, 2019a). A continued challenge in TB control is the duration and complexity of treatment regimens (Kruk *et al.*, 2008). Treatment success rates are still suboptimal and have fallen slightly in recent years, from 86% in 2013 to 82% in 2017(World Health Organization, 2018). First-line treatment for drug-susceptible TB usually requires 6 months of multi-drug therapy. Shorter duration regimens are needed to decrease logistical burden for patients and programs, improve adherence, and limit the emergence of resistance. Poor adherence, defined as taking 90% or fewer prescribed doses, is known to portend poorer outcomes (Imperial *et al.*, 2018) and treatment default increases over the course of treatment (Kruk *et al.*, 2008), hence the continued interest in shortened TB regimens. One model-based analysis suggested that a 4-month regimen for drug-susceptible TB, priced at 1 US dollar per day, would increase treatment completion and decrease mortality (Gomez *et al.*, 2016). Additionally, a regimen with higher efficacy than the standard first-line combination of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) would reduce mortality as well as TB incidence (Kendall *et al.*, 2017). Earlier efforts at treatment shortening have yielded mixed results, likely due to heterogenous pools of participants as well as the inherent challenge of killing both replicating and dormant *Mycobacterium tuberculosis* (*M.tb*) bacilli. Three trials comparing relapse rates of four-month fluoroquinolone-containing treatment regimens versus standard of care (OFLOTUB, REMoxTB, RIFAQUIN) were unsuccessful (Gillespie *et al.*, 2014; Jindani *et al.*, 2014; Merle *et al.*, 2014; Imperial *et al.*, 2018). If our goal is to offer all patients the opportunity for shortened treatment duration, a regimen comprised of so-called “sterilizing agents,” with potent activity against dormant (“persister”) populations of bacilli, may offer the most promise (Zhang *et al.*, 2012).

Pretomanid, the newest anti-tuberculosis medication approved by the US Food and Drug Administration (FDA), is a novel nitroimidazole with activity against both replicating and dormant bacilli. Pretomanid requires activation by deazaflavin (F420) dependent nitroreductase (Ddn), present in *M.tb*, and has various mechanisms of action including disruption of cell wall mycolic acid synthesis (Singh *et al.*, 2008). Pretomanid is highly effective in combination with linezolid and bedaquiline, comprising the first six-month regimen for extensively drug resistant (XDR) TB (*M.tb* resistant to isoniazid, rifampicin, fluoroquinolones, and injectable agents) (TB Alliance, 2019). Given its spectrum of action, there is interest in pretomanid as a treatment-shortening agent for drug-sensitive TB (Tweed *et al.*, 2019). A murine model of aerosol TB infection demonstrated potent treatment-shortening effect of pretomanid combined with either pyrazinamide or rifampicin (Tasneen *et al.*, 2008). Murine models have described pretomanid activity as time dependent, where the bactericidal activity was best correlated with the cumulative percentage of the dosing interval that the free drug concentration exceeds the minimum inhibitory concentration (% $fT_{>MIC}$). Free drug $T_{>MIC}$ of 48 and 77% were associated with 1-$\log_{10}$ kill (bactericidal activity) and 1.59-$\log_{10}$ kill (accounting for 80% of the maximum observed kill effect), respectively (Ahmad *et al.*, 2011). The unresolved question is how best to use pretomanid in shortened combination TB treatment regimens in humans.

Pretomanid is extensively metabolized, with seven primary metabolites identified so far (Dogra *et al.*, 2011). Though cytochrome P450 enzyme 3A (CYP3A) is thought to be a minor metabolic pathway, prior data in healthy volunteers showed that on average, rifampicin (a potent inducer of CYP3A) reduced pretomanid exposures by 66% (Dooley *et al.*, 2014). Rifamycins (rifampicin, rifabutin, rifapentine) provide a vital backbone to TB treatment, therefore the feasibility of combining one with pretomanid is of great interest in potential treatment-shortening regimens.

To assess the safety and efficacy of a regimen that incorporates pretomanid with a rifamycin, the "Assessing Pretomanid for Tuberculosis (APT)" trial was designed (Dooley, 2014). Participants with drug-susceptible pulmonary TB are randomized into three arms: pretomanid (Pa), isoniazid (H), pyrazinamide (Z), plus either rifampicin (R) (PaHZR), or rifabutin (Rb) (PaHZRb); or standard of care (HRZE). The hypothesis prior to study commencement was that pretomanid exposures would be lower when given together with rifampicin versus rifabutin (rifabutin is a less potent inducer of CYP3A), potentially falling into a range that could reduce microbiologic response. Here, we report results from the planned interim pharmacokinetics analysis from APT, incorporating data from the earlier healthy volunteer trial drug-drug interaction trial, A5306 (Dooley *et al.*, 2014).

4.3 Materials and Methods

4.3.1 Study population

Adults (age > 18 years) with drug-susceptible pulmonary tuberculosis were recruited from the hospital and clinics of University of Cape Town in Cape Town, South Africa, between October 2014 and June 2019. Participants were eligible if they weighed 40-80 kg, had Karnofsky score ≥ 60, had acid-fast bacilli on stained smear from expectorated sputum, and if HIV positive, CD4 count >350 cells/mm^3 without plans to start antiretroviral therapy during the experimental phase of the trial (Dooley *et al.*, 2014; Mfinanga *et al.*, 2014). Participants were excluded if they were pregnant or breast-feeding, or had central nervous system TB, history of neuropathy or epilepsy, baseline QTcF >450 milliseconds (msec), lens opacity, resistance to first-line TB regimen components, or more than five days of TB treatment. Participants were also excluded if they had the following laboratory parameters: alanine aminotransferase (ALT) >3 times upper limit of normal (ULN), total bilirubin >2 times ULN, creatinine > ULN, hemoglobin < 7.0g/dL, platelet

count < 100,000/mm^3. Women of child-bearing potential were required to use two methods of contraception through one week after last dose of study medication. Male participants were required to use similar methods with their female partners to prevent pregnancy. The study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine and University of Cape Town's Human Research Ethics Committee and registered with clinicaltrials.gov (NCT02256696).

4.3.2 Experimental protocol

APT study design – APT is an open-label, three-arm, phase 2B randomized clinical trial to assess the mycobactericidal activity of pretomanid 200 mg when substituted for ethambutol and given together with first-line TB treatment (isoniazid, pyrazinamide, a rifamycin). The experimental phase of treatment is 12 weeks, after which all participants transition to standard of care (SOC) to complete 24 weeks of TB therapy. Participants in Arm 1 receive isoniazid, rifampicin, pyrazinamide, and pretomanid for 8 weeks, followed by isoniazid, rifampicin, and pretomanid for 4 weeks (8HRZPa/4HRPa). Participants in Arm 2 receive the same treatment, except that rifabutin 300mg daily is substituted for rifampicin (8HRbZPa/4HRbPa). Participants in Arm 3 receive standard of care (8HRZE/4HR). All study medication administration is directly observed and pretomanid dosing occurs after a standardized meal. Intensive sampling for pretomanid plasma pharmacokinetics (pre-dose, then 1, 2, 5, 8, and 24-hours post-dose) is performed on Day 14. Sparse sampling for pretomanid pharmacokinetics is performed pre-dose, and 2 and 4-hours post-dose on Days 28, 56, and 84. Serial sputum cultures are collected at baseline and on Days 7, 14, 21, 28, 42, 56, 70, and 84. A pharmacokinetics dosing occasion is any dosing record with at least one sampling point where a pharmacokinetics visit is any pharmacokinetics sampling visit as defined by the protocol.

Follow-up – Participants are followed for a total of twelve months. Laboratory and clinical assessments are performed weekly for the first month, followed by biweekly for the subsequent two months and include targeted symptom and adverse event assessment. On Days 7, 14, 28, 42, 56, and 84, blood is collected to measure complete blood count, creatinine, ALT, total bilirubin. An ECG is performed on Days 7 and 28; follow-up visual acuity and color perception is assessed on Day 28.

4.3.3 Drug concentration analysis

Blood samples were collected in EDTA tubes, centrifuged at 1500-2000 g for 10 minutes and plasma then transferred to cryovial and frozen at -70°C within one hour. Pretomanid plasma concentrations were quantified using liquid chromatography-tandem mass spectrometry (LC/MS/MS) in the Division of Clinical Pharmacology, University of Cape Town. The calibration range was 0.01 (the lower limit of quantification [LLOQ]) to 8 mg/L. Precision (expressed as coefficient of variation) was lower than 9% at all concentrations with accuracies 95.2-110%.

4.3.4 Pharmacokinetics (PK) and statistical analyses

Pretomanid plasma concentrations were analyzed using nonlinear mixed-effects modelling (NONMEM 7.4 with FOCE-I (Icon Development Solutions, Ellicott City, MD, USA)). PsN (Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden), Xpose, and Pirana (Certara USA, Inc., 100 Overlook Center, Suite 101, Princeton, NJ 08540 USA) (Keizer *et al.*, 2013) were used for model run execution and tracking. Data preparation and statistical comparisons were performed using R statistical software (version 3.6.3; https://www.r-project.org/) and Stata (version 15; Stata Corporation, College Station, TX, USA).

Different structural models describing typical pharmacokinetics characteristics were evaluated. To describe the absorption process, we tested first-order absorption with lag or chain of transit compartments (R M Savic *et al.*, 2007); for the disposition process, we tested one- and two-compartment models with first-order elimination. We tested proportional, additive and combined error models to describe residual unexplained variability. The typical value of relative oral bioavailability (F) was fixed to one, thus, the clearance and volume parameters are reported relative to oral F.

The model included between-subject and between-occasion variability on the pharmacokinetics parameters assuming log normal distribution. Allometric scaling (Anderson *et al.*, 2008) was applied to disposition parameters to account for effect of body size: we tested total body weight (TBW), fat-free mass (FFM), and body fat proportion as body size descriptors. The individual values of FFM were derived from observed TBW, height, and sex (Janmahasatian *et al.*, 2005). Fat mass was obtained as the difference between TBW and FFM. Different covariates were tested on the pharmacokinetics parameters including, age, sex, HIV, serum creatinine, albumin levels, sex, smoking status and treatment arm. The development of the model and the inclusion of covariates were based on physiological plausibility, inspection of diagnostic plots including visual predictive checks (Holford, 2005), and decreases in the objective function value (OFV), which was assumed to follow a chi-square (χ^2) distribution. The statistically significant cut-off for an additional degree of freedom (inclusion of one additional parameter) was an OFV drop of at least 3.84 points, corresponding to $p<0.05$.

To evaluate % $fT_{>MIC}$ and obtain the probability of target attainment (PTA) for each treatment arm at specific MICs, a simulation of 10,000 replicates was performed using final parameters estimates of the typical median patient with TB observed in the APT study for each treatment

arm, assuming protein binding to be 85% (personal communication with TB Alliance) and MIC range of 0.015 to 0.25 mg/L. The corresponding PTA was calculated as the proportion of simulated replicates with $\%fT_{>MIC}$ of at least 48 or 77%. (Ahmad *et al.*, 2011).

4.3.5 Interim analysis

An interim analysis was planned for once 50% of patients had completed treatment to evaluate safety, efficacy, and pharmacokinetics. An unadjusted hazard ratio for time to culture conversion was estimated using Cox-proportional hazards model, and a hazard ratio of at least 1.20 was required for an experimental arm to continue enrollment. The full sample size of 183 participants was based on a two-sided type 1 error of 5%, power of 90%, target hazard ratio of ≥ 1.9, and 15% invaluable or lost to follow-up. The interim analysis was powered at 95% to ensure end of study power at 90%. The interim pharmacokinetics analysis was intended to contextualize interim efficacy results and, if necessary, to inform dosing. Aggregated safety data, as well as pharmacokinetics data were reviewed by the study team and data safety monitoring board (DSMB), and arm-specific efficacy and safety data were reviewed in a closed session by the DSMB. Despite the COVID-19 pandemic, study activities have resumed, and complete enrollment is anticipated.

4.3.6 ACTG 5306 Data

In order to fully evaluate the effect of rifampicin on pretomanid pharmacokinetics, taking into account the contribution of food, permission was obtained to analyze data from AIDS Clinical Trials Group (ACTG) 5306 (Dooley *et al.*, 2014). This phase I study sequentially assigned healthy volunteers to receive pretomanid with either lopinavir-ritonavir, efavirenz, or rifampicin. In the rifampicin arm, participants received pretomanid for 7 days (period 1), rifampicin for 7 days (period 2), then combination therapy with rifampicin and pretomanid for 7 days (period 3).

All study medications on pharmacokinetics sampling days were taken on an empty stomach. Pretomanid was dosed 200 mg once daily; adherence was assessed by pill counts and medication diaries. Pharmacokinetics samples for pretomanid were obtained pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose at the ends of periods 1 and 3. Plasma concentrations for pretomanid were quantified using LC/MS/MS. The bioanalytical method was validated over a linear range of 0.01 to 10 mg/L. The inter-day precision (CV%) ranged from 2.65 to 4.71% and the intra-day precision (%CV) was 1.58 to 6.28% (Dooley *et al.*, 2014).

4.4 Results

Data from 58 participants from the APT pretomanid treatment arms and 32 participants from the A5306 trial were included, 16 of whom (in A5306) provided paired pharmacokinetics profiles in the rifampicin treatment arm. Baseline characteristics by study and treatment arms are summarized in **Table 4.1**. Participants contributed a total of 1157 pharmacokinetics samples with a total of four pharmacokinetics visits and eight sampling occasions. Five samples (0.8%) had concentrations below LLOQ (BLQ) which was considered to reflect non-adherence in the preceding days and dosing and sampling records from those days were excluded.

Pretomanid pharmacokinetics was best described by a one-compartment disposition model with first order elimination and dynamic transit compartments absorption. The typical value of clearance (CL/F) for the median patient receiving pretomanid alone or with rifabutin was 3.90 (L/h). Treatment arm by study was a significant covariate when tested on clearance (a drop of -244 point in OFV, 2 degree of freedom, $p < 0.001$). Patients receiving rifampicin in the APT trial had 80% higher clearance while patients in the A5306 trial had 146% higher clearance resulting in 44.4 and 59.4 % reduction in exposure in terms of overall area under concentration curve (AUC), respectively. Fat-free mass was used to allometrically scale clearance while volume of

distribution was scaled by total body weight via power relationship; the exponent was fixed to 1.0 and 0.75 for volume and clearance, respectively. The model detected pretomanid in the A5306 study to have 42.2% lower bioavailability, 53% faster absorption rate constant and 34.5% shorter absorption mean transit time (ΔOFV -159, 2 degrees of freedom and $p < 0.001$). The model did not detect a significant effect of rifabutin on pretomanid clearance. The residual unexplained variability was best described by combined error model incorporating both proportional and additive components. A visual predictive check showing adequate model fit to the data is depicted in **Figure 4.1**. The final model parameters are summarized in **Table 4.2**, model-estimated secondary pharmacokinetics parameters are shown in **Figure 4.2** .

Table 4.1. Baseline characteristics and disease severity of studies participants with smear positive pulmonary tuberculosis (TB) receiving pretomanid (Pa) containing regimens, by treatment arm

	Treatment regimens			
Characteristics	A5306 (n=32) [b]	Pa-H-Z-Rifampicin (n=30)	Pa-H-Z-Rifabutin (n=28)	Total (n=90)
Male (%)	18 (56.3)	22 (73.3%)	19 (67.8%)	59 (65.6)
Age (Years)	28.5 (25.0 - 39.2)	31 (23.0 - 38.3)	30.0 (22.5 - 33.8)	30.0 (24.0 - 38.0)
Weight (Kg)	77.0 (69.0 - 91.3)	53.0 (48.5 - 58.3)	53.4 (49.0 - 60.8)	58.0 (51.0 - 72.9)
FFM (kg)	53.6 (44.4 - 60.7)	44.8 (41.5 - 46.7)	44.0 (39.6 - 47.9)	46.3 (41.9 - 51.9)
Albumin(g/L)	-	35.0 (31.0 - 39.0)	37.0 (33.3 - 41.8)	36.0 (32.8 - 40.0)
Female	-	36.5 (34.0 – 40.8)	38.0 (36.0 – 40.5)	38.0 (34.0 – 40.0)
Male	-	34.5 (31.0 – 38.3)	37.0 (33.5 – 42.0)[a]	36.0 (33.0 – 39.0)
HIV positive (%)[c]	-	2 (6.7)	1 (3.57)	3 (5.17)
Diabetes (%)[c]	-	0 (0)	1 (3.4)	1 (1.72)
Smoking[c]				
Non-Smoker	-	11 (36.7)	6 (21.4)	17 (29.3)
Current	-	13 (43.3)	17 (60.7)	30 (51.7)
Quit < 1 year ago	-	5 (16.7)	4 (14.3)	9 (15.5)
Quit > 1 year ago	-	1 (3.33)	1 (3.57)	2 (304)
Disease Severity				
Baseline smear grade[c]	-			
Scanty	-	1 (3.3%)	0 (0%)	1 (1.72)
1+	-	7 (23.3%)	8 (27.6%)	15 (29.9)
2+	-	10 (33.3%)	8 (27.6%)	18 (31.0)
3+		12 (40.0%)	13 (44.8%)	25 (43.1)
Cavitary disease (%)[c]	-	25 (83.3%)	24 (85.7%)	49 (84.5)

Notes: Data reported as median (IQR).

pretomanid (Pa), isoniazid (H), pyrazinamide (Z), rifampicin (R), rifabutin (Rb), fat-free mass (FFM)

[a] median was imputed for 2 missing values

[b] number of participants receiving rifampicin were 16

[c] The denominator used is 58 patient (from APT study) as study A5306 did not provide any data on these covariates

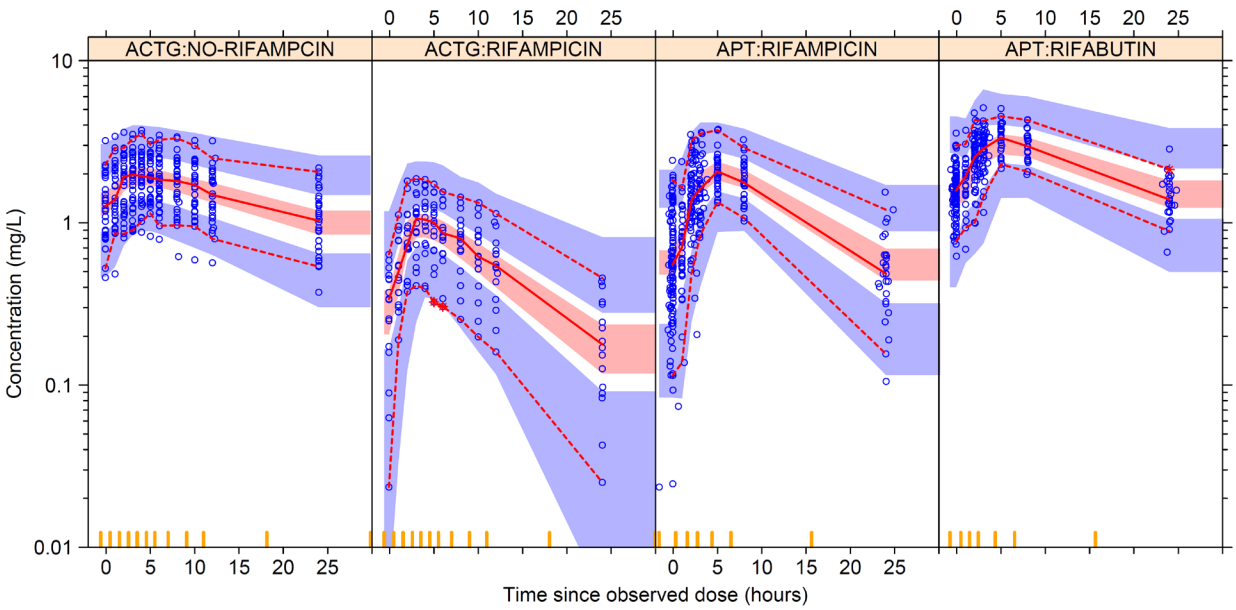

Figure 4.1. Visual predictive check (VPC) for pretomanid concentration (mg/L) versus time (time since observed dose), stratified by study and treatment arms.

Circles represent original data, dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. Vertical yellow lines on the x-axis represent bins for sampling timepoints. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

Table 4.2. Final population pharmacokinetics model parameters

Parameter description	Typical Value (95 % CI)*
Clearance, (L/h) †	3.91 (3.65 ; 4.17)
Central Volume of distribution, Vc (L) †	90.9 (86.7 ; 95.7)
Absorption mean transit Time, MTT (h)	1.16 (1.02 ; 1.30)
Number of Transit Compartment (NN)	6 (FIXED)
Absorption rate constant, Ka (1/h)	0.592 (0.516 ; 0.681)
Bioavailability, F	1 (FIXED)
Proportional error (%)	7.85 (7.18 ; 8.65)
Additive Error (mg/L)	0.0359 (0.0251 ; 0.0480)
APT Rifampicin effect on CL (%)	+80 (63.2 ; 98.7)
ACTG study effect (%)	
Rifampicin effect on CL	+146 (126 ; 171)
Absorption rate constant, Ka$	+ 53.6 (35.9 ; 75.4)
Absorption mean transit Time, MTT$	-34.9 (-26.4 ; - 43.0)
Bioavailability	-41.9 (-46.3 ; -36.9)
Between-subject variability (%)§	
Clearance	19 (15.7 ; 23.0)
Bioavailability	12.5 (7.20 ; 17.5)
Between-visit variability (%)‡§	
Clearance	11.3 (8.83 ; 14.2)
Between-occasion variability (%)‡§	
Absorption mean transit time	56.8 (49.6 ; 66.2)
Absorption rate constant	39.9 (25.5 ; 53.2)
Bioavailability	19.8 (17.0 ; 23.2)

* 95 % confidence intervals obtained with sampling importance resampling technique using PsN software

† Allometric scaling used for CL, Vc; typical values reported for typical median patient with 58 kg weight, 45 kg FFM and not receiving rifampicin under APT study conditions.

$ Study effect was modeled on Ka and MTT^{-1} with same parameter

‡ A "visit" is any PK sampling visit as defined in the protocol, whereas an "occasion" is any dosing event followed by at least one sampling point.

§ Between- subject variability (BSV), -visit (BVV) and -occasion variability (BOV) were assumed to be log-normally distributed and reported as approximate %CV

Table 4.3. Summary of pharmacokinetics (PK) parameters from Assessing Pretomanid for Tuberculosis (APT) trial compared to prior studies, among both healthy volunteers and TB patients.

	CL-009[¥]		APT*[§] (this study)		A5306 (this study)*		CL-010[£]		
Population	Healthy		Patient		Healthy		Patient		
Fed	No	Yes	Yes		No		No		
Regimen	Pa	Pa	Pa-HZR	Pa-HZRb	Pa-R	Pa	Pa_{50}	Pa_{100}	Pa_{200}
AUC_{0-24} (mg·h/L)	28.1 (8.0)	51.6 (10.1)	30.1 (23.5, 35.3)	59.5 (48.0, 65.2)	13.4 (9.94, 18.2)	34.5 (26.3, 45.8)	12 (1.4)	17 (1.5)	36 (1.4)
C_{max} (mg/L)	1.1 (0.2)	2.0 (0.3)	2.14 (181, 2.42)	3.35 (2.93, 3.74)	1.07 (0.731, 1.43)	1.98 (1.41, 2.59)	0.75 (1.4)	1.1 (1.4)	2.1 (1.3)
CL_F (L/h)	7.6 (2.5)	3.9 (0.8)	6.78 (6.35, 8.39)	3.79 (3.62, 4.54)	14.7 (10.5, 20.3)	4.48 (3.46, 5.50)		4.8 (0.22)	

Notes: PK data collected on day 14 (APT, CL-010, CL-007), day 7 (A5306), or after single dose (CL-009).
APT Doses: Pretomanid (Pa) 200 mg, isoniazid (H) 300 mg, pyrazinamide (Z) 1000-2000 mg, rifampicin (R) 600 mg, rifabutin (Rb) 300 mg (all pretomanid doses 200mg unless specified)
CL-009: mean (SD)
APT: median (IQR)* model-estimated individual exposure metrics
§ at day 14 data from 57 patients was available
A5306: median (IQR)* model-estimated individual exposure metrics
CL-010: geometric mean (geometric SD)
¥ (Winter, Ginsberg, *et al.*, 2013)
£ (Lyons, 2018)

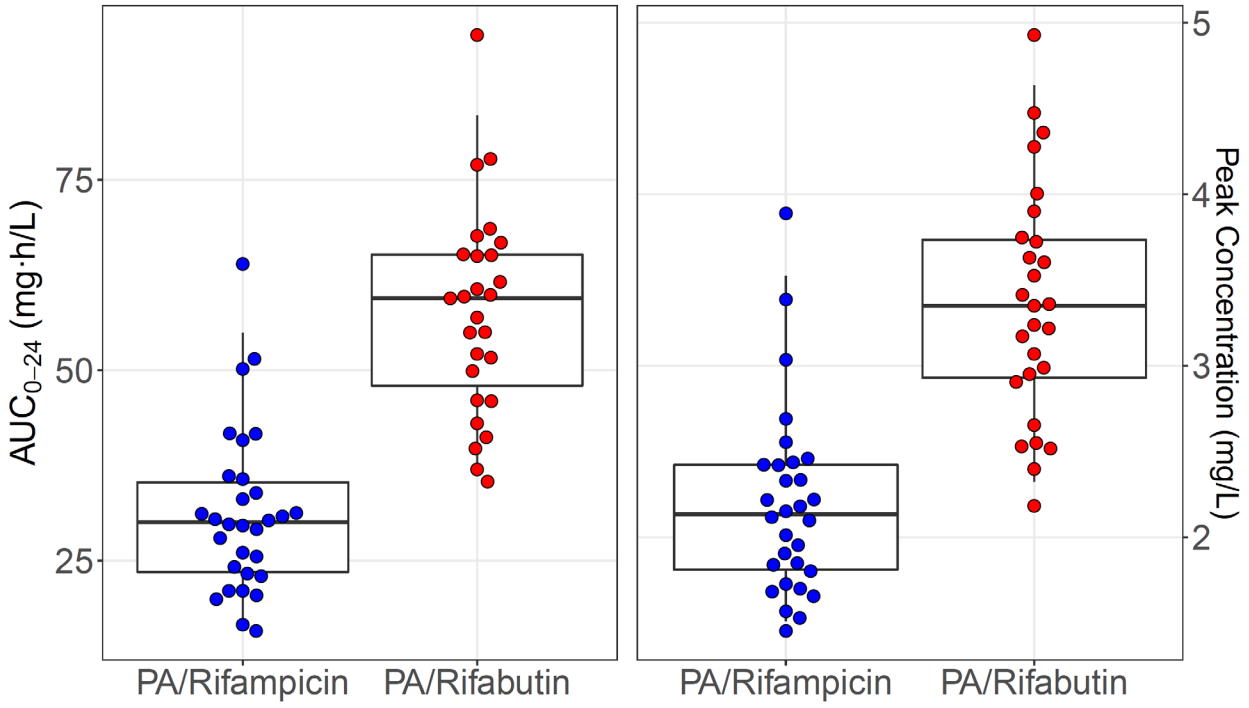

Figure 4.2. Box and whisker plots showing individual model-predicted pretomanid AUC_{0-24h} and C_{max} on day 14 in the APT study, stratified by treatment arm.

The dots represent individual values, the box is the IQR, and the whiskers show 2.5th and 97.5th percentiles.
*Data was available for 57 patients at day 14.

4.4.1 Probability of target attainment

The probability of target attainment for pretomanid is depicted in **Figure 4.3**, using the target for 1-$\log_{10}$ bactericidal activity (48% $fT_{>MIC}$) (Ahmad *et al.*, 2011). Pretomanid co-administered with rifampicin or rifabutin under fed conditions showed favorable PTA at the recommended dose of 200 mg daily. The PTA was above 90% in both the rifampicin and rifabutin arms at MIC level of 0.03125 or 0.0625 mg/L. When using the target corresponding to 1.59-log10 bactericidal activity (77% fT>MIC), the PTA was above 90% at MIC level of 0.03125 or 0.0625 mg/L.

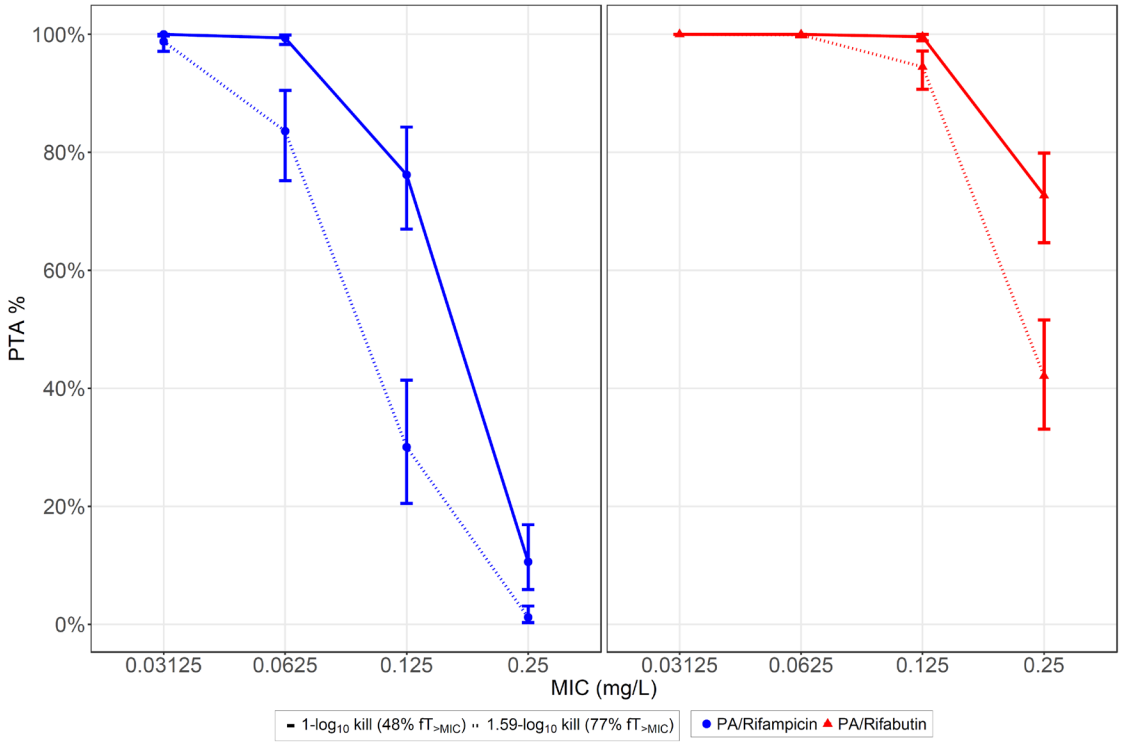

Figure 4.3. Probability of target attainment versus MIC levels assuming 15% protein binding in each treatment arm at steady state.

1-$\log_{10}$ kill (48% $fT_{>MIC}$) represent pharmacokinetics/pharmacodynamics target of bactericidal activity while 1.59-$\log_{10}$ (**77% $fT_{>MIC}$**) PK/PD target represent 80% of maximum observed kill. Calculations were based on 10,000 simulations of the median TB patient pharmacokinetic observed in APT study. Vertical bars represent 2.5th and 97.5th percentiles.

4.5 Discussion

In this analysis, we evaluated the pharmacokinetics of pretomanid, when administered with isoniazid, pyrazinamide, and either rifampicin or rifabutin, for the treatment of smear-positive pulmonary tuberculosis, or when administered with or without rifampicin in healthy volunteers and found that pretomanid exposures were reduced by nearly half when given with rifampicin versus rifabutin or pretomanid alone. Pretomanid is currently only approved for the treatment of XDR and treatment-intolerant or -refractory MDR TB but holds potential as a treatment shortening agent for drug-susceptible TB, hence the need to study pretomanid in combination with first-line drugs.

The APT trial was originally designed to determine whether or not pretomanid, when combined with a rifamycin-containing first-line regimen, demonstrated enhanced microbiologic activity and thus showed treatment-shortening potential for drug-susceptible TB. Results from the A5306 study, in which healthy volunteers received either pretomanid 200 mg alone or in combination with rifampicin 600 mg, had previously shown that pretomanid exposures were reduced markedly, with $AUC_{0\text{-}24h}$ falling from 34.5 to 13.4 mg·h/L.66% (Dooley *et al.*, 2014). The pretomanid exposures observed in A5306, when pretomanid was given with rifampicin, were comparable to those seen when pretomanid was given at a much lower dose of 50 mg without rifampicin. From dose-finding early bactericidal activity (EBA) studies, doses of 50 mg given without food showed decreased activity compared to doses of 100 mg or higher (Diacon *et al.*, 2012). Therefore, there was concern that co-administration of pretomanid with rifampicin could lower pretomanid exposures into a potentially sub-therapeutic range. For this reason, the package insert currently reads that pretomanid should not be combined with any rifamycins (though prior to the current study, pretomanid had not been studied in combination with any rifamycin other than rifampicin).

In this analysis, pretomanid concentrations in the APT study were measured at steady state (day 14, 28, 56 and 84), and, as predicted, co-administration with rifampicin significantly reduced pretomanid exposures. On average, patients receiving rifampicin had pretomanid AUC reduced by about 44.4% compared to patients receiving rifabutin driven by an 80% increase in clearance. Though the observed reduction in pretomanid exposure in these results is significant, it is slightly smaller in magnitude than that observed in the A5306 cohort (44.4 % versus 59.4%). More importantly, the absolute individual model-predicted values of $AUC_{0\text{-}24h}$ and C_{max} in the APT rifampicin arm are similar to those in the pretomanid only arm of the A5306 study and to those seen in trials of the now-registered dose, wherein pretomanid was given without a rifamycin (Diacon *et al.*, 2010, 2012). In these earlier trials, the 200 mg dose, which was subsequently approved based on robust clinical efficacy, produced a pretomanid AUC of 36 mg·h/mL (Diacon *et al.*, 2010, 2012). Even with the relative reduction in exposures, the rifampicin arm in the APT trial produced similar exposures, in absolute terms, to those seen in registration trials (**Error! Reference source not found.**). If the exposures seen in the APT trial can be replicated in clinical practice, it would seem to suggest pretomanid could be co-administered with rifampicin without compromising effect.

One reason for the observed pretomanid exposures in the rifampicin-containing arm of the APT cohort being comparable with pretomanid given without rifamycins in A5306 and other efficacy trials is likely due to the effect of food on pretomanid absorption. Unlike in the licensing trials, in which participants were fasting, participants in the APT trial were given a standard meal prior to dosing, usually consisting of coffee and toast with butter. Interestingly, this simple breakfast appeared to enhance absorption and exposures to a similar degree as the high-fat meal provided in the earlier food effect trials. Earlier phase I trials observed a significant food effect on

pretomanid exposures, with C_{max} and AUC increasing to 176% and 188% in the fed versus the fasting state (Winter, Ginsberg, *et al.*, 2013). By incorporating data from A5306, the healthy volunteer trial of pretomanid plus rifampicin in which participants were dosed in a fasting state, we were able to more fully explore the hypothesis that food effect drove the acceptable pretomanid exposure levels, even in the presence of rifampicin. As expected, A5306 participants had faster absorption and reduced bioavailability, fitting with the fasting state conditions. Interestingly, the model combining APT and A5306 data showed different rifampicin induction effect on pretomanid pharmacokinetics between the two studies. Rifampicin co-administration was associated with a 59.4% decrease in pretomanid AUC in A5306, versus an 44.4% decrease in APT. This differential induction effect could be attributed to several factors, including administration with food and use of fixed dose combination (FDC) in APT, both of which are known to reduce rifampicin exposure (Saktiawati *et al.*, 2016; Court *et al.*, 2018). An additional distinction between APT and the earlier study of pretomanid with rifampicin is that APT is a treatment trial of participants with pulmonary TB, while the prior drug-drug interaction (DDI) study was among healthy volunteers. However, patients in APT were overall healthy except having pulmonary TB, and prior work has demonstrated negligible differences in the pharmacokinetics of other TB drugs among outpatient and hospitalized patients (Schutz *et al.*, 2020). There also remains the potential that some unidentified drug-drug or metabolic effect is affecting the observed pretomanid exposures, either with the companion drug or with rifabutin. Though isoniazid is an inhibitor of some CYP2C/E and CYP3A enzymes (Desta *et al.*, 2001), there is no current evidence to support an interaction between pretomanid and isoniazid. Additionally, a prior healthy volunteers trial explored potential pharmacogenetic effects on pretomanid pharmacokinetics and found no influence of SLCO1B1 521 or rs4149032, CYP3A5,

or CYP2B6 polymorphisms (Dooley *et al.*, 2014). Ultimately, the observed AUC in APT in a fed state seems comparable to exposures seen with standard 200 mg dose in a fasting state, which produced potent early bactericidal activity in earlier trials.

One limitation is that we did not explore the disposition of pretomanid on rifamycins, as we did not measure concentrations of rifampicin and rifabutin. However, we would expect any effect of pretomanid on rifamycin metabolism to be minimal. Pretomanid is a time-dependent inhibitor of CYP3A4/5 in vitro, but a prior healthy volunteer study found no clinical interaction between pretomanid and midazolam (traditional probe drug for CYP3A4/5) (Winter, Egizi, *et al.*, 2013). Additionally, though pretomanid is an inhibitor of organic anion-transporting polypeptide (OAT) 3 (Everitt, 2019), rifampicin and rifabutin metabolism is mediated by OAT1 (Sloan *et al.*, 2017). Finally, though our model used the published range of MIC (Ahmad *et al.*, 2011), there have been some trial patients with MIC above the range described here (personal communication with TB Alliance).

Interestingly, the rifabutin-containing arm showed an apparent increase in pretomanid exposure when compared to historical data of pretomanid given alone. Pretomanid AUC in this analysis is 59.5 mg·h/L, a value in between the exposures seen with 200 mg and 600 mg when pretomanid was given as monotherapy on an empty stomach in the dose-finding trial (AUC 36 and 69 mg·h/L, respectively) (Diacon *et al.*, 2010; Lyons, 2018). Given that pretomanid clearance is relatively unchanged between earlier monotherapy trials (4.8 L/h) and the rifabutin-containing arm in APT (3.79 L/h), this suggests that higher pretomanid AUC and C_{max} in the rifabutin-containing arm of APT may indeed be driven by food effect. This is further supported by the fact that pretomanid exposures in the presence of rifabutin in APT are quite similar to those observed after a single dose of pretomanid in a fed state. Whether or not these higher exposures in the

rifabutin arm present safety issues is not yet known, but interim data have been reviewed by the DSMB and did not lead to any safety-related recommendations for protocol modification. Also, these values fall squarely within the range of exposures of pretomanid from other trials.

Our simulations showed that favorable PTA can be achieved when pretomanid is co-administered with rifamycins under fed conditions. Pretomanid achieved a PTA of more than 90% with rifabutin for 1.59-log10 bactericidal activity (near maximal kill effect). Pretomanid given with rifampicin achieved similar PTA for 1-$\log_{10}$ bactericidal activity. The predicted PTAs should be interpreted while keeping in mind that the simulation was performed for the median patient in our cohort and patients with different weights are expected to have different exposure and thus might lead to slightly different PTA results. Also, these are PTA results for a single drug which is usually given as part of combination regimen for TB treatment and the PTA results might be different due to synergism or antagonism effect of other administered TB drugs.

4.6 Conclusion

In this pharmacokinetics analysis of the APT trial, bolstered by healthy volunteer data from A5306, co-administration with rifampicin increases pretomanid clearance compared to rifabutin, resulting in reduced pretomanid AUC by 40-50%. Pretomanid AUC in the fed state of this trial, even in the presence of rifampicin, is comparable to exposures seen in a fasting state, which were associated with excellent early bactericidal activity. Additionally, pretomanid AUC with rifabutin in a fed state is slightly higher than that observed in pretomanid monotherapy in a fasting state, a finding likely explained by food effect.

Chapter 5:Clofazimine pharmacokinetics in patients with tuberculosis: dosing implications

5.1 Abstract

Clofazimine is in widespread use as a key component of drug-resistant tuberculosis regimens, but the recommended dose is not evidence-based. Pharmacokinetic data from relevant patient populations are needed to inform dose optimization. We aimed to determine clofazimine exposure, evaluate covariate effects on variability, and simulate exposures for different dosing strategies in South African tuberculosis patients.

Clinical and pharmacokinetic data were obtained from participants with pulmonary tuberculosis enrolled in two studies with intensive and sparse sampling for up to 6 months. Plasma concentrations were measured by liquid chromatography-tandem mass spectrometry and interpreted with nonlinear mixed-effects modeling. Body size descriptors and other potential covariates were tested on pharmacokinetic parameters. We simulated different dosing regimens to safely shorten time to average daily concentration above a putative target concentration of 0.25 mg/L.

We analyzed 1,570 clofazimine concentrations from 139 participants; 79 (57%) had drug-resistant tuberculosis and 54 (38%) were HIV-infected. Clofazimine pharmacokinetics was well characterized by a three-compartment model. Clearance was 11.5 L/h and peripheral volume 10,500 L for a typical participant. Lower plasma exposures were observed in women during the first few months of treatment, explained by higher body fat fraction. Model-based simulations estimated that a loading dose of 200 mg daily for 2 weeks would achieve average daily concentrations above a target efficacy concentration 37 days earlier in a typical TB participant. Clofazimine was widely distributed with a long elimination half-life. Disposition was strongly influenced by body fat content, with potential dosing implications for women with tuberculosis.

5.2 Introduction

Drug-resistant tuberculosis remains a major obstacle to achieving End TB targets (World Health Organization, 2019a). A key driver of the drug-resistant tuberculosis epidemic has been a lack of effective therapy, leading to low cure rates, amplification of resistance, and ongoing transmission. New therapeutic options with improved efficacy and tolerability have recently become available, including the new antituberculosis agents bedaquiline and delamanid, and the repurposed drugs linezolid and clofazimine. As a result, there has been a shift in treatment guidelines towards shorter injection-free regimens. (World Health Organization, 2019b) Clofazimine is recommended by the World Health Organization and the American Thoracic Society for patients with rifampin-resistant tuberculosis (Nahid *et al.*, 2019; World Health Organization, 2019c) and also has a potential role in treatment-shortening regimens for drug-susceptible tuberculosis. (O'Donnell *et al.*, 2016) First discovered in 1957, clofazimine has been used almost exclusively in combination therapy for leprosy. There have been no studies evaluating dose-exposure relationships in patients with drug-resistant tuberculosis, and the optimal dose for this condition is unknown. Clofazimine is highly protein-bound(Swanson *et al.*, 2015) and undergoes duration-dependent accumulation in fat, tissue macrophages, and reticuloendothelial organs, resulting in an extremely long terminal half-life, (Cholo *et al.*, 2017) with implications for risk of adverse effects and resistance emergence. Furthermore, because clofazimine may be a substrate of cytochrome P450 (CYP) and the P-glycoprotein transporter, (Horita *et al.*, 2014; Te Brake *et al.*, 2016) there are potential pharmacokinetic (PK) drug-drug interactions, including with antiretrovirals and other antituberculosis agents. Though such research has been undertaken, it is unknown how well murine models of clofazimine dosing predict human pharmacokinetic. (Swanson *et al.*, 2016) As a consequence of this limitation, plus

the lack of pharmacokinetic data from tuberculosis patients, pharmacodynamic (PD) targets for efficacy and toxicity for clofazimine in tuberculosis treatment have not been established.

A model-based approach that can account for the unusual pharmacokinetic characteristics of clofazimine and predict individual exposures is required to estimate dose-response relationships and inform dose optimization in tuberculosis treatment. (Svensson *et al.*, 2016) Using data from two cohorts of South African patients with tuberculosis, we developed a model to describe the population pharmacokinetic of clofazimine, evaluate covariate effects on pharmacokinetic variability, and simulated exposures for optimized dosing strategies.

5.3 Patients and methods

5.3.1 Study design and population

Clinical and drug concentration data were obtained from a prospective observational cohort study (PROBeX) of adults treated with bedaquiline for pulmonary extensively drug-resistant (XDR)- and pre-XDR-tuberculosis recruited from three tuberculosis hospitals in South Africa. Most participants were treated with regimens that also included clofazimine 100 mg daily, as per local standard of care. Detailed clinical and laboratory data were collected at monthly study visits over 6 months. Sparse pharmacokinetic sampling was performed at roughly 1, 2, and 6 months after starting clofazimine at a single pre-dose timepoint after self-reported dosing. A subgroup of consecutive participants at a single site consented to intensive sampling (pre-dose and at 1, 2, 3, 4, 5, 6, 8, and 24 hours after an observed dose and a standard meal of peanut butter on brown bread) at the Month 2 visit. Clofazimine plasma concentrations were measured at the Division of Clinical Pharmacology at the University of Cape Town using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay. The lower limit of

quantification (LLOQ) was 0.00781 mg/L. The inter-day accuracy ranged from 101% to 105%, and the precision (%CV) ranged from 3.3% to 4.6% during sample analysis.

Additional data were obtained from a 14-day Phase 2A early bactericidal activity (EBA) trial of clofazimine alone or in combination with bedaquiline, pretomanid, and pyrazinamide.(Diacon *et al.*, 2015) Clofazimine was administered as a loading dose of 300 mg daily on Days 1 - 3, followed by 100 mg daily on Days 4 - 14. pharmacokinetic sampling was performed pre-dose and 5 and 10 hours after observed dose on days 1, 2, 3 and 8; pre-dose, hourly up to 5 hours, and at 10, 16, and 24 hours after observed doses on day 14, plus an additional sample at day 28 (2 weeks after clofazimine discontinuation). Bioanalysis for drug plasma concentrations was conducted by PRA (Lenexa, KS) using liquid–liquid extraction and ultra-performance LC/MS/MS. LLOQ was 0.004 mg/L; inter-day accuracy ranged from 98.5% to 103%, and the precision (%CV) ranged from 2.3% to 3.7% during sample analysis.

5.3.2 Pharmacokinetic analysis

Nonlinear mixed-effects modelling was used to analyze clofazimine concentrations from both clinical cohorts simultaneously using NONMEM version 7.4.3, (Beal, 2001) Pirana, Perl-speaks-NONMEM (PsN) version 4.9.0, and Xpose4. (Keizer *et al.*, 2013) We tested one-, two-, and three-compartment disposition models. For the absorption process we tested first-order absorption with and without lag, saturable absorption, sum of inverse gaussians,(Weiss, 1996) and chain of transit compartments. (Radojka M. Savic *et al.*, 2007) Values below LLOQ were excluded from the dataset.(Beal, 2001)

Allometric scaling was applied on all disposition parameters to account for the effect of body size descriptors, including body weight (TBW), fat-free mass (FFM), and body fat.(Anderson *et*

al., 2008) Individual values of FFM were derived from observed TBW, height, and sex using a validated formula (provided in supplementary material).(Janmahasatian *et al.*, 2005) Fat mass was obtained as the difference between TBW and FFM. Age, sex, race, HIV status, clofazimine dose, treatment arm, duration on treatment, and use of lopinavir/ritonavir (a strong CYP3A4 and P-glycoprotein inhibitor) were evaluated as additional covariates. Sampling importance resampling (SIR) (Dosne *et al.*, 2016) was used to assess the robustness of the final parameter estimates and to obtain 95% confidence intervals. Details of the modelling approach are provided in the online data supplement.

5.3.3 Simulations

Using the final model, we simulated time to steady state for typical body size descriptors of female and male participants observed in our cohort. The final model was also used to simulate different dosing regimens to shorten the time to average daily exposure above a putative target concentration of 0.25 mg/L extrapolated from a murine model (Swanson *et al.*, 2016) while avoiding excessive peak values above those attained at steady-state with standard dosing to reduce risk of QT prolongation. Various loading doses and durations were explored, including 300 mg daily for 1 - 2 weeks and 200 mg daily for 2 - 8 weeks. For the latter simulations, characteristics of a typical TB patient weighing 56 kg and different proportions of fat mass (13, 20 and 34%) to reflect body size composition in the average TB patient and genders in the cohort, including random interindividual variability, were repeated 10,000 times. Simulations were performed using PsN 4.9.0, Berkeley Madonna version 9.1.19, and NONMEM version 7.4.3.

5.4 Results

5.4.1 Demographics and clinical profile

Seventy-nine participants on clofazimine-based regimens with complete 6-month follow up data were included from the PROBeX observational cohort, in addition to 60 participants from the EBA trial. Overall, median age was 31.0 years (IQR, 24.0 – 39.5), 68 (48%) were female, and 54 (38%) were HIV-infected. Median weight was 55.1 kg (IQR, 48.1 – 60.9) and percentage body fat was significantly higher in women (median 33.8% (IQR, 30.9 – 37.7) versus 13.9% (IQR, 12.0 - 16.6) in men) (**Table 5.1** and **Figure 5.1**).

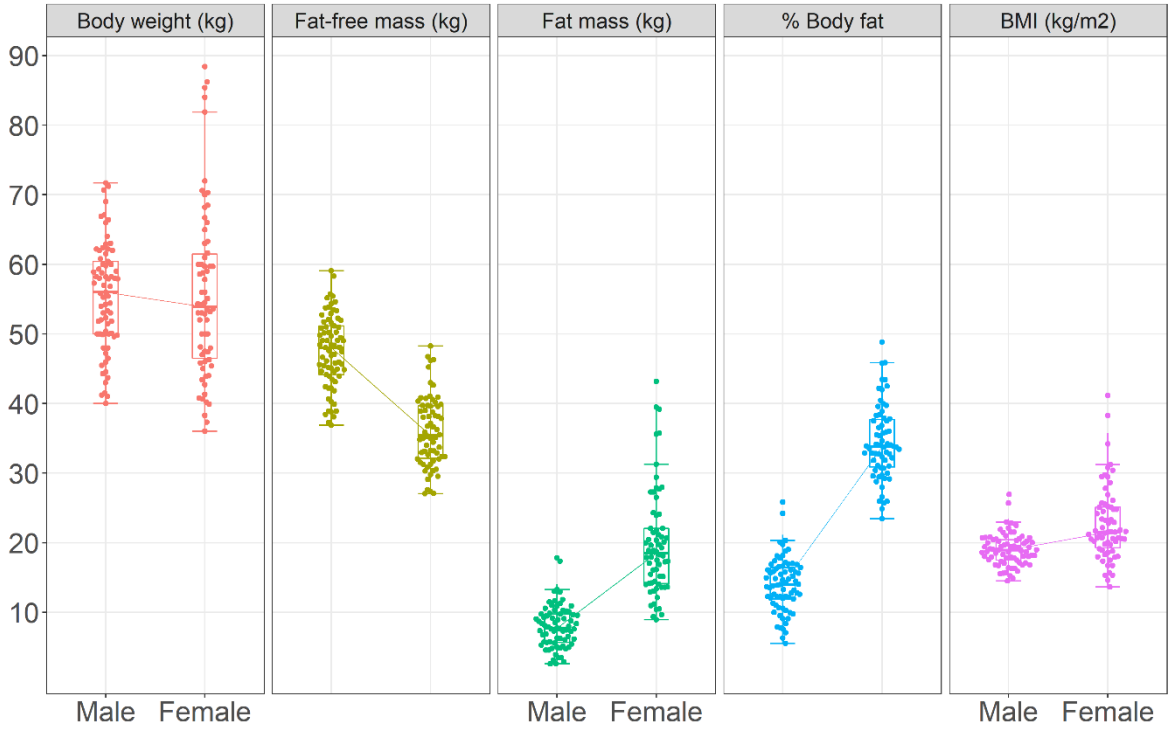

Figure 5.1. Distributions of body composition components, stratified by sex

Table 5.1. Baseline participant characteristics.

Variable	PROBeX* (n = 79)	Phase 2A trial (n = 60)	Total (n=139)
Age, yr	32.5 (26.5-40.0)	29.5 (23.0 - 39.0)	31.0 (24.0 – 39.5)
Females, n (%)	45 (56)	23 (38)	68 (48)
Ethnicity, n (%)			
Black	55 (66)	29 (48)	84 (60)
Mixed race	24 (30)	31 (51)	55 (39)
White	2 (3)		2 (1)
Weight, kg	54.0 (48.0 - 60.0)	55.9 (50.0 - 61.7)	55.3 (48.1 – 61.5)
Males	54.2 (50.0 – 58.4)	57.9 (50.4 – 62.2)	56.0 (50.0 – 60.4)
Females	53.2 (45.7 – 63.2)	54.3 (47.5 – 59.7)	53.9 (46.5 – 61.5)
FFM, kg	40.3 (35.0 - 46.2)	44.9 (37.1 - 50.1)	42.0 (36.3 – 48.3)
Males	46.6 (43.4 – 49.9)	49.1 (45.1 – 52.9)	48.0 (44.1 – 51.2)
Females	35.5 (32.0 – 39.8)	35.5 (32.9 – 38.9)	35.4 (32.1 – 39.7)
Body fat, kg	11.2 (7.91 – 19.3)	11.0 (7.2 – 17.5)	11.2 (7.6 – 18.3)
Males	7.60 (5.75 – 9.48)	8.07 (5.59 – 11.0)	7.74 (5.69 – 9.77)
Females	18.1 (14.1 –24.0)	18.7 (14.7 – 21.1)	18.5 (14.1 – 22.1)
Percentage body fat, %†	25.9 (14.4 - 34.0)	17.1 (12.7 – 32.8)	20.3 (13.9 – 33.7)
Males	13.8 (12.2 – 16.1)	14.3 (11.0 – 17)	14.0 (11.9 – 16.4)
Females	33.8 (30.6 – 38.1)	33.9 (32.1 – 36.0)	33.8 (30.9 – 37.7)
Height, cm	164 (157 – 168)	167 (161 – 173)	164 (158 – 172)
BMI, kg/m^2	20.0 (18.0 – 22.5)	20.0 (17.9 – 22.0)	20.0 (18 – 21.9)
HIV-positive, n (%)	49 (61)	5 (8)	54 (38)
CD4 count, cells/mm^3	196 (96 - 437)	715 (515 – 893)	540 (268 – 831)
Antiretroviral therapy	40 (82)	0	40 (74)
Lopinavir-ritonavir	11 (23)	0	11 (20)
M. TB resistance, n (%)			
Drug-susceptible	0		60 (43)
Pre-XDR (Inj-R)	14 (18)	60 (100)	14 (10)
Pre-XDR (FQ-R)	39 (49)		39 (28)
XDR	26 (33)		26 (19)
Serum creatinine, µmol/L	57.0 (48.5 – 68.0)	61 (51.4 – 70.8)	58.0 (50.5 – 69.3)
Duration on clofazimine, days	100 (55 – 182)	7.5 (4 – 11)	94 (48 – 180)

Data are median (range).
BMI = body mass index; FFM = fat-free mass; ART = antiretroviral therapy; XDR = extensively-drug resistant; Inj-R = injectable-resistant; FQ-R = fluoroquinolone-resistant
*Median was imputed for missing values in continuous variables; 3 for age, 1 for weight and height, and 2 for serum creatinine.
†Calculated as fat mass/total body weight

5.4.2 Model development and pharmacokinetic parameters

Clofazimine concentrations from 1,570 plasma samples (n =139 participants) were included in the analysis: 367 observations from 3 sampling visits in the PROBeX cohort (including intensive sampling from 22 participants) and 1,203 observations from sampling over the 14-day EBA trial. Six samples had concentrations below the limit of quantification and were excluded from the analysis. Twenty-five sparse samples from PROBeX participants with poor treatment adherence or missing dosing history had concentrations significantly lower than predicted on visual inspection and were also excluded.

Clofazimine pharmacokinetic was best characterized by a three-compartment disposition model with first-order elimination and transit compartments absorption (**Figure 5.2**). Size descriptors were normalized to median population values. The best size descriptors for scaling of disposition parameters were: TBW for total (CL) and intercompartmental (Q1, Q2) clearance and volume of distribution in the 'shallow' peripheral compartment (V_{p2}); FFM for central volume (V_c); and fat mass for volume of distribution in the 'deep' compartment (V_{p1}). The latter parameter resulted in the largest change in objective function value, indicating significant effect, when included in the model. Age, sex, race, HIV status, duration on treatment, and treatment arm were not identified as influential covariates according to stratified visual predictive checks and change in objective function, performed using the final model. The model detected an effect of lopinavir-ritonavir on clofazimine exposure, leading to higher bioavailability; however, the estimate was not sufficiently robust in terms of change in objective function to be included in the final model (The dOFV following removal of the covariate effect did not meet the cut-off criteria of 6.63 (p value of 0.01)). Residual unexplained variability was best described by a combined model utilizing both additive and proportional components, with separate additive error estimates for the sparse dataset from PROBeX (due to uncertainty in self-reported dosing times and adherence). A

prediction-corrected visual predictive check suggested adequate fit for the pooled data **Figure 5.3** and **Figure 5.4**).

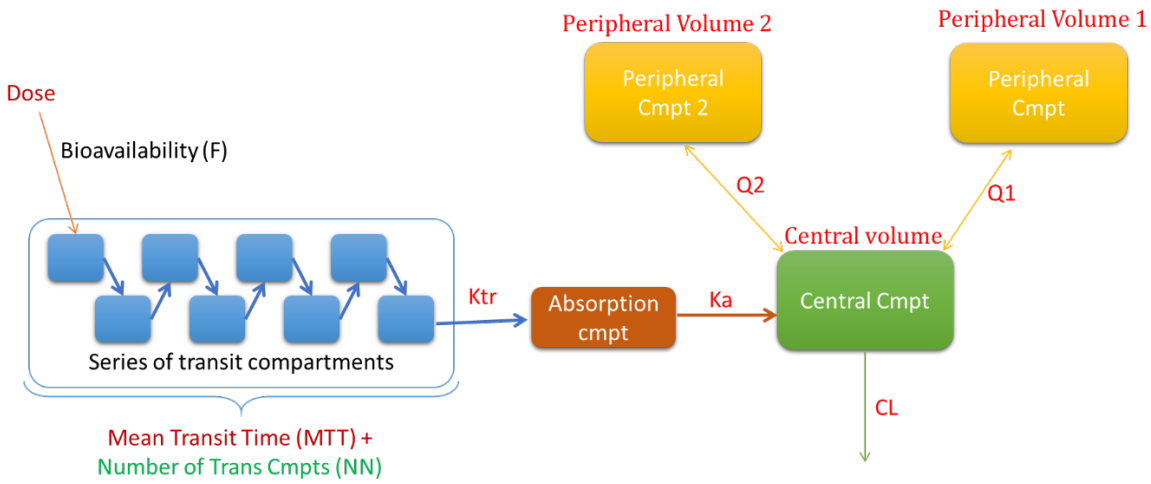

Figure 5.2. Schematic of the final clofazimine population pharmacokinetic model.

The dose is assumed to go through a series of transit compartments, where NN describes the number of transit compartments and the transit rate constant (Ktr) the transfer rate, calculated as NN + 1 divided by the mean transit time (MTT). Drug is then absorbed into the central compartment (representing the plasma concentration of clofazimine), described by the absorption rate constant (Ka). Bidirectional equilibration (Q1 and Q2) occurs with two peripheral tissue compartments, deep (V_{p1}) and shallow (V_{p2}), while drug is eliminated from the central compartment with first-order kinetics (CL).

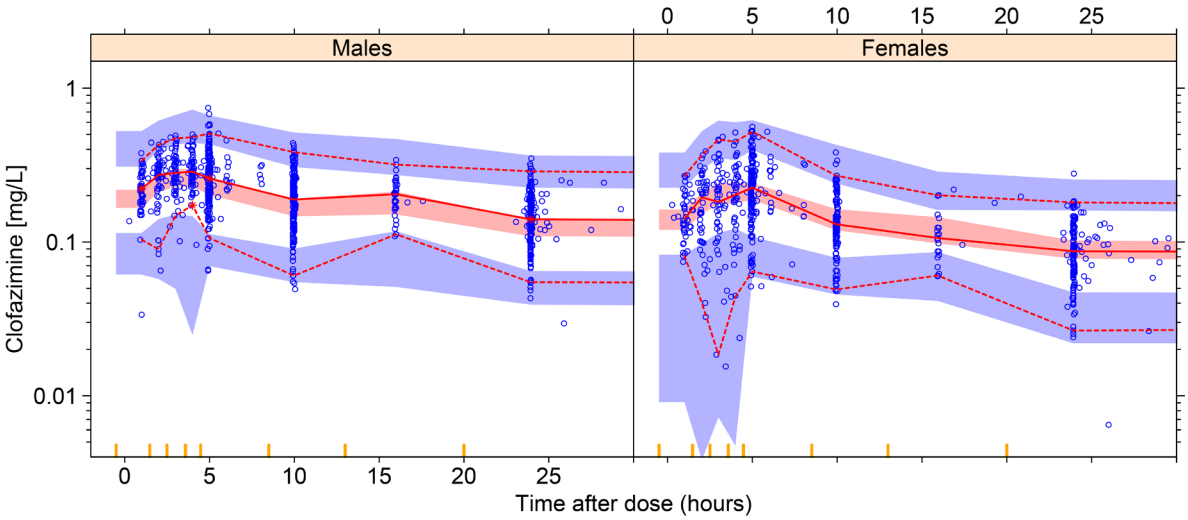

Figure 5.3. Prediction-corrected visual predictive check (pc-VPC) for pooled clofazimine concentration versus time (time after dose), stratified by sex.

Circles represent original data, dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. Vertical yellow lines on the x-axis represent bins for sampling timepoints. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

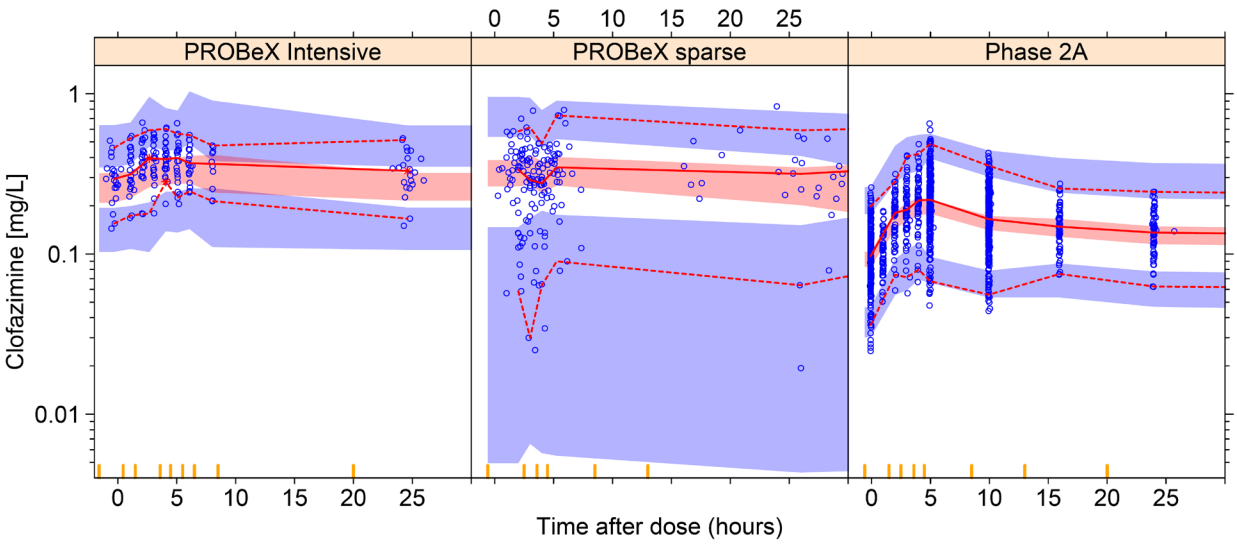

Figure 5.4. Prediction-corrected visual predictive check (pc-VPC) for pooled clofazimine concentration versus time (time after dose), stratified by dataset.

Circles represent original data, dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. Vertical yellow lines on the x-axis represent bins for sampling timepoints. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

The final model parameter estimates are summarized in

Table 5.2. The typical value for clearance (CL/F) was 11.5 L/h, and 10,500 L for the 'deep' peripheral volume. Women had much larger 'deep' peripheral volume (13,700 liters for a typical woman versus 5,720 liters for a typical man) explained by significantly higher body fat percentage compared with men. The model detected an increase in bioavailability over the first few days of treatment, from a baseline of 68% to 95% of reference value by the 4th dose. Because participants received a larger daily dose (300 mg versus 100 mg) in the first 3 days of the EBA trial, dose effect was investigated as a potential explanation, but a time-dependent exponential increase model (described in online data supplement) fitted the data better, even after testing several alternative absorption processes.

Table 5.2. Final population pharmacokinetic model parameters

Parameter description	Typical Value (95 % CI)*	BSV+ or BOV++ (CV%)§
Clearance, (L/h) †	11.5 (10.5 – 12.5)	25.6 (17 – 33.5) +
Central Volume of distribution, Vc (L)†	262 (178 – 375)	23.5 (8.39 – 35.1) +
Inter-compartmental clearance, Q1 (L/h) †	56.3 (49.6 – 62.6)	
Peripheral Volume 1, Vp1 (L)†	10500 (9320 – 11600)	29.6 (20.4 – 38.1) +
Inter-compartmental clearance, Q2 (L/h)†	86 (74.6 – 99.5)	
Peripheral Volume 2, Vp2 (L)†	889 (696 – 1070)	54.6 (42.3 – 73.9) +
Absorption mean transit Time (h)	1.41 (1.10 – 1.67)	46.6 (38.1 – 56.9) ++
Number of Transit Compartment (NN)	4.75 (3.01 – 7.65)	
Absorption rate constant, Ka (1/h)	0.209 (0.175 – 0.261)	32.6 (27.1 – 38) ++
Relative bioavailability baseline	0.685 (0.615 – 0.771)	
Bioavailability, F	1 [FIXED]	30.1 (25.2 – 35.5) + 35.4 (31.8 – 39.6) ++
Proportional error (%)	11.4 (10.8 – 12.1)	
Additive Error (mg/L)‡	0.00156 [FIXED]	
Additive error (PROBeX sparse data) (mg/L)	0.0905 (0.077 – 0.107)	
P-glycoprotein inhibition half-life (days)^	1.44 (0.683 – 2.85)	
Terminal half-life (days)ll		
Median patient	34.2	
Female	49.5	
Male	21.8	

* 95 % confidence intervals obtained with sampling importance resampling technique using PsN software

† Allometric scaling used for CL, Vc, Vp1, Vp2, Q1 and Q2; typical values reported for the median weight (55 kg), fat free mass (42 kg) and fat mass (13 kg) as reported in Table 1

‡ Estimate of the additive error was not statistically significant from the lower bound (LLOQ/2), and was thus fixed to that value

^ Inhibitory effect of clofazimine on P-glycoprotein using an exponential maturation function (described in supplementary material)

§ Between- subject variability (BSV) and -occasion variability (BOV) were assumed to be log-normally distributed and reported as approximate %CV

ll Derived parameters outside the estimation software: calculated for the typical male and female median values as reported in **Table 5.1**

Model-predicted clofazimine exposure (C_{max}, maximum concentration; AUC_{0-24}, area under concentration-time curve at 24 hours; C_{avg}, average daily concentration) was higher at 2 months compared to 14 days, reflecting clofazimine accumulation over time. Estimated plasma exposures were lower in women (**Table 5.3** and **Figure 5.5**).

Table 5.3. Model-predicted secondary PK parameters from rich sampling occasions.

Study		Females	Males	Total
PROBeX (Month-2)	**C_{max} (mg/L)**	0.310 (0.161 – 0.646)	0.473 (0.307 – 0.688)	0.363 (0.161 – 0.688)
	AUC_{0-24} (mg·h/L)	6.08 (3.17 – 13.7)	10.3 (6.61 – 14.3)	7.33 (3.17 – 14.3)
	C_{avg} (mg/L)	0.254 (0.132 – 0.572)	0.430 (0.275 – 0.596)	0.305 (0.132 – 0.596)
Phase-2A (Day 14)	**C_{max} (mg/L)**	0.199 (0.0687 – 0.403)	0.263 (0.168 – 0.413)	0.218 (0.0687 – 0.4130)
	AUC_{0-24} (mg·h/L)	3.22 (1.26 – 6.16)	4.87 (2.73 – 8.60)	4.2 (1.26-8.60)
	C_{avg} (mg/L)	0.134 (0.0523 – 0.257)	0.203 (0.114 – 0.358)	0.177 (0.0578 – 0.3580)

Data are given as median (interquartile range). C_{max} = maximum concentration, AUC_{0-24} = area under concentration-time curve at 24 hours, C_{avg} = average daily concentration.
n = 22 for PROBeX, sampled at ~2 months; n = 57 for the Phase 2A trial, sampled at day 14

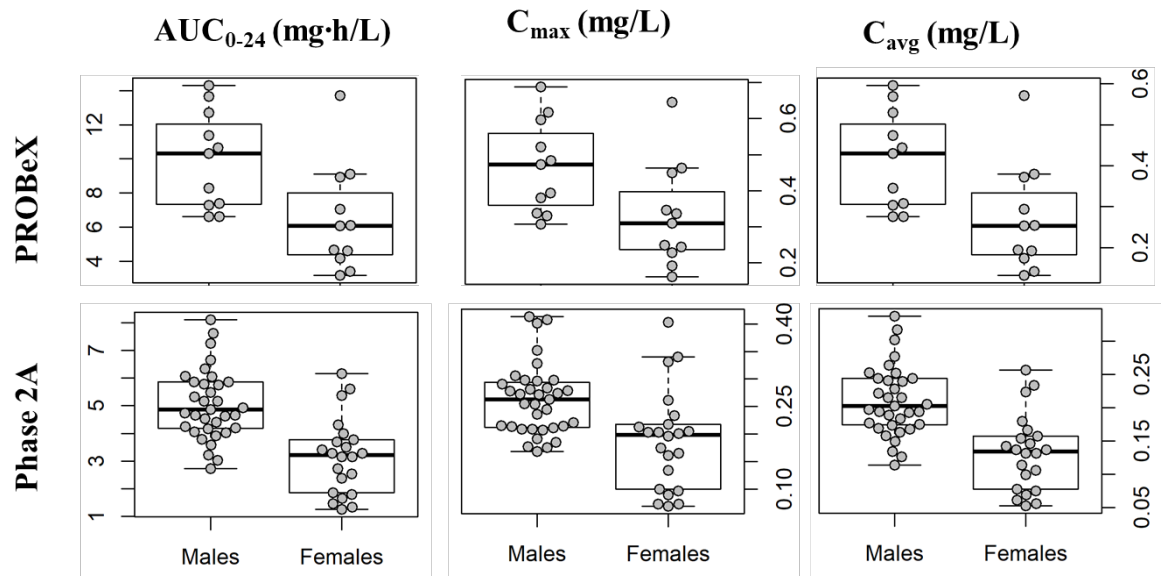

Figure 5.5. Box and whisker plots showing secondary model-derived non-compartmental parameters, stratified by sex.

The dots represent individual values, whiskers are 2.5th and 97.5th percentiles. n = 22 for PROBeX, sampled at ~2 months; n = 57 for the Phase 2A trial, sampled at day 14.

5.4.3 Simulations

Median terminal elimination half-life was estimated at 34.2 days and was significantly longer for women (49.5 days versus 21.8 days for men), resulting from differences in body composition. Consequently, the median time to steady-state (approximately 5 times the terminal half-life), which was 150 days overall, was much shorter for men (105 days versus 230 days for women) (**Figure 5.6**).

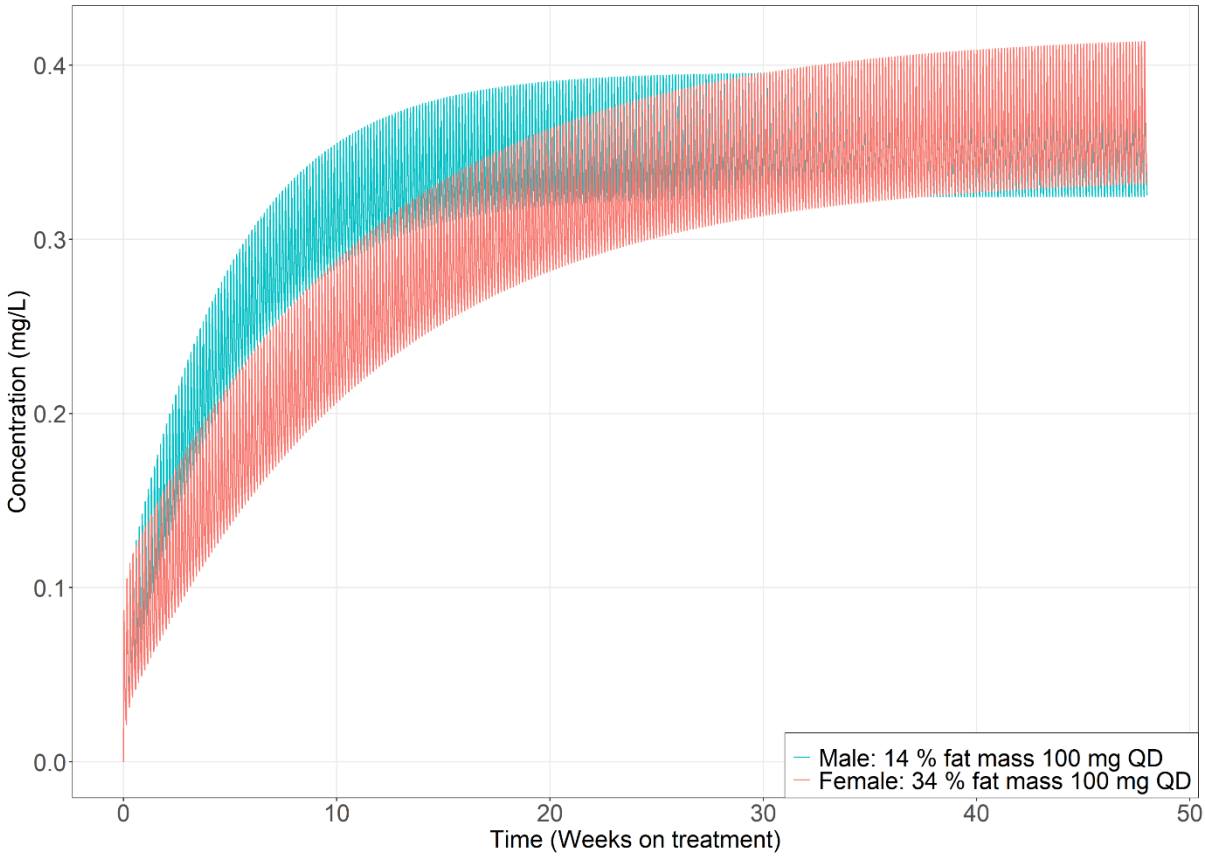

Figure 5.6. Predicted clofazimine concentrations at steady state with standard dosing (100 mg daily), stratified for typical male/female participants in the cohort.

Simulations of a 300 mg loading dose for either 1- or 2-week durations predicted peak concentrations (Cmax) that exceeded those estimated at steady-state, a potential safety concern, particularly for QT prolongation (**Figure 5.7**). A simulated schedule of 200 mg daily loading dose given for the initial 2 weeks of therapy, followed by standard dosing (100 mg daily) predicted average daily plasma concentrations above the M. tuberculosis wild type MIC value (0.25 mg/L) 37 days earlier compared with standard dosing for a typical TB patient in our cohort. For typical male patients, with 13% body fat, the 2-week loading dose achieved a 21-day reduction in time to target concentration. However, female patients, who had an average of 34 % body fat, required a longer loading period: a simulation of 4-weeks' loading led to target attainment 56 days earlier compared to standard dosing in women **Figure 5.8**. Predicted median Cmax with use of this loading dose was 0.277 mg/L at the end of the loading period, compared with median Cmax 0.343 mg/L at steady state.

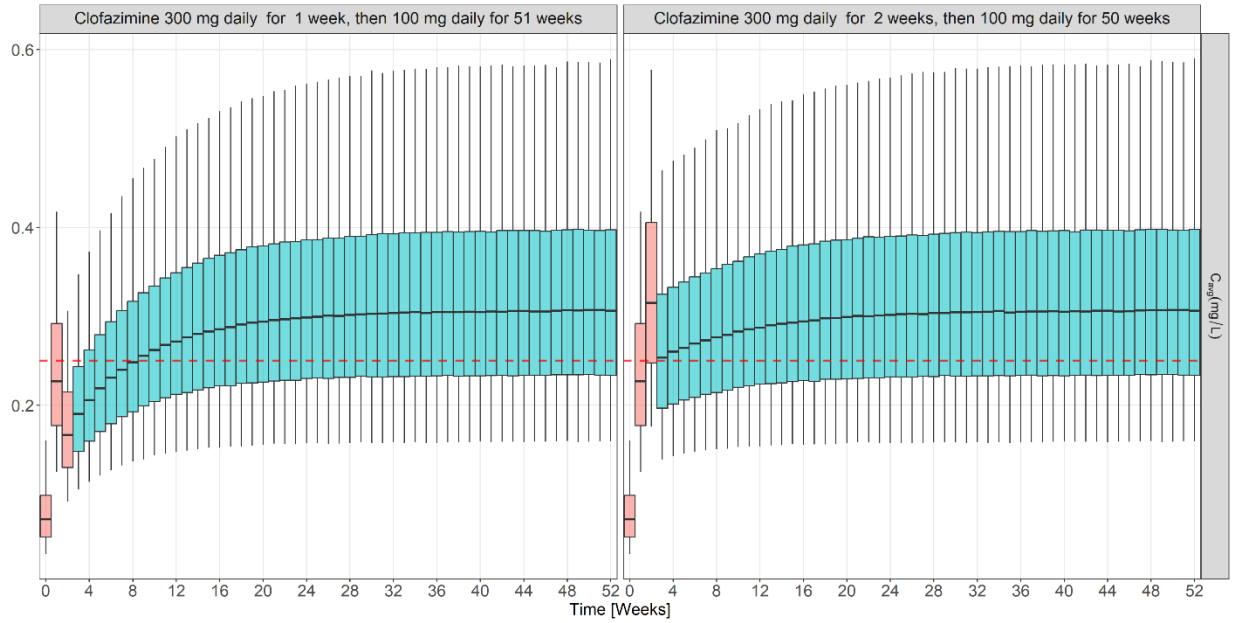

Figure 5.7. Simulated peak exposures with different loading doses for a typical patient.

Weight :70 kg; fat-free mass: 56 kg; fat mass:14 kg. Dashed line represents the suggested concentration target (0.25 mg/L). whiskers are 2.5th and 97.5th percentiles. Orange shaded boxplots represent first two weeks of treatment.

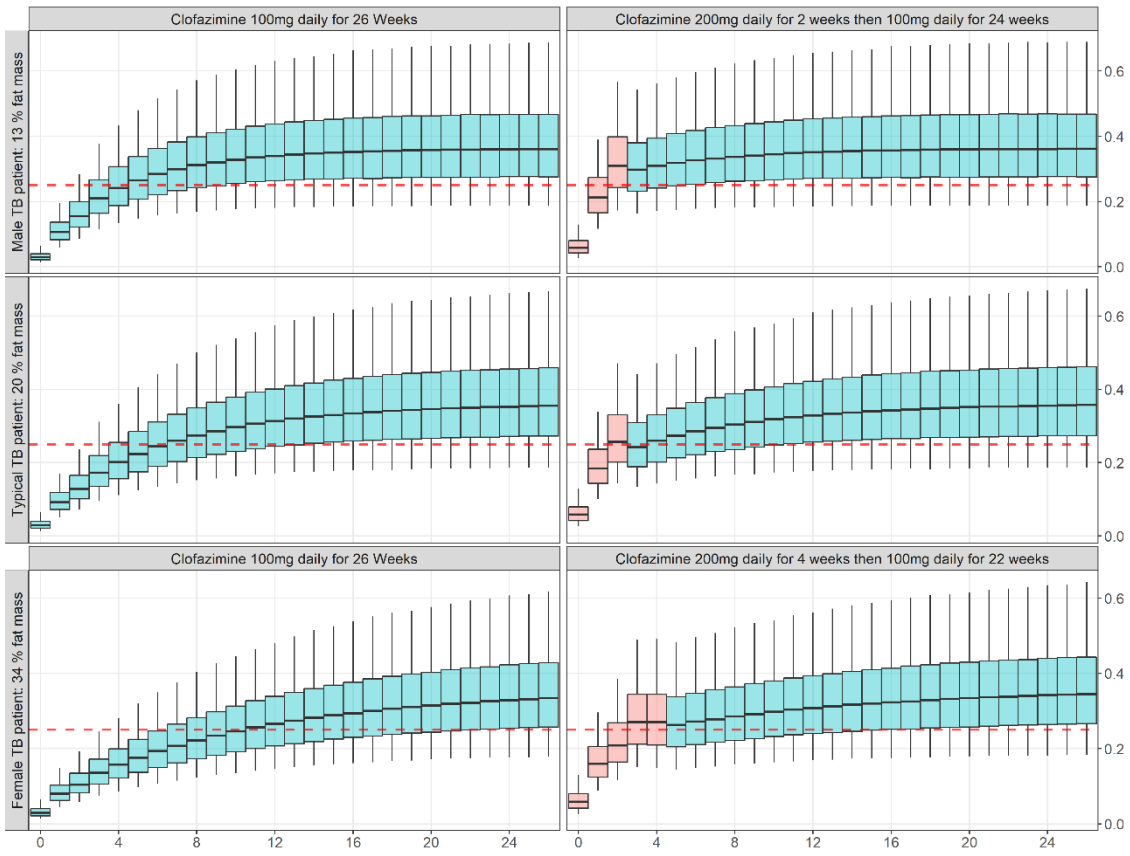

Figure 5.8. Simulated exposures with standard dosing and loading dose for typical male, female, and all TB patients in the cohort

Dashed line represents the suggested target concentration (0.25 mg/L). whiskers are 2.5th and 97.5th percentiles. Orange shaded boxplots represent the loading dose period. Note, time truncated at 26 weeks for improved visualisation.

5.5 Discussion

Clofazimine pharmacokinetic has not been adequately studied and data from tuberculosis patients is especially scarce. Using data from a prospective observational study and an EBA trial, we developed a population pharmacokinetic model that describes the compartmental kinetics and accumulation of clofazimine in South African tuberculosis participants with 38% prevalence of HIV co-infection. Clofazimine disposition was strongly influenced by body fat percentage, thus resulting in initially lower plasma exposure amongst women. We simulated a loading dose that would achieve steady state faster without increasing expected peak concentrations, hence

limiting the likelihood of added toxicity. These findings have implications for clofazimine dosing in tuberculosis.

Our model-predicted pharmacokinetic parameters confirm a large volume of distribution (~10,000 L) and long terminal half-life of ~30 days, which is consistent with known pharmacological properties of clofazimine. (Cholo *et al.*, 2017) Clofazimine is highly lipophilic (Cholo *et al.*, 2012) and distributes widely into fatty tissues; (Barry *et al.*, 1965; O'connor *et al.*, 1995) murine experiments have demonstrated clofazimine primarily accumulates in reticuloendothelial tissues with slow decline in serum and organs after discontinuation (ranging from 45 to 70 days). (Conalty *et al.*, 1971; Banerjee *et al.*, 1974; Swanson *et al.*, 2015, 2016) These murine observations were recapitulated in single- and multiple-dose healthy volunteer studies which applied exponential functions to model biphasic elimination of a 50-mg daily dose; estimated time to steady state was ~60 days with marked accumulation over time. (Schaad-Lanyi *et al.*, 1987) The widely-cited terminal elimination half-life of 70 days in humans was derived from urine clofazimine concentrations in leprosy patients and healthy volunteers over four decades ago. (Levy, 1974) The complex pharmacokinetic of (Schaad-Lanyi *et al.*, 1987) with multi-phase disposition and very long terminal half-life, is difficult to accurately characterize using non-compartmental analysis. (Svensson *et al.*, 2016) There have been few attempts to model clofazimine pharmacokinetic to accurately estimate disposition in people. An unpublished two-compartment disposition model using data from leprosy patients and healthy volunteers with variable dosing schedules estimated a peripheral volume of around 4,000 L and a half-life of 15 days. (Ganesan *et al.*, 2015) Another study, applying a one-compartment model to quantify the effect of food on clofazimine bioavailability in healthy volunteers, reported a mean volume of distribution of 1,470 L, although they were unable to estimate the terminal elimination phase due

to limited assay sensitivity. (Nix *et al.*, 2004) The much higher volumes predicted by our model could reflect important differences in the physiology of tuberculosis patients, as well as the influence of population-specific covariates.

The pooled data and observed variance in our cohort were well-described by a three-compartment structural model that accounted for the complex multi-phase disposition. (Schaad-Lanyi *et al.*, 1987) Lopinavir/ritonavir use was associated with a moderate increase in clofazimine exposure. Clofazimine metabolism is poorly characterized; one study found clofazimine to be a P-glycoprotein substrate on in vitro screening (Horita *et al.*, 2014) and thus a potential victim of P-glycoprotein inhibition by HIV protease inhibitors. This has been an inconsistent finding (Te Brake *et al.*, 2016) and formal drug-drug interaction studies are needed to investigate effect of co-administration with lopinavir/ritonavir on clofazimine exposure and toxicity.

Body composition explained our key finding of major sex differences in clofazimine plasma exposure. In our combined cohorts, women had a higher proportion of body fat and consequently a larger peripheral volume of clofazimine distribution compared to men. Because pharmacokinetic sampling occurred before steady state attainment while drug was still accumulating in peripheral tissues, women from both cohorts had much lower observed clofazimine plasma concentrations and derived exposure parameters ($AUC_{0\text{-}24}$, C_{max}, C_{ave}), which is in agreement with reported findings from non-compartmental analyses of the EBA trial (Diacon *et al.*, 2015) and the observational PROBeX study. (Wasserman *et al.*, 2018) The clinical consequence of larger peripheral volumes is extended terminal half-life, prolonging the predicted number of repeated daily doses necessary to achieve clofazimine steady state in women, demonstrated by our simulations in **Figure 5.6**.

Average clofazimine plasma concentrations measured before steady state were much lower than the recommended critical concentration of 1 mg/L and published MIC distributions in drug-resistant M tuberculosis strains. (Xu *et al.*, 2017) Clofazimine is highly protein-bound (Irwin *et al.*, 2014) resulting in free plasma drug concentrations below the MIC, indicating a potentially suboptimal antibacterial effect. Clofazimine has been shown to partition in the cellular rim of explanted lung granulomas, achieving much higher intracellular concentrations relative to plasma. (Prideaux *et al.*, 2015) Tissue accumulation and the long terminal elimination half-life of clofazimine may contribute to efficacy and treatment-shortening as a consequence of high site-of-disease concentrations despite failure to exceed MIC in plasma. (Prideaux *et al.*, 2015; Strydom *et al.*, 2019) Clofazimine has no discernible EBA at 14 days (Diacon *et al.*, 2015) and consistently demonstrates delayed and concentration-dependent activity in murine models. (Swanson *et al.*, 2015, 2016) Simulations based on sparse data from two Korean MDR-tuberculosis patients on standard doses predicted attainment of clofazimine concentration above efficacy target in cellular lesion compartments at steady state. (Strydom *et al.*, 2019) While steady-state tissue exposures are likely to exceed bactericidal concentrations (0.25 mg/L) (Ammerman *et al.*, 2017) and contribute to sterilizing activity against intracellular bacilli, early treatment efficacy could be optimized using a loading dose to achieve steady state more rapidly.

There is no established clinical PK/PD index for clofazimine efficacy in tuberculosis, precluding empirically based dosing simulations. In a murine model clofazimine was shown to contribute sustained antimycobacterial activity for up to 6 weeks after discontinuation, and this 'post-antibiotic effect' was associated with plasma concentrations above 0.25 mg/L; (Swanson *et al.*, 2016) we therefore selected average daily concentration above this value as the target efficacy parameter for our dosing simulations. The relationship between clofazimine exposure and

toxicity (QT prolongation and skin changes) is unknown. Peak serum drug concentrations generally correspond to peak effect on QT interval and our loading dose simulations aimed to balance more rapid attainment of efficacy target concentration with anticipated effects of higher initial C_{max} on QT prolongation. The principles guiding selection of dosing strategies were thus to: (1) avoid substantially higher predicted C_{max} after loading period than average steady state peak concentrations to reduce risk of serious QT prolongation; (2) achieve shorter time to average daily concentrations exceeding the efficacy target; and (3), use of a simple dosing regimen with once daily administration. A dosing schedule of 200 mg for 2- or 4-weeks depending on the fat percentage followed by 100 mg daily achieved these objectives and requires further investigation in future clinical trials to delineate impact on important endpoints and treatment shortening.

As with all modeling exercises, our analysis has limitations. While the model presented here was able to describe complex data with relatively few parameters, mechanistic assumptions were based on very limited knowledge of clofazimine metabolism and may have limited predictive ability outside the range of observed data. (Danhof *et al.*, 2008) There was also some uncertainty in the data, particularly around accuracy of dosing times and adherence relating to sparse pharmacokinetic sampling in the PROBeX cohort; we accounted for this by introducing a separate additive error estimate to the model. Furthermore, we based our model on pooled data from two separate clinical cohorts and drugs assays from different laboratories, which may add unexplained variability. Our model detected a moderate increase in clofazimine bioavailability over the first few days of therapy, which we attribute to putative autoinhibition of intestinal P-glycoprotein. However, this finding could be due to the limits of model extrapolation: EBA trial participants received a larger dose for 3 days and there was a high degree of variability in

bioavailability. Although time-dependent rather than dose-dependent absorption describes the data better, dose-dependent saturation of absorption remains a possibility. Finally, assumptions for our dosing simulations were made in the absence of clofazimine PK/PD data from tuberculosis patients and reflect theoretical rather than empirically based targets.

In conclusion, we successfully developed a clofazimine population pharmacokinetic model for South African tuberculosis participants, describing massive peripheral distribution volume and prolonged terminal elimination. Clofazimine disposition was strongly influenced by body fat content resulting in lower plasma exposure among women. The clinical consequences are unknown but clofazimine may require dose individualization at extremes of body composition to optimize use. A 2-week loading dose may support treatment shortening by enabling more rapid attainment of efficacy targets within a safe window of peak concentrations in this population; longer loading periods may be required in patients with high fat mass. This needs to be evaluated in clinical trials. Dose optimization of clofazimine is a research priority in tuberculosis, and our model is a necessary first step to understanding concentration-response relationships of this key antituberculosis drug.

5.5.1 Supplementary data

5.5.1.1 Population pharmacokinetic modeling

Between-subject and -occasion random effects were included on the pharmacokinetic parameters assuming log-normal distribution; a combined additive and proportional structure described the residual unexplained variability, with the additive component of the error constrained to be least 20% of lowest level of quantification (LLOQ). Values below LLOQ (BLQ) were excluded from the dataset based on the M1 method. We also dropped observations that were lower than predicted based on visual inspection and confirmed poor treatment adherence.

We tested total body weight (TBW), fat-free mass (FFM), and body fat proportion as body size descriptors. Individual values of FFM were derived from observed TBW, height, and sex using a validated formula. Fat mass (FAT) was estimated from the difference between TBW and FFM. Allometric scaling was applied on all disposition parameters to adjust for the effect of body size; scaling exponents were fixed to 0.75 for clearance parameters, and 1 for volumes:

$$Allomt_{WT} = \left(\frac{TBW}{TBW_{median}}\right)^{\theta} \quad 5.5.1.1$$

$$Allomt_{FFM} = \left(\frac{FFM}{FFM_{median}}\right)^{\theta} \quad 5.5.1.2$$

$$Allomt_{FAT} = \left(\frac{FAT}{FAT\_median}\right)^{\theta} \quad 5.5.1.3$$

$$FFM = \frac{WHS_{max} \cdot Ht^2 \cdot TBW}{Ht^2 \cdot WHS_{50} + TBW} \quad 5.5.1.4$$

θ was fixed to 0.75 for clearance parameters (CL, Q1, Q2) and to 1 for volume parameters (Vc, Vp1, Vp2)

WHSmax is 42.92 and WHS50 is 30.93 in males and 37.99 and 35.98 in females, Ht is height in meters.

The development of the model and the inclusion of covariates were based on physiological plausibility, inspection of diagnostic plots, including visual predictive checks (VPCs), and decreases in the NONMEM objective function value (OFV), which was assumed to follow a Chi-squared ($\chi 2$) distribution. The statistical significance cut-off for an additional degree of freedom (inclusion of one additional parameter) was an OFV drop of at least 3.84 points, corresponding to $p < 0.05$. Covariates were tested in a stepwise fashion in order of importance determined by the largest significant decrease in OFV.

We modelled the inhibitory effect of clofazimine on P-glycoprotein using an exponential maturation function which was added on bioavailability as follows:

$$TVBIO = (BIO\_BS + (BIO\_SS - BIO\_BS) \cdot (1 - e^{(-ln(2) \cdot \frac{DUR}{Inib_{50}})})) \qquad 5.5.1.5$$

The function estimated the effect of treatment duration (DUR) from a relative baseline bioavailability (BIO_BS) to an "effect steady-state" (BIO_SS) with inhibition half-life, $Inhib_{50}$.

Chapter 6:: The effect of Clofazimine Concentration on QT prolongation in patients treated for tuberculosis

6.1 Abstract

Clofazimine is classified as a WHO group B drug for the treatment of rifampicin-resistant tuberculosis. QT prolongation, which is associated with fatal cardiac arrhythmias, is caused by several anti-tubercular drugs, including clofazimine, but there are no data quantifying the effect of clofazimine concentration on QT prolongation

Fifteen adults drug-susceptible tuberculosis patients received clofazimine mono-therapy as 300 mg daily for three days followed by 100 mg daily in one arm of a 2-week, multi-arm early bactericidal activity trial in South Africa. Pre-treatment Fridericia-corrected QT (QTcF) (105 patients, 524 ECGs) and QTcF's from the clofazimine-monotherapy arm matched with clofazimine *plasma* concentrations (199 ECGs) were interpreted with a nonlinear mixed-effects model.

Clofazimine was associated with significant QT prolongation described by an E_{max} function. We predicted clofazimine exposures using 100-mg daily doses and two-weeks loading with 200 and 300 mg daily, respectively. The expected proportions of patients with QTcF change from baseline above 30 ms (ΔQTcF>30) were 2.52 %, 11.6 %, and 23.0 % for 100, 200, and 300-mg daily doses, respectively. At steady state, the expected proportion with ΔQTcF>30 ms was 23.7 % and for absolute QTcF>450 ms was 3.42 % for all simulated regimens.

The use of loading doses of 200 and 300 mg is not predicted to expose patients to increased risk of QT prolongation, compared to the current standard treatment, and is, therefore, an alternative option to achieve therapeutic concentrations faster.

6.2 Introduction

Clofazimine, a repurposed leprosy drug, is a key component of WHO-recommended treatment regimens for drug-resistant tuberculosis (DR-TB).(World Health Organization, 2020b) Clofazimine undergoes duration-dependent accumulation in tissue macrophages and reticuloendothelial system. (Cholo *et al.*, 2016) Clofazimine pharmacokinetics is characterized by multi-compartment disposition kinetics, very long terminal half-life (~30 days), and huge peripheral volume of distribution, causing steady-state concentrations to be achieved only after approximately five months of repeated daily dosing. With the current 100-mg daily dosing, the average daily clofazimine plasma concentrations before steady-state are much lower than the recommended critical concentration of 1 mg/L and published MIC distributions in drug-resistant M tuberculosis strains. Alternative dosing regimens are being evaluated to optimize treatment by using loading doses to attain concentrations above therapeutic target more rapidly. (Xu *et al.*, 2017; Abdelwahab *et al.*, 2020)

The toxicities associated with clofazimine include skin discoloration, increased liver enzymes, and QT prolongation, but it is unknown how these toxicities relate to clofazimine dose or plasma concentrations. (Choudhri *et al.*, 1995; Diacon *et al.*, 2015; Wallis, 2016) Clofazimine exerts its cardiotoxic effects by inhibiting the human ether-a-go-go-related (hERG) channel. (Wallis, 2016) Clofazimine-induced QT prolongation is a concern since several other drugs recommended by WHO for DR-TB (bedaquiline, fluoroquinolones, and delamanid) also prolong the QT interval, and a pharmacodynamic drug-drug interaction is often observed when QT-prolonging drugs are used in combination. (Meid *et al.*, 2017)

The STREAM study compared outcomes of a long (20 month) regimen with a shorter (9-11 months) regimen including clofazimine and high-dose moxifloxacin for the treatment of

multidrug-resistant tuberculosis (MDR-TB); QT intervals above 500 ms, where the risk of ventricular arrhythmias is highest, (Zareba, 2007) were recorded in 6% of participants in the long regimen arm (A locally-used WHO-approved MDR-TB regimen in accordance with 2011 WHO MDR-TB treatment guidelines) versus 11% in the short regimen arm. In a phase 2 study of bedaquiline in MDR-TB regimens, the mean increase in QTcF from baseline at 24 weeks was 31.9 ms and 12.3 ms with and without concomitant clofazimine. (Brian Dannemann *et al.*, 2012) A previous analysis using the current study data showed that clofazimine mono-therapy was associated with an increase in Bazett's heart rate-corrected QT interval above baseline (ΔQTcB) by 16-20 ms over 14 days in participants with drug-sensitive tuberculosis. (Diacon *et al.*, 2015) While the reports above provide reassurance about QT prolongation during clofazimine treatment at the current dose levels, the relationship between clofazimine concentration and QT prolongation has not been characterized. Such knowledge is of particular importance to adequately evaluate how alternative dosing regimens, especially with loading doses, may affect exposure-safety and efficacy relationships.

Model-based approaches are a powerful tool to analyse pharmacokinetic-pharmacodynamic relationships, and their advantage over traditional noncompartmental analysis is particularly marked when interpreting data from slowly accumulating drugs with long terminal half-life (Svensson *et al.*, 2016), such as clofazimine.

In this analysis, we explored the relationship between clofazimine exposures and QTcF prolongation in a randomised controlled trial comparing the early bactericidal activity (EBA) of several anti-tuberculosis drugs or regimens. (Diacon *et al.*, 2015) We used population modelling to characterize the concentration-QTcF relationship and then simulate the effect of different clofazimine dosing regimens and loading dose strategies

6.3 Methods

Adult treatment-naïve drug-susceptible patients with pulmonary tuberculosis were enrolled in a 14-day phase 2A study of early bactericidal activity (EBA) of clofazimine, alone or in combination with other tuberculosis drugs. One hundred and five patients (105) were randomized into seven different treatment arms. Clofazimine was administered as a loading dose of 300 mg for three days, followed by 100 mg until day 14 of treatment. (Diacon *et al.*, 2015)

6.3.1 QT monitoring

Triplicate 12-lead ECGs performed approximately five minutes apart were scheduled on the day before treatment initiation and on days 1, 2, 3, 8, and 14 at the following timepoints: predose, 5, and 10 hours postdose. The pre-treatment ECG measurements were performed at Hours 0, 5 and 10 relative to the time the dosing was anticipated to occur at day 1 of treatment. As a reference, additional sets of triplicate ECGs were performed between 9 and 3 days prior to treatment initiation and on day 28 post-treatment cessation. QT intervals were measured by a central cardiology service and corrected for the effect of heart rate using Fridericia's formula (QTcF). Additional correction methods were explored, namely, Bazette's (QTcB) and study-specific correction method (QTcN). The results were not significantly different among the three methods (data is not shown). QTcF was chosen as it is widely accepted among clinicians and regulatory agencies. We used the arithmetic mean of triplicate QTcF per time point to perform the data analysis and model building. Clofazimine plasma concentrations were obtained hourly from time 0 to 5 hours after dosing and again at 10, 16, and 24 hours on day 14. Additional figures are presented in supplementary material.

6.3.2 Model development

A population pharmacokinetic model previously developed was used to predict clofazimine concentrations at each ECG measurement time point for the 15 patients in the clofazimine monotherapy arm. The population PK model was developed using pooled data from two clinical trials, an observational study in patients with drug-resistant TB (79 patients providing 367 plasma sample) and the PK data from the current study (60 participants providing 1203 plasma sample). The median (IQR) duration of clofazimine daily dosing was 94 (48–180) days (Abdelwahab et al., 2020)

The observed QTcF was analyzed using the following general model:

$$QTcF = BSL \cdot (1 + Circ) + Drug\ effect + ERR \qquad 6.3.2.1$$

where BSL represents the baseline QTcF when drug effect and circadian variation are zero, *Circ* represents diurnal variation in ECG measurements, and *ERR* is the residual error.

Diurnal variation was characterized by using multi-oscillator functions with different number of cosine terms and different periods (Fernandez *et al.*, 2009), according to the following formula:

$$Circ = \sum_{k=0}^{n} A_k \cdot cos\left[\frac{2\pi \cdot (clock - \phi_k)}{period}\right] \qquad 6.3.2.2$$

Where A_k represents the amplitude associated with each term, *clock* is the clock time of the ECG measurement, and ϕ_k *is* the acrophase parameter for each cosine term. We tested 1 to 3 cosine terms, with periods 24, 12, and 6 hours. First, the diurnal variation model was developed using pre-treatment data from all study arms, then re-evaluated after the data was pooled with the clofazimine mono-therapy data. Between-subject variability was tested on amplitude and

acrophase parameters. We tested different residual error models with both additive and proportional components.

Different exposure predictors (individual model-predicted concentrations, predicted peak plasma concentration, Area under concertation time curve from time 0 to 24h (AUC_{0-24}), and average daily concentration) and relationship shapes (linear, E_{max} and sigmoidal E_{max}) were tested to describe the effect of clofazimine. We tested covariates in a model developed using only pre-treatment data then re-validated our findings, also including the clofazimine mono-therapy data. The following covariates: age, sex, body weight, fat-free mass, and electrolyte concentrations (calcium, potassium, and sodium) have been known to affect baseline QT, and we explored their effect in the model on the base QTcF parameter and circadian model parameters. (Piotrovsky, 2005; Malik *et al.*, 2019)

The development of the model and the inclusion of covariates were based on physiological plausibility, inspection of diagnostic plots including visual predictive checks (Holford, 2005), and significant decreases in the objective function value (OFV). Between-subject variability was considered and tested on all parameters assuming log-normal distribution. The statistically significant cut-off for an additional degree of freedom (inclusion of one parameter) was a drop in OFV of at least 3.84 points, corresponding to a p-value of <0.05. We used NONMEM 7.4 (Beal *et al.*, 2019) for parameters estimation, and Pirana, Perl-speaks-NONMEM (PsN) version 4.9.0, and Xpose4 (Keizer *et al.*, 2013) to aid the model development process. Precisions of the final model parameters were obtained using sampling importance resampling (SIR) available in PsN. (Lindbom *et al.*, 2004)

6.3.3 Simulations

We used the final model parameters to explore the risk of QT prolongation when using clofazimine regimens with two weeks of loading doses with 200 or 300 mg daily followed by 100 mg daily compared with the standard dose of 100 mg daily from treatment start. We performed a simulation of 10,000 replicates using final parameter estimates of a typical tuberculosis patient in our cohort weighing 55 kg with a fat-free mass of 42 kg. The simulations considered the variability in the parameters of the pharmacokinetic and pharmacodynamic models. The simulated QTcF & ΔQTcF were analyzed according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, which recommend the following different limits and cut-off points when analyzing QT/QTc interval prolongation data: (ICH. 2005, 2005) Absolute QTc interval prolongation of >450, >480 and >500 ms or a change in QTc from baseline >30 and >60 ms, respectively.

6.4 Results

6.4.1 Demographics

The baseline characteristics of 105 participants included in seven different treatment arms for drug-sensitive tuberculosis are summarized in **Table 6.1**.

Table 6.1. Clinical characteristics of 15 patients treated with clofazimine for drug-sensitive tuberculosis.

Characteristic	Clofazimine monotherapy arm
Age, year	24 (22 – 37.5)
Males	9 (60)
HIV-1+	1 (6.67)
Total body weight, kg	54 (45 – 61.9)
FFM, kg	38 (34 – 51.8)
BMI, kg/m^2	18 (17 – 20.8)
Overall-Baseline QTcF (ms)	389 (379 – 400)
Predose QTcF(ms)	388 (379 – 401)
5-hours QTcF(ms)	391 (381 – 397)
10-hour QTcF(ms)	389 (380 – 340)
Overall-Baseline heart rate (bpm)	88 (75 – 98.3)
Predose HR (bpm)	89.3 (74.7 – 101)
5-hours HR (bpm)	86.3 (76.3 – 92.3)
10-hour HR (bpm)	87.3 (75.8 – 95)

Fat-free mass (FFM), body mass index (BMI), beat per minute (bpm).

Data presented as median (IQR)/ n (%)

6.4.2 Model development and Final parameters

The pre-treatment data from all 105 patients was used to characterize the baseline QTcF and between-subject variability. The model then accounted for circadian variation in QTcF using three cosine functions (ΔOFV of 37, df=7, P=4.69e-06). The effect of covariates we explored in the baseline model (electrolytes, age, weight, lean body mass, and sex) was not statistically significant. The model estimated a baseline QTcF value of 391 ms and 3.75% between-subject variability. Individual model-predicted instantaneous concentrations at the same time as the ECG measurement were found to be the best predictor of the QTcF-clofazimine exposure relationship, and the relationship was best described by E_{max} function (ΔOFV of 93, 2 degrees of freedom, P=7.87e-22) versus linear slope model (ΔOFV of 83, 1 df, P= 8.21e-20), $\Delta AIC_{Emax\text{-}linear}$ =-11.9. The median (95% confidence interval) E_{max} value was 28.0 (17.4 – 61.0) ms increase in QTcF from baseline with EC_{50} value of 0.261 (0.0957 – 0.949) mg/L. The unexplained residual variability was best described with an additive model. A visual predictive check showing adequate model fit to the data is depicted in **Figure 6.1**. The final model parameters are summarized in **Table 6.2**.

Table 6.2. Final model parameters of clofazimine.

Parameter description	Typical Value (95% CI) *
QTcF base (ms)	392 (388 – 396)
Diurnal model parameters	
24-hour cycle amplitude (%)	2.05 (1.34 – 2.94)
12-hour cycle amplitude (%)	0.969 (0.495 – 1.73)
6-hour cycle amplitude (%)	0.979 (0.640 – 1.37)
24-hour cycle acrophase (h)	4.64 (3.57 – 6.23)
12-hour cycle acrophase (h)	3.64 (3.15 – 4.12)
6-hour cycle acrophase (h)	5.84 (5.44 – 6.22)
Additive error (ms)	8.40 (8.03 – 8.87)
Drug-effect parameter	
E_{max} (ms)	28.0 (17.4 – 61.0)
EC_{50} (mg/L) ‡	0.261 (0.0957 - 0.949)
Between-subject variability (%) §	
QTcF base (CV%)	3.75 (3.34 – 4.34)
12-hour cycle amplitude (CV%)	59.0 (17.9 – 143)

* 95 % confidence intervals obtained with Sampling Importance Resampling (SIR)

§ Between-subject variability (BSV) was assumed to be log-normally distributed and reported as approximate %CV

‡ EC_{50} was calculated as a fraction of E_{max} as the two parameters are positively correlated and to stabilize the model estimates.

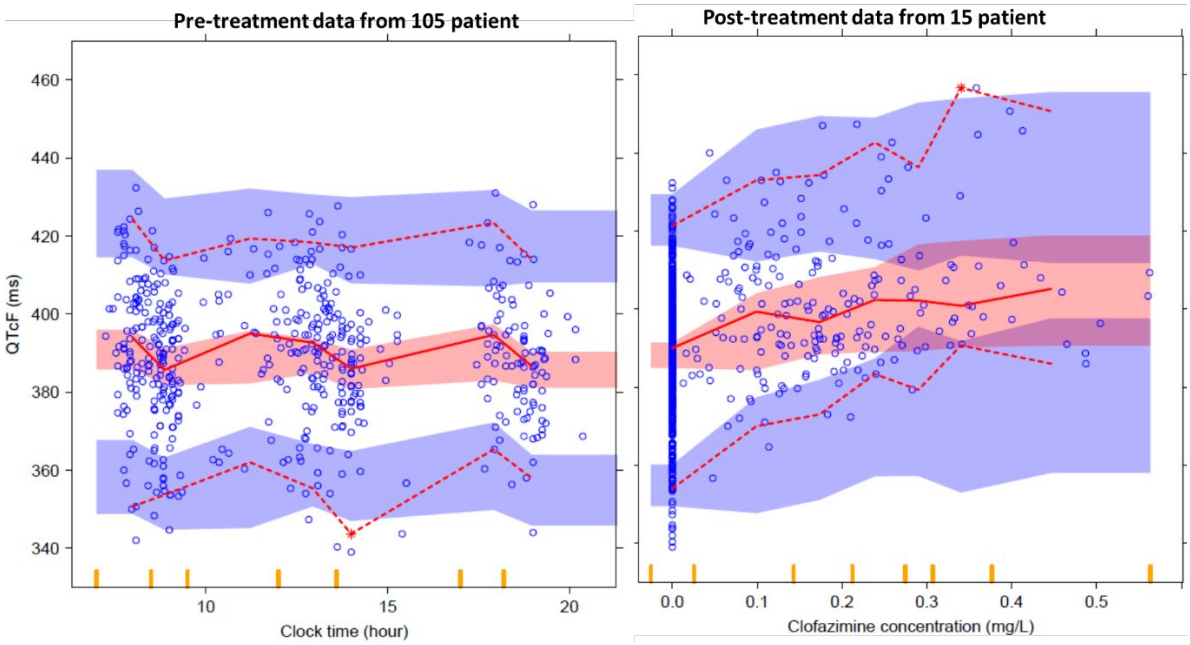

Figure 6.1. Visual predictive check (VPC) for QTcF (ms) versus clock time (hour) in the left panel and clofazimine concentration (mg/L) in the right panel.

Circles represent original data, dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. Vertical yellow ticks on the x-axis represent bins for sampling timepoints. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

6.4.3 Simulations

Figure 6.2 summarizes the simulation results for QTcF/ΔQTcF with the standard 100-mg daily dosing and the two-weeks loading-dose strategy with 200 or 300 mg daily, followed by 100 mg daily. The median simulated QTcF/ΔQTcF reached a value of 418/25.3 for 200 mg regimen and 420/28.0 ms for 300 mg regimen at the end of the loading dose period compared to 414/21 ms after two weeks of daily dosing with the standard 100 mg regimen. The proportion for which the change from baseline was above 30 ms (ΔQTcF >30) at the end of the loading dose period (2 weeks) were 14.3, and 31.1 % for 200, and 300 mg regimen, respectively compared to 33.6% obtained at steady with either regimen. At steady state all simulated regimens were predicted to have the same QT prolongation, with a median QTcF/ΔQTcF of 420/28.5 ms. The proportion

with absolute QTcF>450 ms was 3.42% for all simulated regimens at steady state. The simulation results are summarised in **Figure *6.3***. The proportions for the higher ICH cut-off points we explored (QTcF>480 ms or QTcF>500 ms) were negligible. (ICH. 2005, 2005)

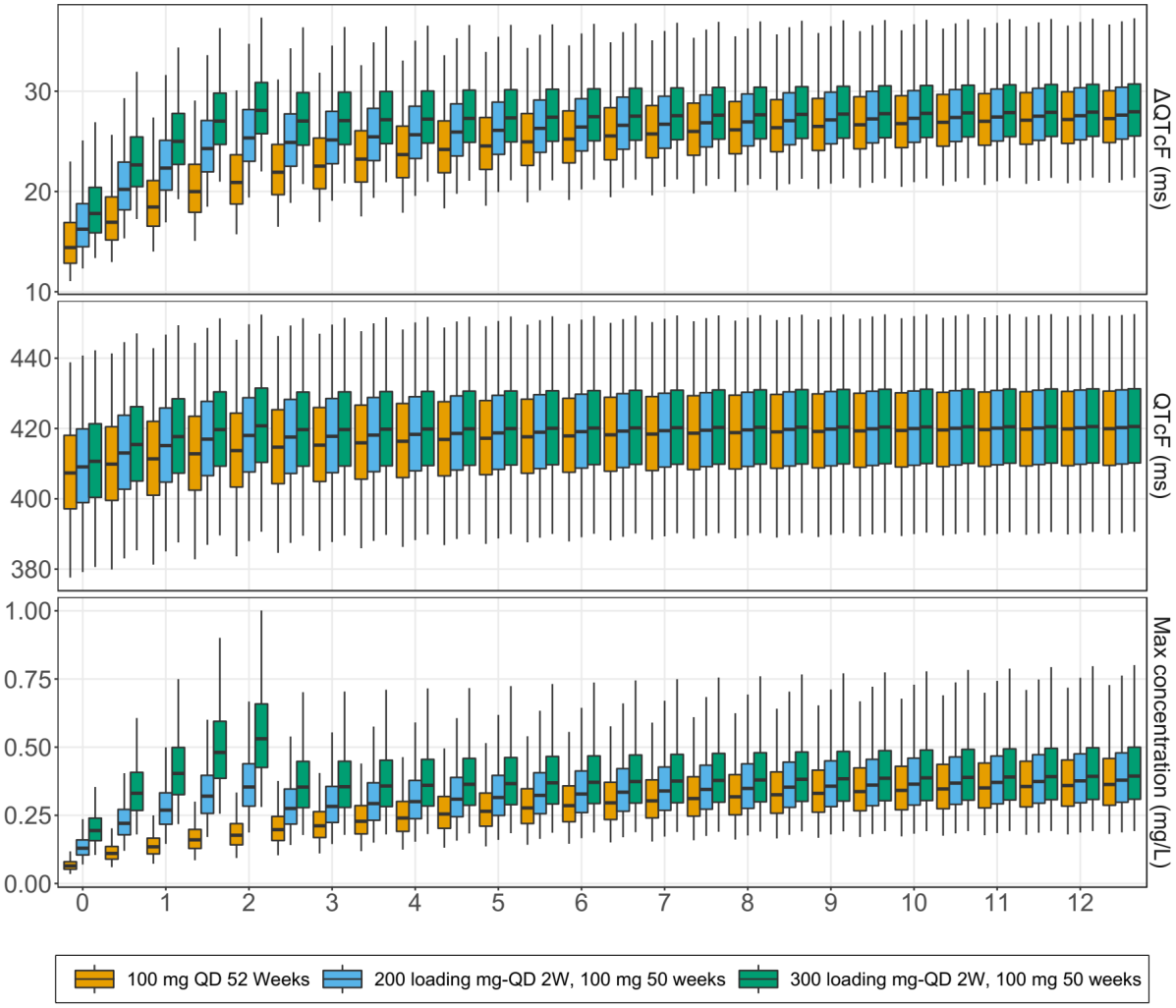

Figure 6.2. Simulated ΔQTcF, QTcF (ms) and peak concentrations (mg/L) with standard 100-mg daily dosing and loading dose regimens for a typical TB patient observed in the cohort.

The central lines in boxes represent median values; upper and lower horizontal lines are 75th and 25th percentiles, respectively, and whiskers are 2.5th and 97.5th percentiles.

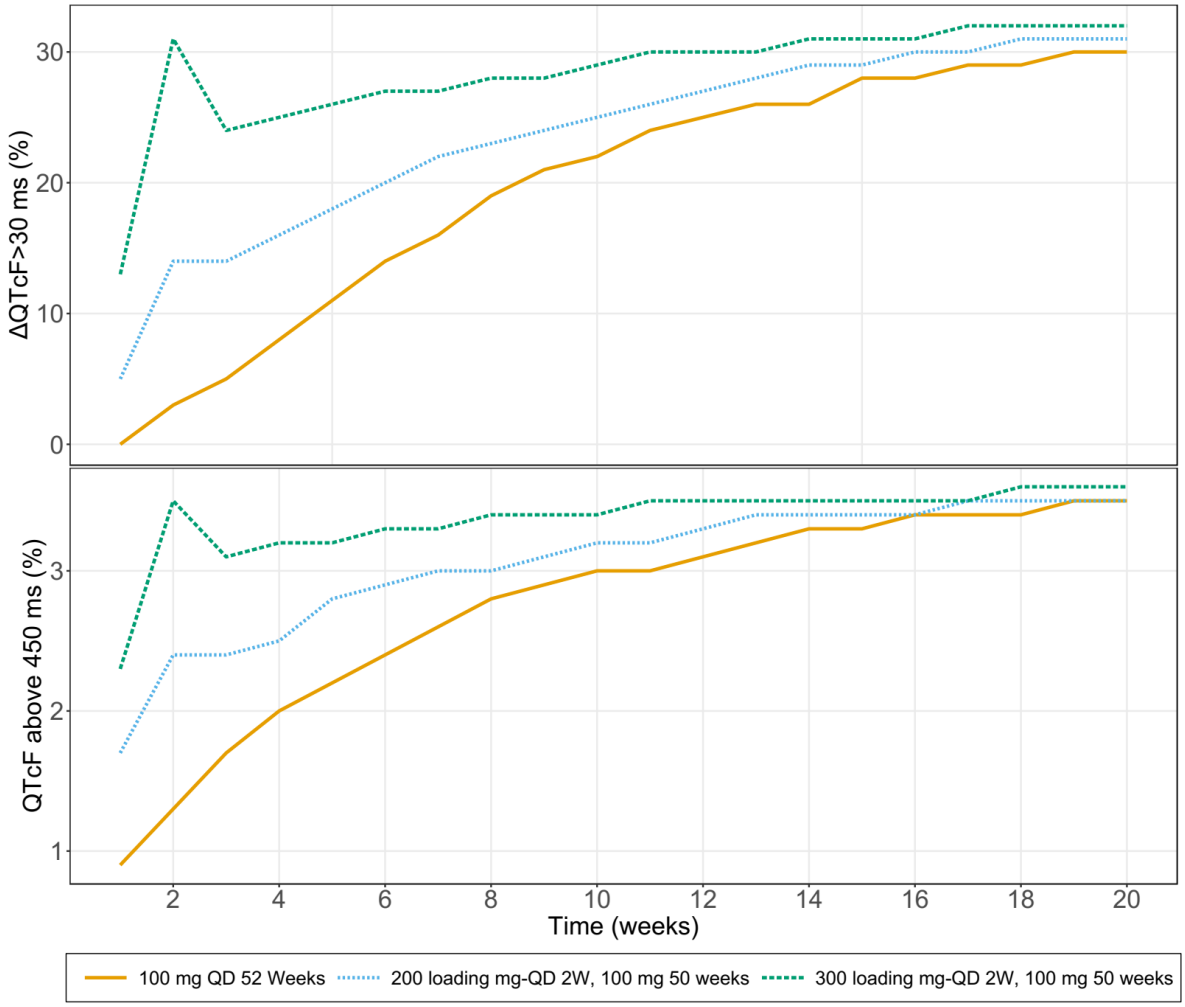

Figure 6.3. Proportions of simulated replicates with QTcF above 450 ms (lower panel) and dQTcF above 30 ms (upper panel) with standard 100 mg daily dosing and suggested loading dose regimens for a typical TB patient observed in the cohort.

6.5 Discussion

We characterized the exposure-response relationship between clofazimine and QT interval prolongation, controlling for the circadian rhythm of QT and the slow accumulation of clofazimine concentrations. We simulated two different two-weeks loading-dose strategies and, while they resulted in more QT prolongation than standard 100 mg daily dosing during the first treatment weeks, the prevalence of ΔQTcF>30 ms was not higher than the levels predicted with the current standard regimen at steady state; suggesting that the loading doses will have a

minimal increased risk of greater QT prolongation compared to the standard 100 mg daily dosing. At steady state with standard clofazimine dosing regimen, we estimated absolute ΔQTcF to be 28.5 ms, which is higher than the ΔQTcF reported for moxifloxacin (standard and high dose), bedaquiline, or delamanid. (Moon *et al.*, 2014; von Groote-Bidlingmaier *et al.*, 2019) Our study highlights the importance of QT monitoring in patients treated with clofazimine-containing regimens for DR-TB as the QT prolongation effect of clofazimine-induced is likely to be additive.

The risk of life-threatening cardiac arrhythmias increases with a QT interval measured >500 ms. Although none of the participants in the clofazimine mono-therapy arm crossed the 500-ms threshold, the QT effect is significant considering clofazimine is usually included in DR-TB treatment regimens containing other QT-prolonging drugs (bedaquiline, delamanid, and fluoroquinolones). (Novartis Pharma., 2019) Additive QT-prolongation has been shown when clofazimine is combined with bedaquiline, resulting in a mean±se QTcF interval increase from baseline of 41.5±8.4 ms; by contrast, the QTcF interval increased by only 12.9±4.1 ms in patients whose background regimen did not include clofazimine. (B Dannemann *et al.*, 2012; Wallis, 2016)

Pre-treatment data was used to account for inherent factors affecting QT interval, such as circadian rhythm. Due to the limited size of our dataset, QTcF was used rather than population-based correction methods; the results across different QT correction methods were not significantly different. Most of the pre-treatment data were clustered around three time points, and fewer spread throughout the day, as shown in **Figure 6.1**. Nevertheless, the model fit improved significantly (ΔOFV of 37, df=7, P=4.69e-06) after accounting for the circadian variation using harmonic functions (between-subject variability was only retained in one

parameter). We also investigated the impact of circadian model on estimates of drug effect by repeating the analysis without circadian model but found no significant difference. The circadian variation caused a maximum ΔQTcF of 13 ms; previous studies reported a maximum increase up to 20 ms in ΔQTc (Ishida *et al.*, 1997). While the CIs for the estimates of E_{max} and Ec_{50} are wide, 28.0 (17.4 – 61.0) ms for Emax and 0.261 (0.0957 - 0.949) mg/L for Ec_{50}, the uncertainty in these two parameters is highly correlated. This results in a relatively tight CI for the overall PK/PD effect, as shown in **Figure 6.4**. The median (95% CI) QT prolongation at the maximum observed concentration of 0.56 mg/L was 19.0 (14.7 – 25.1) ms. The extrapolated QT at higher concentrations, up to 1 mg/L, was 22.4 (16.0 – 32.9) ms. We also evaluated the simulation results assuming linear drug effect on QT (**Figures provided in supplemental**). Overall, the results between the two approaches were not significantly different.

6.6 Limitations

Our study has several limitations. First, we explored the effect of clofazimine exposure in the clofazimine-monotherapy treatment arm only, we were therefore unable to quantify the additive QT effect when clofazimine was included in a treatment regimen including other QT-prolonging drugs. Second, the predicted QT effect was extrapolated to concentrations higher than those observed in the current data, these higher concentrations were predicted during the simulation of alternative dosing regimen in the population pharmacokinetic model (Abdelwahab *et al.*, 2020), however, the large uncertainty around the extrapolated QT effect take into account that these concentrations were not observed. as shown **Figure 6.4**. Third, the population pharmacokinetic model used in the simulation has not been validated with steady-state concentrations. Lastly, the number of QT measurements included in our analysis is limited as the ECG monitoring was performed as part of routine safety protocols.

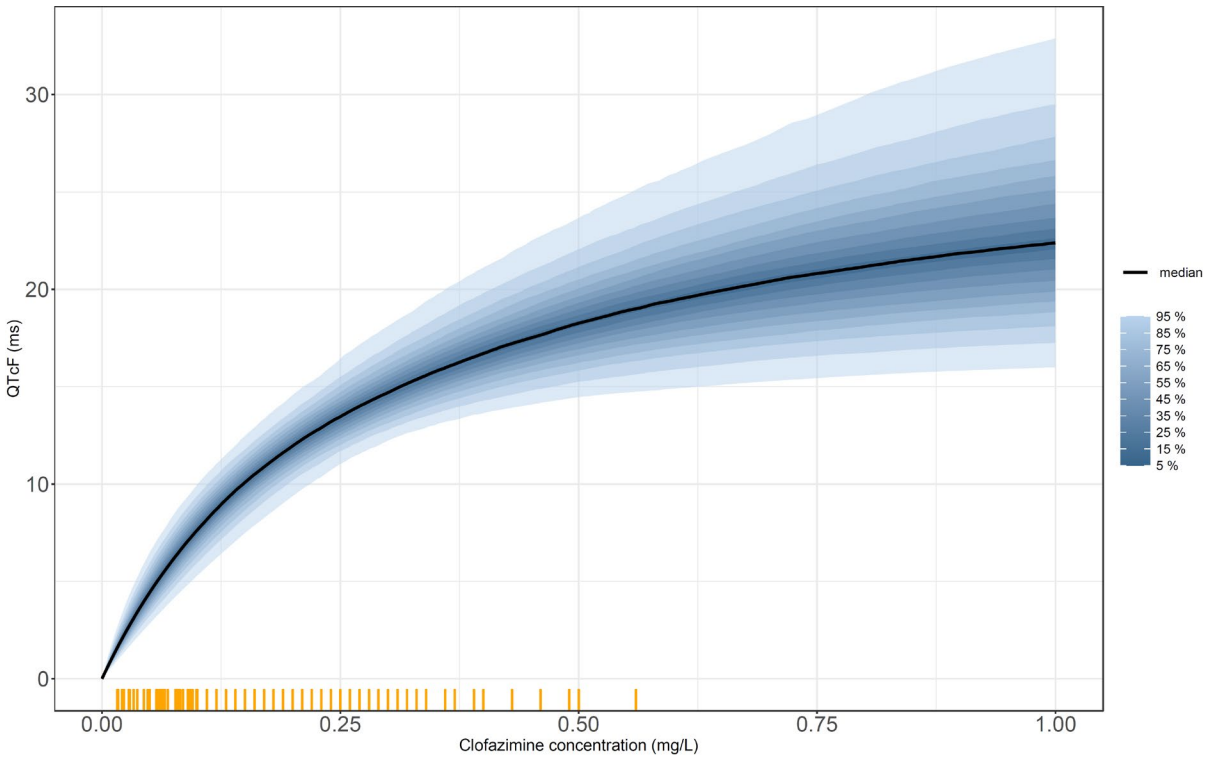

Figure 6.4. The percentiles of uncertainty distribution of the PK/PD relationship on QTcF (ms) vs. clofazimine concentration (mg/L).

The yellow ticks represent clofazimine concentrations observed in our data.

6.7 Conclusion

In conclusion, we have developed the first population pharmacokinetic-pharmacodynamic model characterizing the effect of clofazimine concentrations on QTcF prolongation in tuberculosis patients. Clofazimine has a significant QT prolonging effect driven by plasma concentrations. Our model could be used to better understand the QT-prolonging effects of clofazimine when included with other QT-prolonging drugs for DR-TB. We also recommend more frequent ECG monitoring for patients receiving a loading of clofazimine as a part of multi-drug regimen, at least during the initial phase of treatment to identify patients with higher risk of pronounced QTc prolongation.

6.8 Supplemental figures and tables

Table 6.3. Baseline and clinical characteristics of all 105 patients.

Characteristic	Median (IQR)/ n (%)
Age, year	30 (23 – 40)
Males	65 (61.9)
HIV-1+	12 (11.4)
Total body weight, kg	53.8 (46.9 – 60.4)
FFM, kg	42.7 kg (27.3 – 64.8)
BMI, kg/m^2	19.4 (17.8 – 21.3)
Overall-Baseline QTcF (ms)	390 (379-401)
Predose QTcF(ms)	391 (380 – 402)
5-hours QTcF(ms)	390 (377 – 398)
10-hour QTcF(ms)	388 (378 – 397)
Overall-Baseline heart rate (bpm)	89.3 (77.4 – 100)
Predose HR (bpm)	89.3 (77.0 – 101)
5-hours HR (bpm)	89.7 (80.3 – 99)
10-hour HR (bpm)	88.3 (79.7 – 98)

Fat-free mass (FFM), body mass index (BMI), beat per minute (bpm).

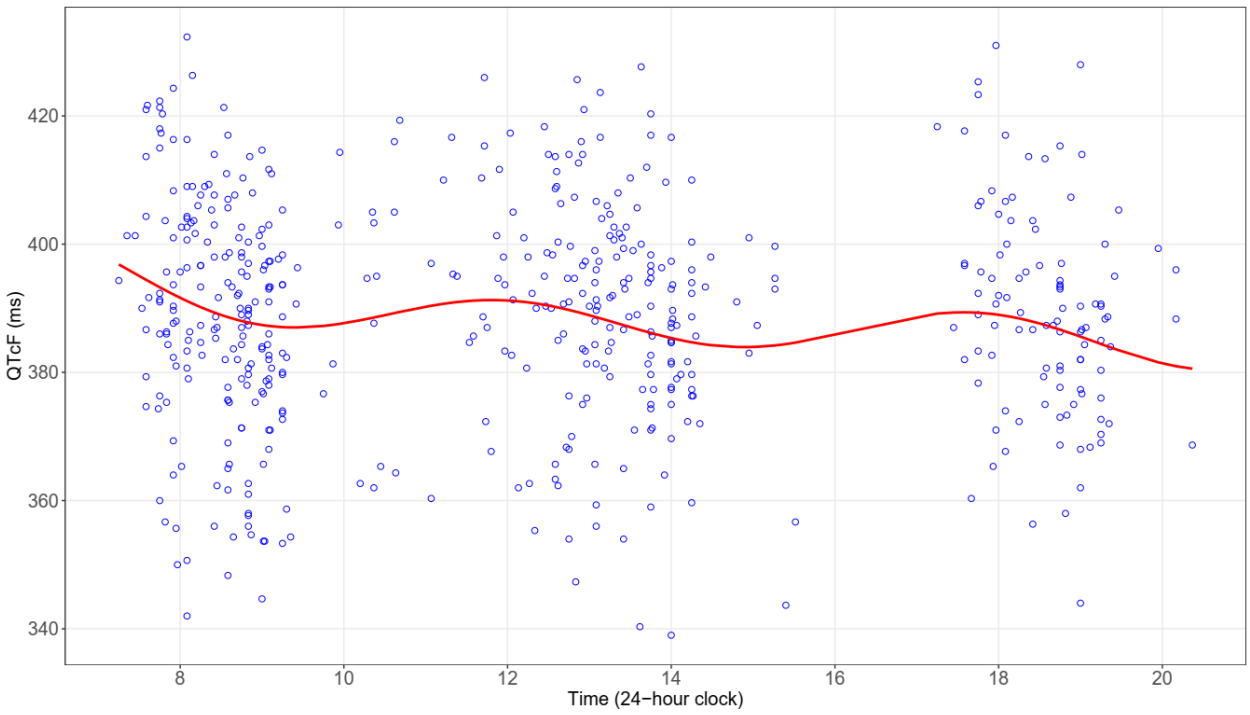

Figure 6.5 Scatter plot of pre-treatment QTcF (105 patient) vs Clock time, overlaid with circadian model for median patient (red line)

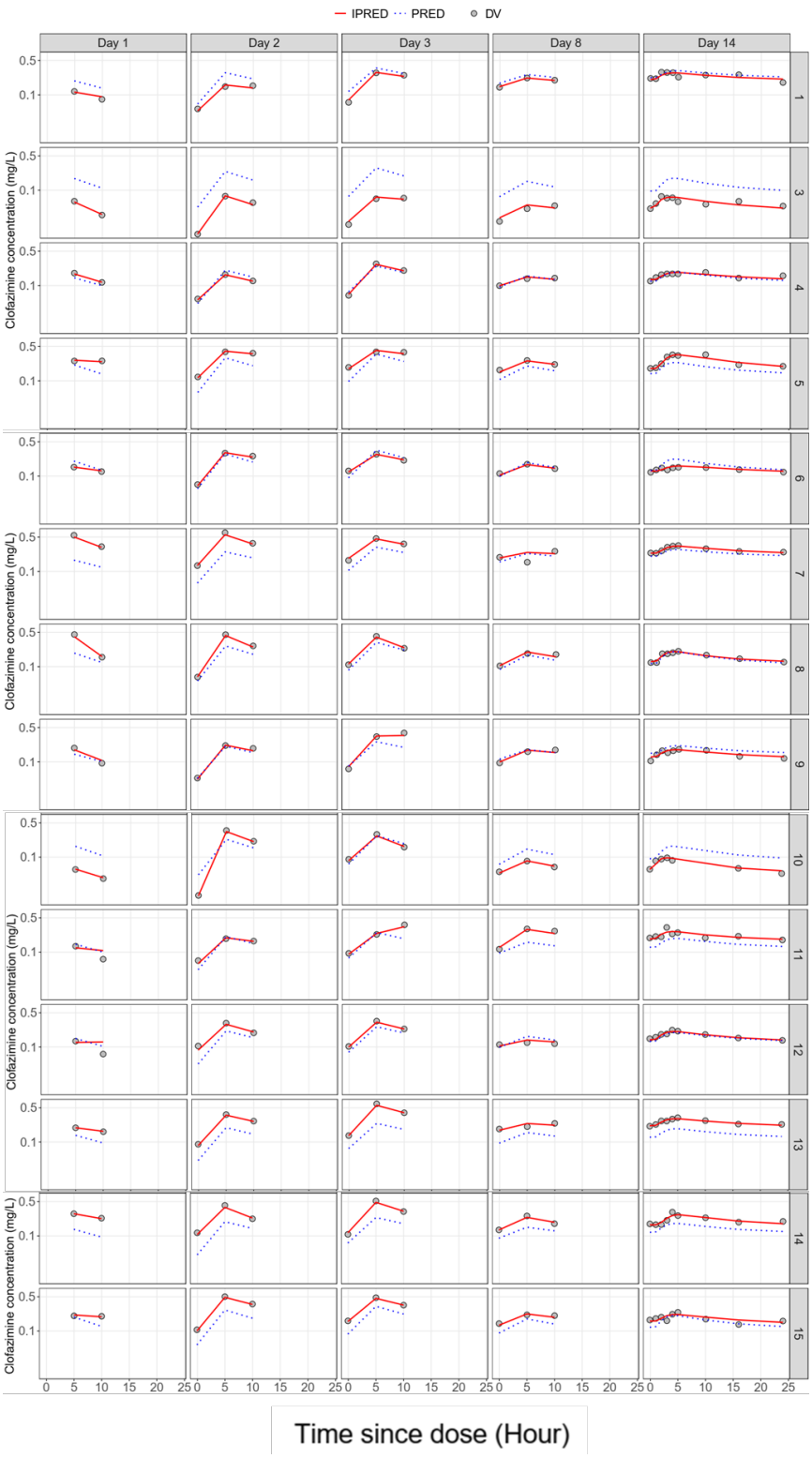

Figure 6.6 Individual pharmacokinetic profiles across visits overlaid with population and individual model prediction (Abdelwahab et al. 2020).

One patient dropped out after first day of dosing (not shown)

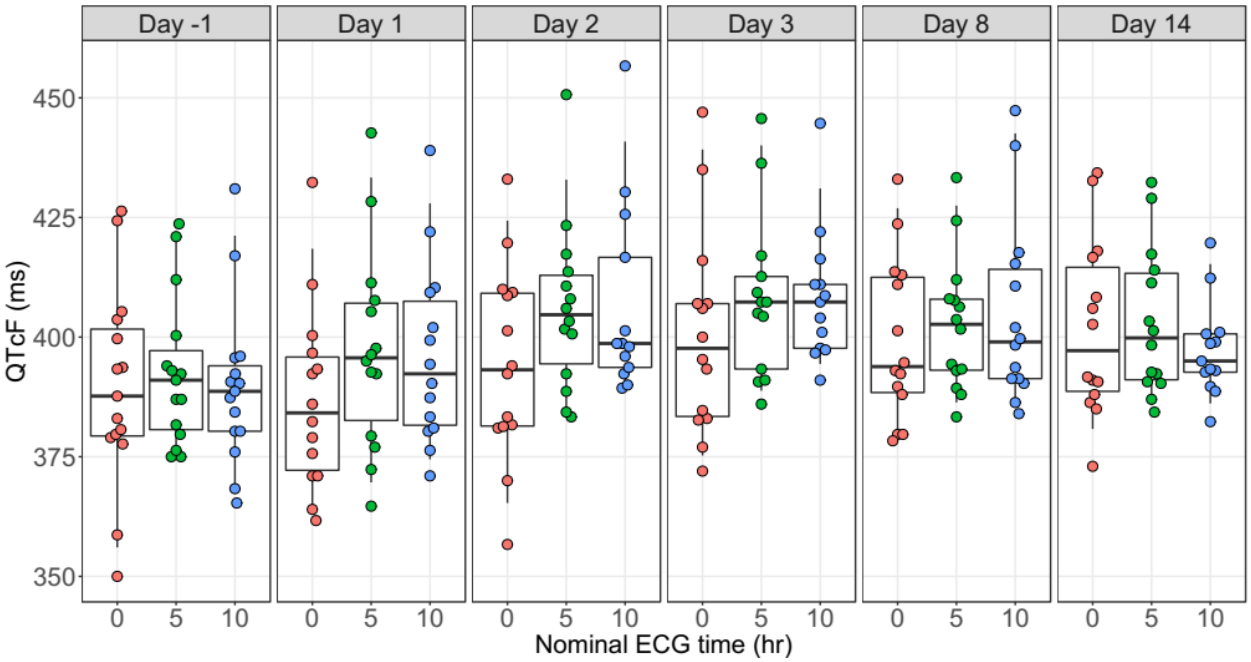

Figure 6.7 Boxplot of QTcF vs nominal ECG time stratified by visit day.

The dots represent individual values. Whiskers show the 5th and 95th percentiles

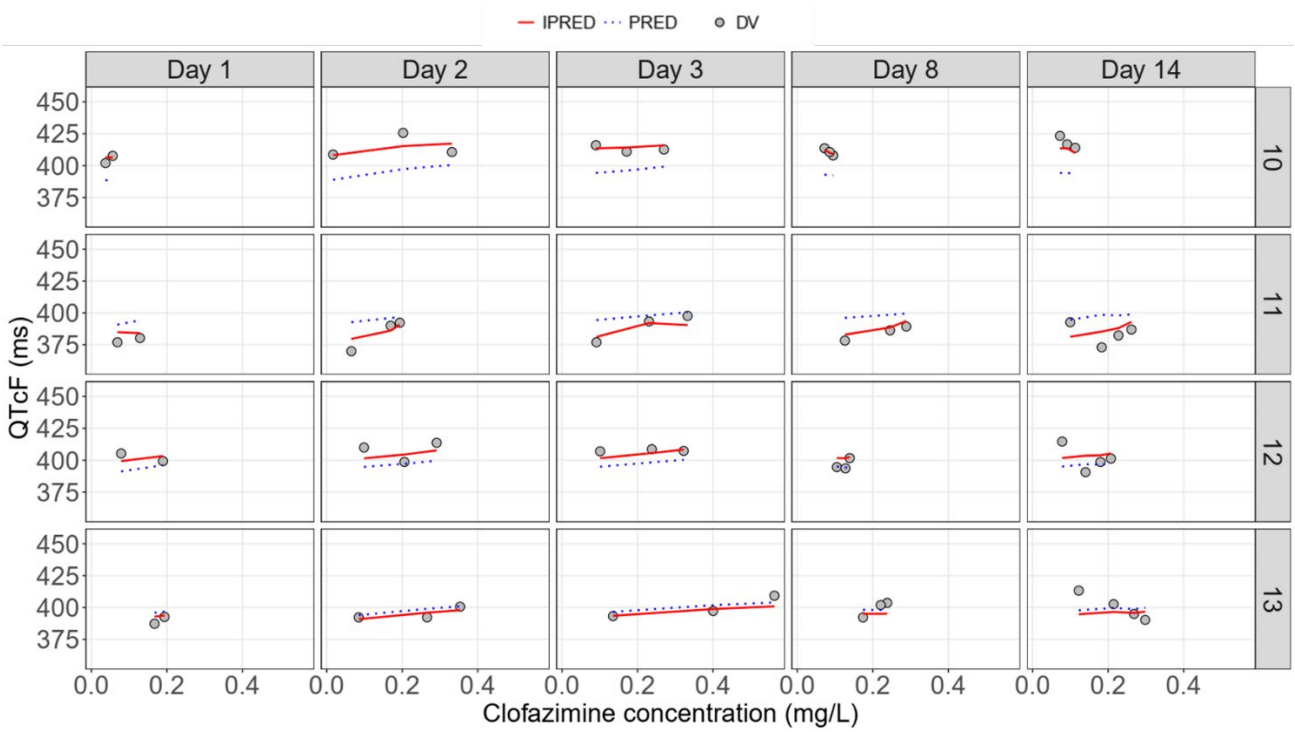

Figure 6.8 Individual QTcF profile across visits overlaid with population and individual model prediction

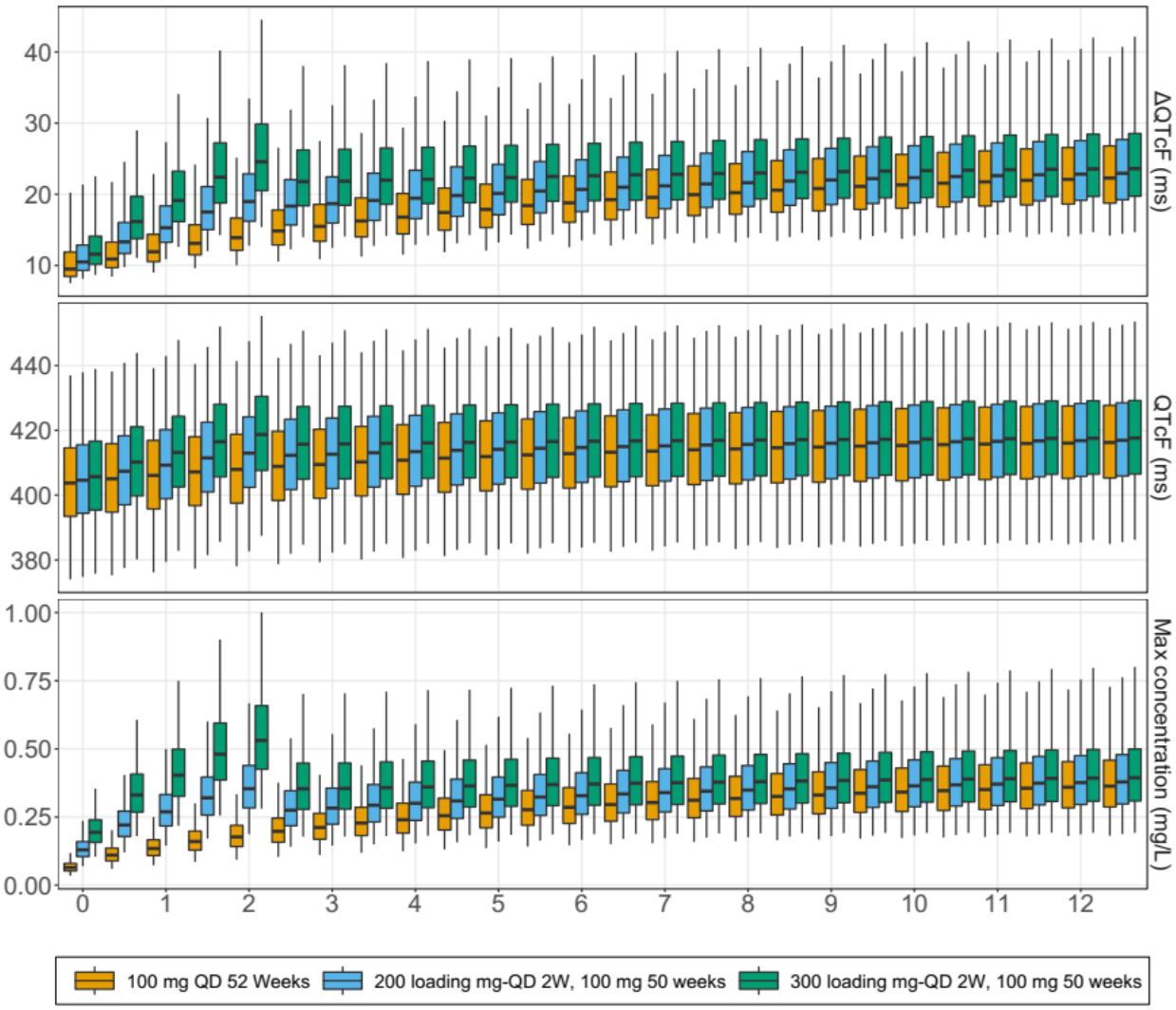

Figure 6.9 Linear model results, Simulated dQTcF, QTcF (ms) and peak concentrations (mg/L) with standard 100-mg daily dosing and loading dose regimens for a typical TB patient observed in the cohort.

The central lines in boxes represent median values; upper and lower horizontal lines are 75th and 25th percentiles, respectively, and whiskers are 2.5th and 97.5th percentiles.

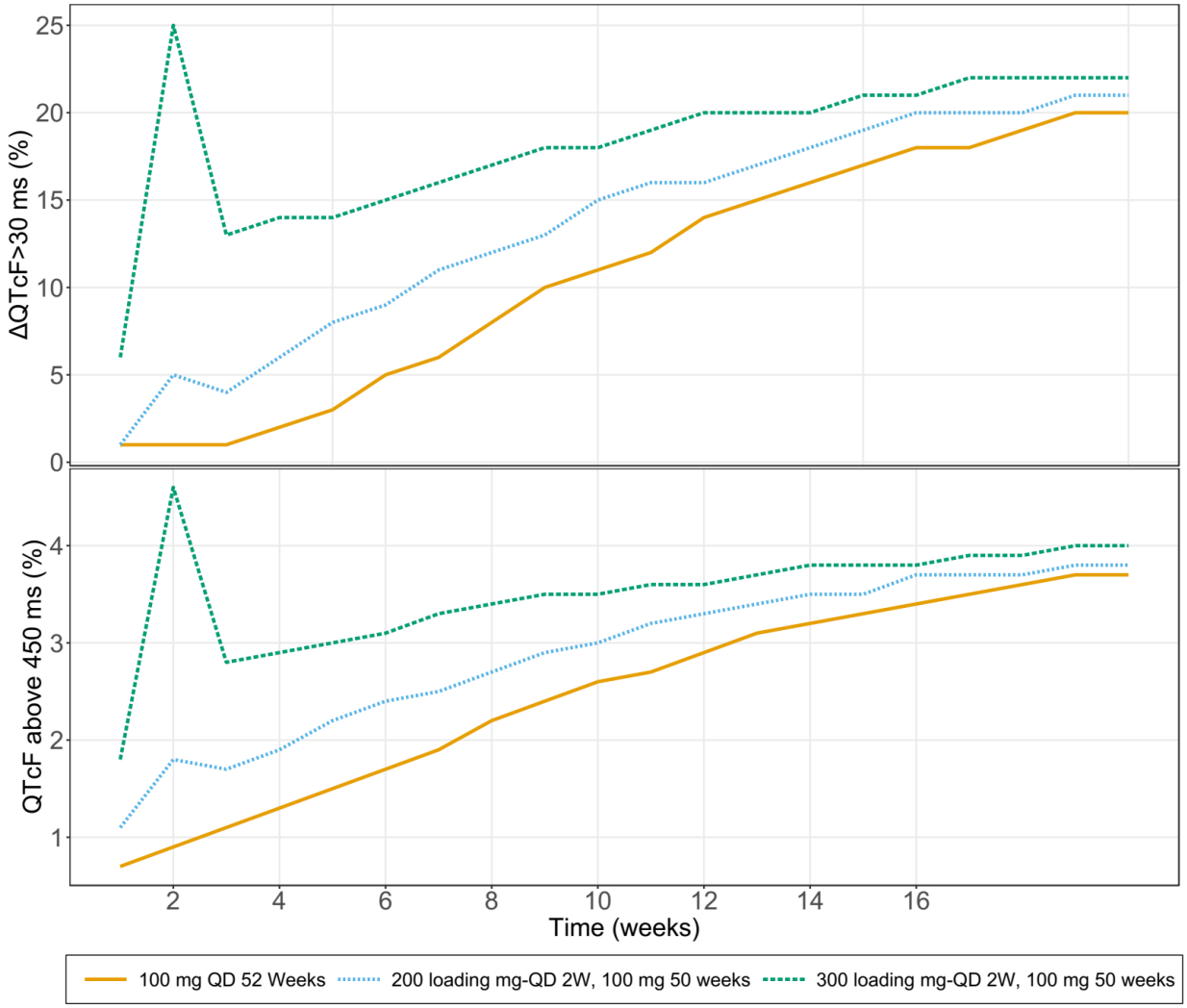

Figure 6.10 Linear model results: Proportions of simulated replicates with QTcF above 450 ms (lower panel) and dQTcF above 30 ms (upper panel) with standard 100 mg daily dosing and suggested loading dose regimens for a typical TB patient observed in the cohort.

Chapter 7:Linezolid population pharmacokinetics in South African patients with drug-resistant TB.

7.1 Abstract

Linezolid is widely used for drug-resistant tuberculosis (DR-TB) but has a narrow therapeutic index. To inform dose optimisation, we aimed to characterise the population pharmacokinetics of linezolid in South African participants with DR-TB and explore the effect of covariates, including HIV-co-infection, on drug exposure.

Data were obtained from pharmacokinetic sub-studies in a randomised controlled trial and an observational cohort study, both of which enrolled adults with drug-resistant pulmonary tuberculosis. Participants underwent intensive and sparse plasma sampling. We analyzed linezolid concentration data using nonlinear mixed-effects modelling and performed simulations to estimate attainment of putative efficacy and toxicity targets.

124 participants provided 444 plasma samples; 116 were on the standard daily dose of 600 mg, while 19 had dose reduction to 300 mg due to adverse events. Sixty-one participants were female, 71 were HIV-positive, and median weight was 56 kg (IQR 50 - 63). In the final model, typical values for clearance and central volume were 3.57 L/h and 40.2 L, respectively. HIV co-infection had no significant effect on linezolid exposure. Simulations showed that 600 mg dosing achieved the efficacy target (fAUC_(0-24h)/MIC>119 at MIC level of 0.5 mg/L) with 96% probability but had 56% probability of exceeding safety target (trough_24h>2 mg/L). The 300 mg dose did not achieve adequate efficacy exposures.

Our model characterised population pharmacokinetics of linezolid in South African patients with DR-TB and supports the 600 mg daily dose with safety monitoring.

7.2 Introduction

Drug resistant tuberculosis (DR-TB) continues to impede global efforts to control the tuberculosis epidemic. In 2019, there were an estimated 10 million new TB cases and half a million cases with rifampicin-resistant TB (RR-TB), 78% of whom had multidrug-resistant TB (MDR-TB).(Zignol *et al.*, 2013; Tola *et al.*, 2020; World Health Organization, 2020a) Until recently, only 54% of patients with DR-TB achieved treatment success and only 30% of patients with extensive-drug resistant tuberculosis (XDR), but there has been marked improvement in outcomes with the introduction of effective new and repurposed antituberculosis agents.(Ndjeka *et al.*, 2018)

Linezolid, the prototype member of the oxazolidinone antimicrobial class, has potent *in vitro* antituberculosis activity and is associated with improved treatment outcomes when added to multi-drug regimens for DR-TB.(Wasserman *et al.*, 2019; Fermeli *et al.*, 2020) WHO recommends linezolid at a dose of 600 mg daily for most patients with RR-TB. Linezolid is associated with a high frequency of haematological and neurological adverse events, which appear to be dose- and duration-dependent, limiting its use in TB treatment.(Zhang *et al.*, 2015; Olayanju *et al.*, 2019) Linezolid toxicity is due to structural homology between target 23s rRNA in *Mycobacterium tuberculosis* and 16s rRNA in human mitochondria, resulting in a narrow therapeutic index and uncertainty around dose optimisation.(Wasserman *et al.*, 2016)

Putative pharmacokinetic targets for linezolid efficacy and toxicity have been proposed, based on *in vitro* infection models and small clinical studies. Previous work has shown that exposures may not be optimal for these targets at the current recommended linezolid dose.(Wasserman *et al.*, 2019; Alghamdi *et al.*, 2020) Population-specific factors such as host genetics,(Wilkinson, 2005) HIV,(Hughes *et al.*, 2015; Olayanju *et al.*, 2019), age (Tsuji *et al.*, 2017; Wasserman *et al.*, 2019), creatinine clearance(Matsumoto *et al.*, 2010; Alghamdi *et al.*, 2020) and body size(Abe *et*

al., 2009; Wasserman *et al.*, 2019) may influence linezolid pharmacokinetic variability and pharmacodynamic effects, potentially leading to toxicity, treatment failure(Pasipanodya *et al.*, 2012) and an increased risk of developing drug resistance.(Srivastava *et al.*, 2011) There are very limited pharmacokinetic data from HIV-positive patients , in whom linezolid-specific adverse events may be potentiated.(Hughes *et al.*, 2015; Wasserman *et al.*, 2016; Millard *et al.*, 2018) Population pharmacokinetic models accurately determine causes of variability in drug exposure. These models can then be used for simulation of optimised dosing schedules that balance efficacy and toxicity.(Upton *et al.*, 2014) We aimed to characterise the population pharmacokinetic of linezolid in South African DR-TB patients with a high prevalence of HIV and estimate the probability of efficacy and toxicity target attainment from simulations of different dosing regimens.

7.3 Methods

7.3.1 Study population

Data were obtained from South African adults treated with linezolid-containing regimens for pulmonary DR-TB. Participants were enrolled into two studies: an observational cohort study (PROBeX) of patients with pre-XDR-TB (resistance to isoniazid and rifampicin (MDR) plus additional fluoroquinolone or second-line injectable resistance) and XDR-TB (MDR with additional resistance to fluoroquinolones plus a second-line injectable agent)(Brust *et al.*, 2021) ; and the intervention arm of an open-label clinical trial examining a shortened injection-free regimen for RR-TB (NExT; ClinicalTrials.gov NCT02454205).(Wasserman *et al.*, 2019) Linezolid was administered as a 600 mg daily oral dose, reduced to 300 mg daily at the discretion of local clinicians or trial staff, in patients who developed toxicity. A subgroup of patients from both cohorts was consecutively enrolled in an intensive PK sub-study; all patients

in PROBeX underwent additional serial sparse pharmacokinetic sampling. The studies were approved by the institutional review boards at the University of Cape Town, Albert Einstein College of Medicine, and Emory University. All participants signed written informed consent

7.3.2 Data source

Clinical and laboratory data were collected monthly over six months for PROBeX participants; data from NExT participants were collected at study entry and during the intensive PK visit at month 2. Data included demographic and biometric information, HIV status, concomitant antituberculosis drugs and antiretroviral therapy (ART), and biochemical profile.

Plasma samples from participants in the intensive pharmacokinetic sub-study were collected pre- and at 1, 2, 3, 4, 5, 6, and 24 hours post-dose at month 2 after study enrolment. Some participants from PROBeX provided additional plasma samples at 8 and 48 hours, as part of other study procedures. Linezolid was administered following a standardised meal and under the supervision of the study team. An additional plasma pharmacokinetic sample was collected at months 1, 2, and 6 after study entry for PROBeX participants following self-reported linezolid dosing times.

Linezolid concentrations were measured at the Division of Clinical Pharmacology at the University of Cape Town using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Using a deuterated internal standard, the LC-MS/MS method for linezolid was validated over a calibration range of 0.100 to 30 mg/L. Over the period of sample analysis (n=8 batches), a mean accuracy of 98.8% was achieved, with a mean precision of 5.93% (CV).(Garcia-Prats *et al.*, 2014)

7.3.3 Model building and analysis

Pharmacokinetic data was analysed with non-linear mixed effects modelling in NONMEM version 7.5 (ICON Development Solutions, Hanover, MD, USA) using expectation

maximization algorithm; we applied stochastic-approximation expectation maximization (SAEM) followed by important sampling (IMP) to obtain objective function value for hypothesis testing. Pirana (Certara, Princeton, NJ, USA), Perl-speaks-NONMEM version 5.0 and Xpose4(Keizer *et al.*, 2013) were used for NONMEM execution and post-processing results. Final parameter estimates and 95% confidence intervals were obtained via sampling-importance resampling (SIR) procedure available in PsN.(Dosne *et al.*, 2016) One- and two-compartment disposition kinetics with linear and non-linear elimination were tested to describe the structural model of the linezolid. To describe the absorption process, we tested first-order absorption with and without lag, saturable absorption, and transit compartments absorption.(Radojka M. Savic *et al.*, 2007) Between-subject and -occasion random effects included on pharmacokinetic parameters were assumed to follow a lognormal distribution. Additive, proportional, and combined error models were tested to describe residual unexplained variability. Allometric scaling(Anderson *et al.*, 2008) was tested on all disposition parameters to account for the effect of body size with total body weight (TBW), fat-mass and fat free-mass(Janmahasatian *et al.*, 2005) as body size descriptors. The effects of HIV status, age, creatinine clearance (estimated by Cockroft-Gault) and linezolid dose were investigated on clearance (CL), the volume of distribution (Vc), and bioavailability.

Model development and inclusion of covariates followed a stepwise approach based on physiological plausibility and improvement in model diagnostics. Model diagnostics included inspection of visual predictive checks (VPC) and the difference in the model objective function (ΔOFV), which was assumed to follow a chi-square distribution (χ^2) with a degree of freedom corresponding to the difference in the number of parameters between two nested models (ΔOFV of at least 3.84 points with $P < 0.05$).

7.3.4 Simulations

We used the final model parameter estimates to perform Monte Carlo simulations to evaluate the probability of target attainment (PTA). The selected targets were free $AUC_{0–24}$/MIC ($fAUC_{0-24h}/MIC$) > 119, which represents an efficacy target of 80% maximal kill based on the hollow fibre infection model(Srivastava *et al.*, 2017; Alghamdi *et al.*, 2020; Kristina M Bigelow *et al.*, 2020) and $C_{min} > 2\ mg/L$ and $> 7\ mg/L$ corresponding to thresholds for mitochondrial toxicity in TB patients and thrombocytopenia in patients with Gram-positive infection, respectively.(Pea *et al.*, 2012; Song *et al.*, 2015)

We simulated exposure (C_{min} and AUC_{0-24}) following 300, 600, and 1200 mg daily dosing assuming steady state had been attained. To ensure the relevance of the simulations, we used demographic characteristics of TB patients obtained from pharmacokinetic studies conducted in West Africa and South Africa (n=1,000).(Chirehwa *et al.*, 2020) Protein binding was assumed to be 30% (Stalker *et al.*, 2003) PTA was calculated as the proportion of simulated participants with PK exposure above the efficacy and toxicity targets.

7.3.5 Microbiological data

Baseline (pre-treatment) *M. tuberculosis* isolates were retrieved from PROBeX participants. Linezolid minimum inhibitory concentration (MIC) testing was performed on available isolates using the mycobacterial growth indicator tube (MGIT) system and continuous growth monitoring with Epicenter software. Dilutions ranged from 0.25 mg/L to 2 mg/L based on published wild-type distributions and the suggested critical concentration of 1 mg/L(World Health Organization., 2018). The expected population probability of target attainment for a specific drug dose and a specific population of microorganisms (i.e., the cumulative fraction of response [CFR])(Mouton *et al.*, 2005) was calculated using the

distribution of observed MICs in our cohort for the different simulated dosing regimens. The simulation was performed in NONMEM 7.5, and post-processing of the results was performed in R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

7.4 Results

7.4.1 Demographics and clinical profile

One-hundred and twenty-four participants provided pharmacokinetic data, including 30 who were intensively sampled, contributing a total of 444 observations over a six-month dosing period. 116 patients were initially receiving 600 mg daily, and 19 patients had their dose reduced to 300 mg (11 participants were sampled at both doses). Out of the 30 patients in the intensive pharmacokinetic visit only 4 were dosed 300 mg daily. The baseline characteristics of the patients are shown in **Table 7.1**; more than half the participants were HIV-positive.

MIC data was available for isolates from 83 participants (**Figure 7.1**). All isolates had MIC ≤ 1.0 mg/L and 77% had an MIC of 0.5 mg/L. There was no apparent association between linezolid MIC level and degree of drug resistance.

Table 7.1 Baseline participant characteristics

Variable	(*n*=124)
Age, years	33 (27.8 - 42)
Females, *n* (%)	61 (49.2)
Ethnicity, *n* (%)	
black	92 (74.2)
mixed race	30 (24.2)
white	2 (1.61)
Weight, kg	56 (50 - 63.1)
Height, cm	164 (157–168)
FFM, kg	43.3 (36.7 - 48.4)
BMI, kg/m^2	20.2 (18.2 - 23)
HIV positive, *n* (%)	71 (57.3)
M. tuberculosis resistance profile, *n* (%)	
MDR	9 (7.3)
pre-XDR (Inj-R)	11 (8.9)
pre-XDR (FQ-R)	32 (25.8)
XDR	72 (58.1)
Serum creatinine, µmol/L	64 (53 - 75) *
Daily 300 mg dose[a]	19 (14%)

Data are expressed as median (IQR) or number (percent). BMI, body mass index; FFM, Fat-free mass; ART, antiretroviral therapy

Inj-R, injectable-resistant; FQ-R, fluoroquinolone-resistant.

* Data were missing for 10 participants

[a]11 patients had dose reduced to 300 mg upon experiencing linezolid related adverse events in addition to 8 patients that were initially started on 300 mg daily dose.

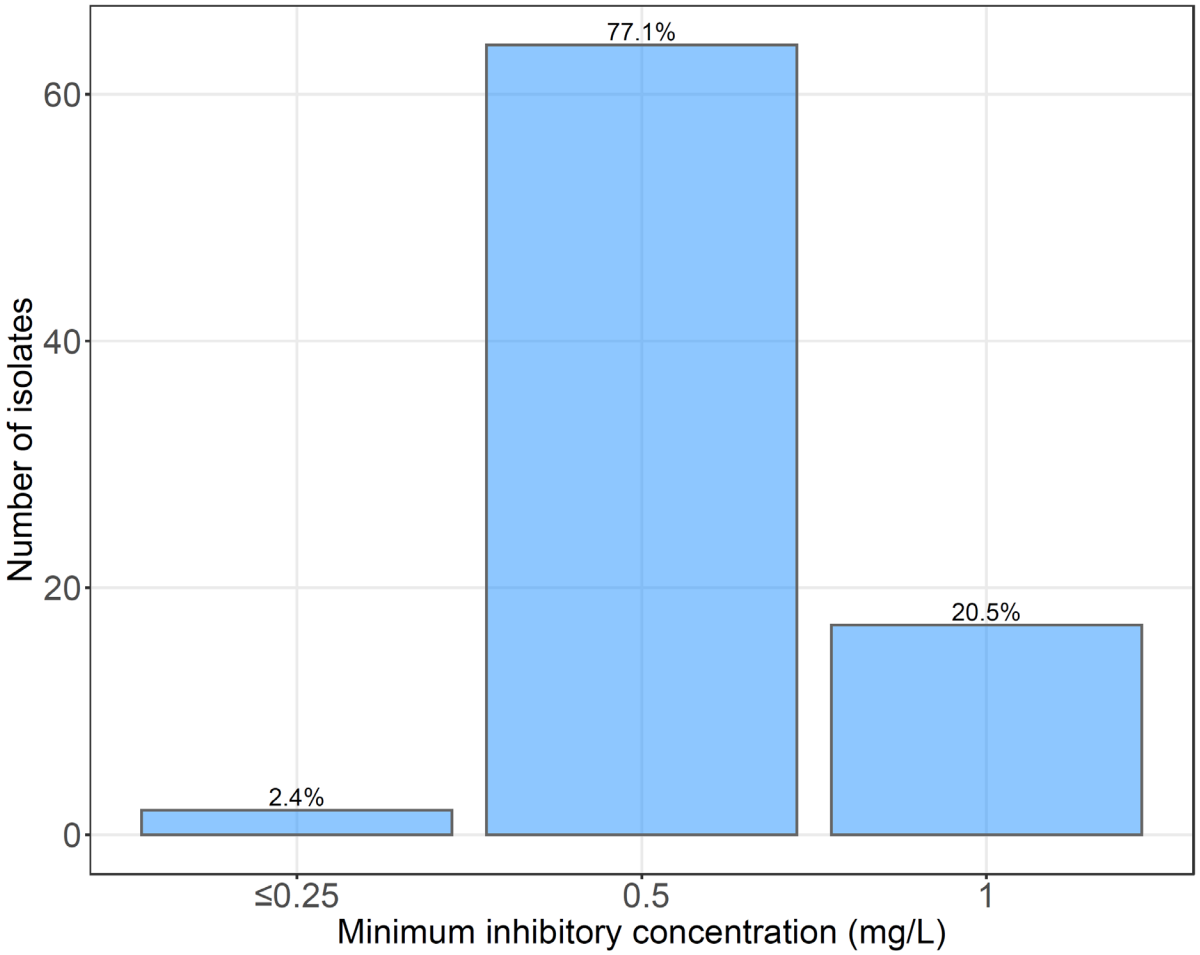

Figure 7.1 Distribution of M. tuberculosis MICs for linezolid done on cultured isolates taken before the start of tuberculosis treatment

7.4.2 Population pharmacokinetic model

Linezolid pharmacokinetic was best described by one-compartment disposition kinetics with linear elimination and a first-order absorption preceded by a series of transit compartments. All disposition parameters (central clearance and volume of distribution) were allometrically scaled by weight normalised to the median weight value observed in the cohorts (51 kg). There was no statistically significant association between creatinine clearance, age, sex and HIV status and linezolid pharmacokinetic exposure (bioavailability and clearance). The typical value of clearance (CL/F) for the median patient was 3.57 L/h (95% CI: 3.34 – 3.87), and central volume of distribution was 40.2 L (38.2 – 42.9) (**Table 7.2**). Residual unexplained variability was best described by a combined additive and proportional error model. For non-observed drug administration, a separate additive error was estimated, and we allowed an extra lag variability fixed to a standard deviation of ± 0.7 h relative to reported time of the dose (more details are provided in supplemental material). Values below the LLOQ were excluded from the dataset.(Beal, 2001), only 4 points were BLQ and all were predose samples. This was considered nonadherence and the dosing records from the previous days were disregarded. Visual predictive check (VPC) showed adequate model fit in **Figure 7.2** Model-estimated secondary pharmacokinetic parameters, stratified by dose, are summarised in **Table 7.3** and depicted in **Figure 7.3**

Table 7.2 Final population pharmacokinetic model parameters

Parameter description	Typical Value (95 % CI)*
Clearance, (L/h) †	3.57 (3.34-3.87)
Central Volume of distribution, Vc (L) †	40.2 (38.2-42.9)
Absorption Mean Transit Time, MTT (h)	0.528 (0.36-0.687)
Number of Transit Compartment, NN ( )	5 (FIXED)
Absorption rate constant, Ka (1/h)	1.22 (0.933-1.69)
Bioavailability, F ( )	1 (FIXED)
Proportional error (%)	9.53 (8.42-11.1)
Additive Error (Observed dosing) (mg/L)[a]	0.05 (FIXED)
Additive error (Unobserved dosing) (mg/L)	0.651 (0.461-0.928)
Between-subject variability (%)§	
Clearance	37.1 (30.3-43.1)
Between-occasion variability (%)‡§	
Absorption mean transit time	56.8 (49.6 ; 66.2)
Absorption rate constant	78.5 (54.7-100)
Bioavailability	22.0 (17.2-26.9)

* 95 % confidence intervals obtained with sampling importance resampling technique using PsN software

† Allometric scaling used for CL, Vc; typical values reported for typical median patient with 56 kg weight.

§ Between- subject variability (BSV), -visit (BVV) and -occasion variability (BOV) were assumed to be log-normally distributed and reported as approximate %CV

[a]The estimate of this additive error was not statistically significant from its lower bound (LLOQ/2); thus, it was fixed to that value

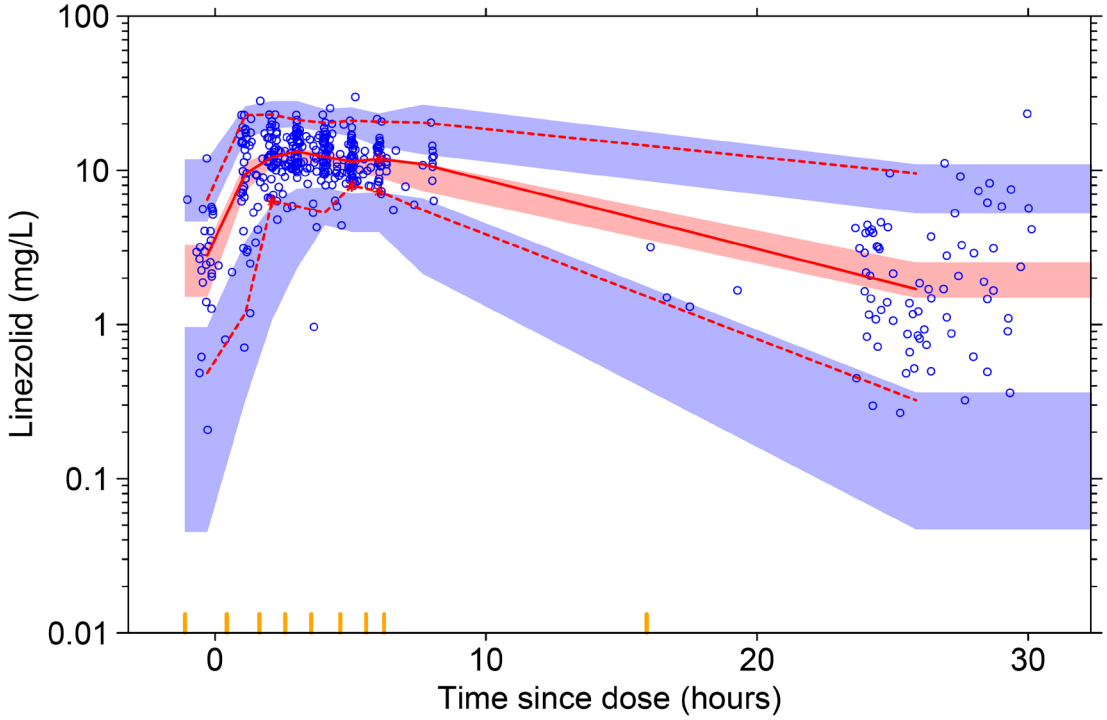

Figure 7.2 Prediction-corrected Visual predictive check (VPC) for linezolid concentration versus time (time since dose).

Circles represent original data, dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. Vertical yellow lines on the x-axis represent bins for sampling timepoints. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

Table 7.3 Summary of model-derived pharmacokinetic (PK) parameters and predicted targets attainment stratified by dose level for patients in the current study

Variable	300 mg (n=19)	600 mg (n=116)	Total (n=135)
C_{24h} (mg/L)	1.16 (0.87 – 1.66)	1.98 (1.41 – 2.47)	1.92 (1.28 – 2.29)
AUC_{0-24h} (mg·h/L)	92.3 (67.1 – 101)	159 (132 – 186)	151 (122 – 183)
$fAUC_{0-24h}/MIC > 119$ MIC = 0.5 mg/L	10/19	115/116	125/135
$fAUC_{0-24h}/MIC > 119$ MIC = 1 mg/L	0/19	51/116	51/135
C_{24h} > 2 mg/L	3/19	56/116	59/135

Data presented as median (IQR). AUC_{0-24}, area under the 24-h concentration-time curve. MIC, minimum inhibitory concentrations.

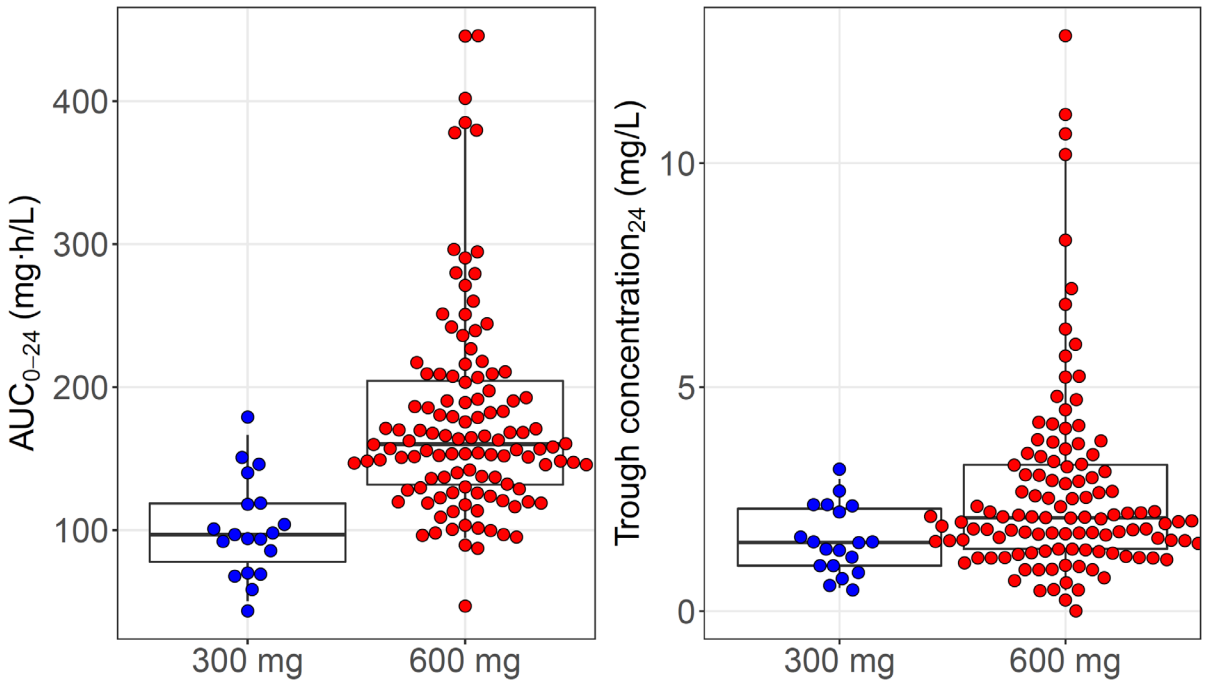

Figure 7.3 Box and whisker plots showing secondary model-derived exposure parameters, stratified by dose.

The dots represent individual values; whiskers are 2.5th and 97.5th percentiles. n = 19 for 300 mg and 116 for 600 mg

7.4.3 Probability of target attainment

At the standard 600 mg daily dose, linezolid achieved favourable PTA (96%) for the efficacy target up to the MIC value of 0.5 mg/L; this dropped to 55% at the critical concentration of 1 mg/L. Daily 1200 mg dosing achieved 96% PTA up to MIC 1 mg/L. The 300 mg dose did not achieve adequate PTA above MIC values of 0.25 mg/L **Figure 7.4**). For toxicity targets, the standard 600 mg daily dose exceeded the 2 and 7 mg/L targets for C_{min} in 54% and 2.2%, respectively; the probabilities of exceeding these targets at 1200 mg dosing were 82.2% and 23.1%, respectively. Daily 300 mg dosing had a 16.5% chance of exceeding 2 mg/L and was predicted not to exceed 7 mg/L **Figure 7.5**). The CFR for 300 mg daily was predicted to be 45%; for the standard 600 mg daily dose the CFR reached 87% and 98% for 1200 mg daily dose.

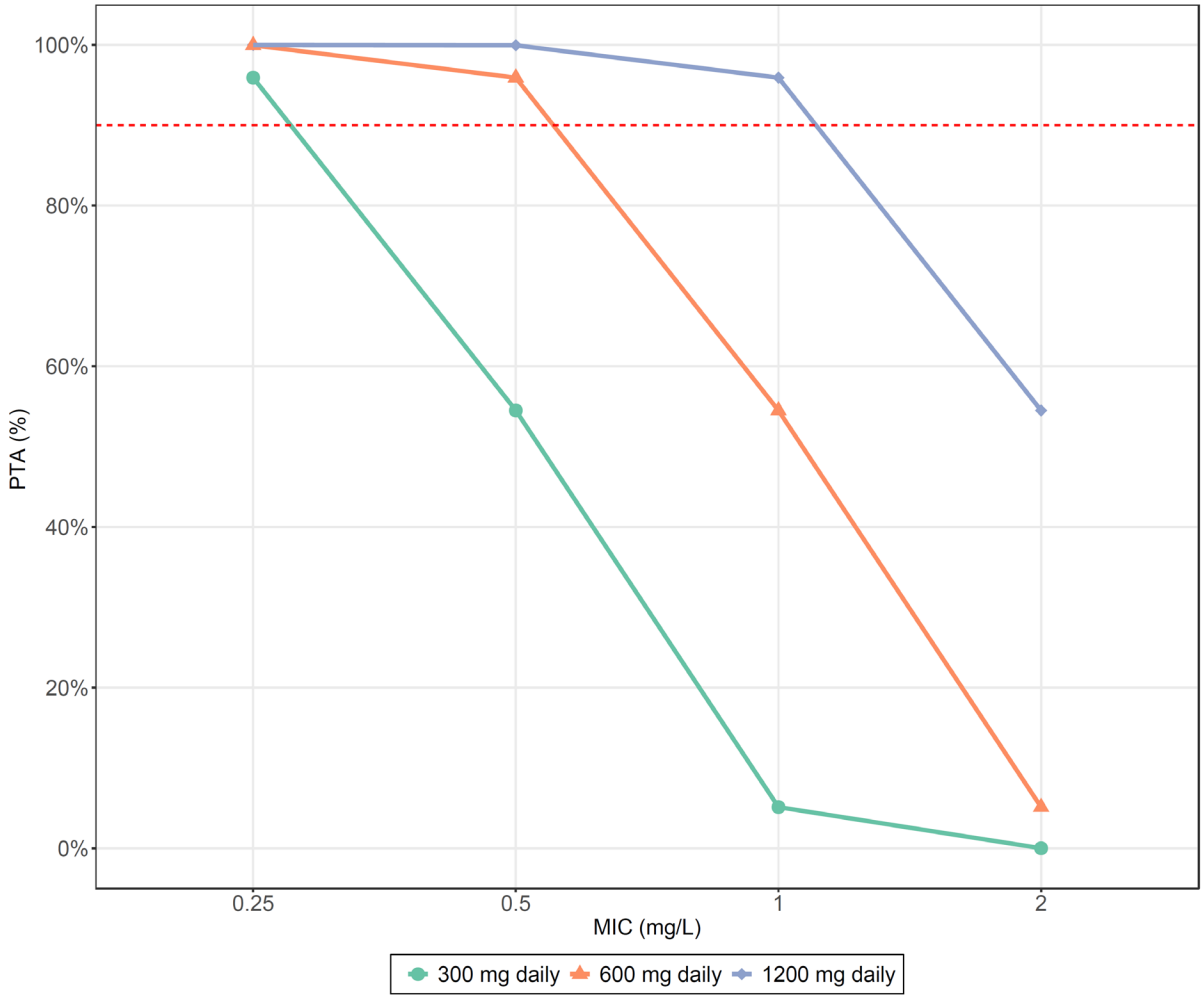

Figure 7.4 Probability of efficacy (the fAUC/MIC>119) target attainment (PTA) for the three simulated linezolid dosage regimens versus MIC distributions.

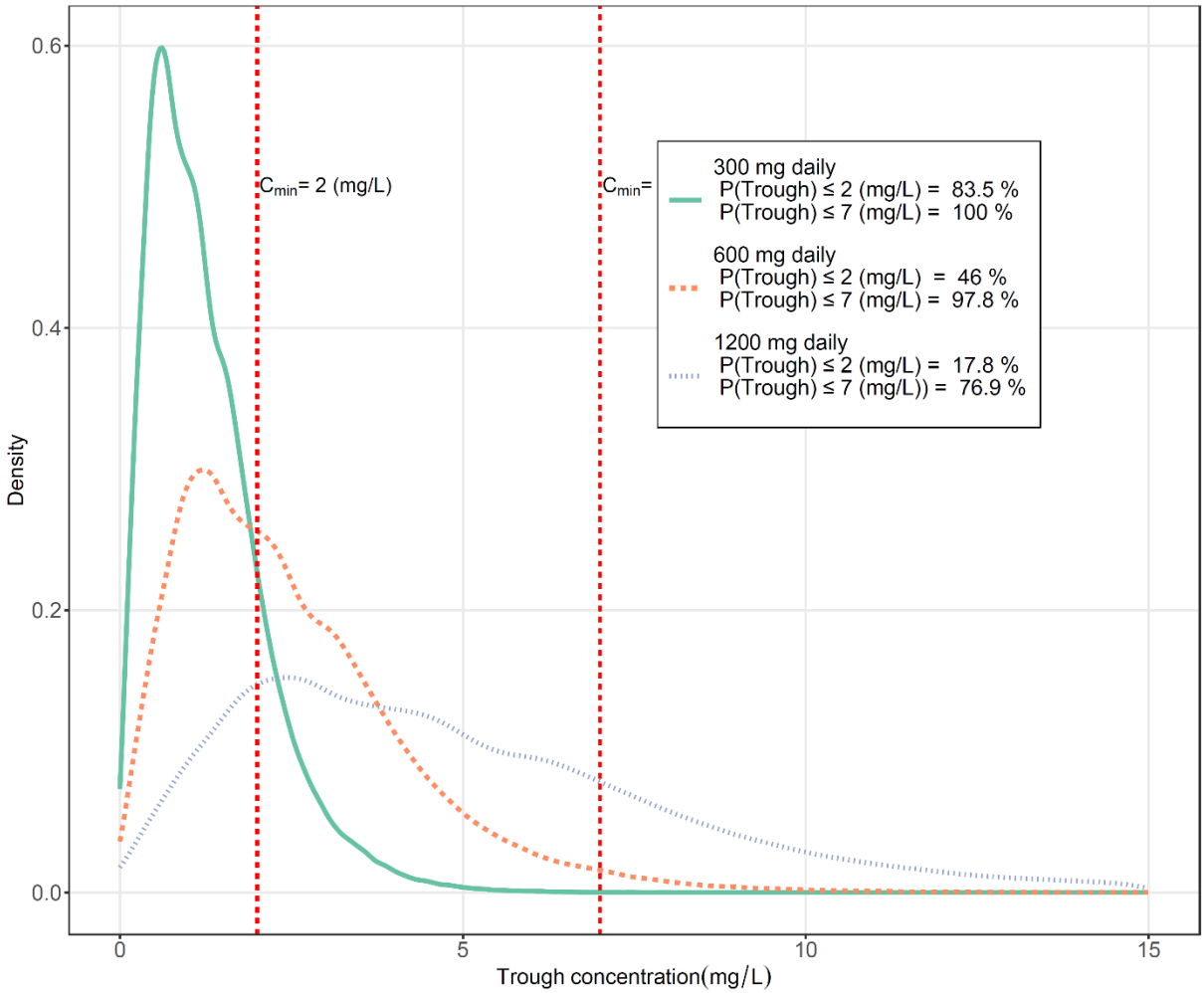

Figure 7.5 Probability density distributions for safety targets attainment following simulation of 300, 600, and 1200 mg daily dosing of linezolid.

The vertical lines on the x-axis represents the experimentally derived safety threshold of 2 mg/L and 7 mg/L

7.5 Discussion

We characterised the population pharmacokinetics of linezolid in South African patients with drug-resistant tuberculosis and demonstrated that the standard 600 mg dose is likely to achieve *in vitro* efficacy targets at the most frequent MIC values, but the 300 mg dose had a low probability of efficacy target attainment. Importantly, HIV co-infection had no effect on linezolid PK parameters. More than half the patients were estimated to exceed putative toxicity targets at the standard 600 mg daily dose, indicating that linezolid has a narrow therapeutic index in tuberculosis.

The value of CL estimated in our population, 3.57 L/h, was lower than previously reported CL values ranging from 7.5 to 9.96 L/h in model-based analyses from tuberculosis patients.(Meagher *et al.*, 2003; McGee *et al.*, 2009; Kamp *et al.*, 2017; Alghamdi *et al.*, 2020) In previous analyses involving non-TB patients or healthy volunteers, the clearance value ranged from 2.06 to 13.5 L/h.(Whitehouse *et al.*, 2005; Plock *et al.*, 2007; Abe *et al.*, 2009; Keel *et al.*, 2012; Boak *et al.*, 2014; Matsumoto *et al.*, 2014; Tsuji *et al.*, 2017; Soraluce *et al.*, 2020; Zhang *et al.*, 2020) Possible explanations for the large variability of clearance in different studies include differing weight distributions across populations and varying duration of linezolid exposure (linezolid may inhibit its own metabolism(Plock *et al.*, 2007)). Additionally, none of the reported models accounted for inter-occasion variability in absorption or bioavailability parameters, which could introduce bias on PK parameter estimates.(Karlsson *et al.*, 1993; Koehne-Voss *et al.*, 2015) However, the estimated value of the central volume of distribution in our analysis, 40.2 L, was similar to those previously reported in TB patients, median (IQR) of 40.6 (36.3 - 57.4).(Meagher *et al.*, 2003; McGee *et al.*, 2009; Alffenaar *et al.*, 2010; Brown *et al.*, 2015; Kamp *et al.*, 2017; Heinrichs *et al.*, 2019; Alghamdi *et al.*, 2020) Our parameter estimates

are comparable with those from a previously reported noncompartmental analysis of the same data(Wasserman *et al.*, 2019) and those from other populations.(Alffenaar *et al.*, 2010)

Almost all patients in the current study receiving standard 600 mg daily dosing had exposure values exceeding the efficacy target (n=115/116), and a large proportion (n = 56/116) had trough concentrations exceeding the safety threshold. For patients receiving 300 mg, around 50% (10/19) achieved exposure values above the efficacy target, and only 3 out of 19 had trough concentrations below the toxicity threshold. This highlights the need for continued toxicity monitoring, even after dose reduction. In contrast to other pharmacokinetic studies in tuberculosis, we did not find a significant effect of age and creatinine clearance on linezolid exposure.(Wasserman *et al.*, 2019; Alghamdi *et al.*, 2020) There was also no impact of HIV infection on linezolid pharmacokinetic in our population. Two small studies have suggested that HIV may be a risk factor for linezolid-associated adverse events.(Hughes *et al.*, 2015; Olayanju *et al.*, 2019) If this association is real it is likely driven by pharmacodynamic effects in HIV rather than increased drug exposure.(Wasserman *et al.*, 2019)

Because of linezolid's narrow therapeutic window and dose-dependent toxicity, it is important to identify the lowest effective dose in tuberculosis treatment, but this has been challenging in single arm cohort studies. Although excellent treatment outcomes were observed with linezolid use at 1200 mg daily in the Nix-TB trial, a substantial number of patients experienced treatment-limiting adverse events.(Conradie *et al.*, 2020) In contrast, a small Korean study demonstrated favourable treatment outcomes with a 4-fold lower dose of 300 mg daily, but over a quarter of patients still suffered linezolid related toxicity.(Koh *et al.*, 2012) Therapeutic drug monitoring (TDM) has been proposed as a strategy for linezolid optimization in tuberculosis therapy (Rao *et al.*, 2020; Sturkenboom *et al.*, 2021) because of low within-person variability, stability on dried

blood spots (Vu *et al.*, 2012), and needed for limited sampling.(Kamp *et al.*, 2017) However, clinical studies are need to better define exposure targets for toxicity (and efficacy) prior to implementation of TDM.

Our simulations showed that a total daily dose of 300 mg would achieve an *in vitro*-derived efficacy target with 90% probability only up to an MIC of 0.25 mg/L, which was found in less than 3% of isolates in our population. The efficacy target was achieved with 600 mg and 1200 mg doses up to MIC values of 0.5 and 1 mg/L, respectively, representing the range of wild-type *M. tuberculosis* isolates in the population. A recent population pharmacokinetic model based on data from HIV-negative tuberculosis patients generated slightly more conservative PTA predictions at published MIC values - this difference is explained by the much higher clearance observed in their population (6.32 L/h).(Alghamdi *et al.*, 2020) Despite a high probability of achieving the efficacy target, the 600 mg dose had 54% probability of exceeding the toxicity trough threshold of 2 mg/L (compared with 17% and 82% for 300 mg and 1200 mg doses, respectively). A small study (n = 9) has shown that some patients may achieve putative PK/PD targets at the 300 mg dose, but this would need to be supported by therapeutic drug monitoring which is unavailable in most high tuberculosis burden settings.(Bolhuis *et al.*, 2019)

Our study has limitations. First, the sparse-sampling data relied on self-reported information on the time of the dose, which introduced uncertainty into the model. We mitigated this by estimating a separate, larger, residual error and allowing extra lag variability (fixed to a standard deviation of ± 0.7 h) relative to the self-reported time of the dose. As shown in our VPC plots, the final model fitted the data adequately despite unobserved dosing. Second the linezolid dose was reduced to 300 mg in a few patients due to the development of toxicity. This raises the possibility of channelling bias and an overestimate of exposure in this group resulting from

intrinsically lower clearance. Third, the pharmacokinetic efficacy target was defined based on *in vitro* data,(Deshpande *et al.*, 2016; Srivastava *et al.*, 2017) which do not fully replicate disease in humans, or closely mimic human kinetics (J.S. Cadwell, 2012), and have not been validated in clinical settings. Fourth, the safety threshold of 2 mg/L is based on a small study involving 38 tuberculosis patients using a visually observed cutoff for any adverse event.(Song *et al.*, 2015) The 7 mg/L toxicity target relates to the development of thrombocytopenia in non-TB patients with short term use; this complication occurs much less frequently in tuberculosis.(Conradie *et al.*, 2020)

7.6 Conclusion

We successfully developed a population PK model in South African patients with RRTB, showing no effect of HIV or other important clinical covariates. We showed that standard dosing achieves putative efficacy targets, but also exceeds putative toxicity targets, which supports close safety monitoring. Further studies are needed to define clinical PK/PD relationships in tuberculosis patients and to explore alternative dosing strategies (e.g. intermittent dosing or dosing for a shorter duration or weight-based dosing regimen) to optimise efficacy and minimise toxicity.(Kristina M. Bigelow *et al.*, 2020)

Chapter 8:Conclusions

Tuberculosis remains a global challenge to public health, especially in low- and middle-income countries. This challenge is further complicated in case of drug-resistant TB. Treatment of tuberculosis relies on a combination of drugs in a long ,and complex regimen. The introduction of novel new agents and repurposing old anti-infective drugs in tuberculosis treatment calls for optimizing effective and safe dosing regimens. Exposure of tuberculosis drugs in pregnancy, pharmacokinetic and safety of repurposed and new TB drugs in diverse populations remain unaddressed open questions that require further investigation and research.

The composite work presented in this thesis aimed at addressing some of the research gaps within tuberculosis research. First, we successfully developed the first population pharmacokinetic models of first-line TB drugs (Isoniazid, pyrazinamide and ethambutol) in pregnant women with TB/HIV infections, then evaluated the exposure of these drugs pre- and postpartum and compared the results against other published exposure targets. We then described the pharmacokinetic of the new novel drug pretomanid in drug-susceptible tuberculosis patients when given with rifamycin's (rifampicin or rifabutin). In case of drug-resistant tuberculosis, we managed to characterize the unusual pharmacokinetic of the repurposed drug clofazimine in patients with drug-resistant tuberculosis and evaluated the effects of key covariates on drug exposure. We then sought to optimize new dosing regimen using different loading doses strategies and evaluate clofazimine exposure-safety relationship and its effect on QT interval prolongation. Lastly, we applied nonlinear mixed-effect modelling to evaluate the exposure-efficacy and safety relationships of second-line TB drug linezolid and its probability of targets attainments. In the following sections, we discuss the key findings, limitations, together with recommendations to further research.

8.1 Population Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Pregnant South African Women with Tuberculosis and HIV.

We applied popPK modelling on sparse data collected opportunistically in pregnant women with TB/HIV infections. Our findings were reassuring that the exposures of isoniazid, pyrazinamide and ethambutol is not significantly different between pre-and postpartum. The results support the use of standard TB dosing without further dose adjustment. The overall study and sample size was relatively small and precluded robust estimation of population parameters without incorporating prior information from non-pregnant population. However, the a posteriori power estimation showed that, with our study design and sampling times, we had a power of 91.8%, 59.2% and 90.1% at $p < 0.01$ to detect a 40% reduction in exposures between pre- and -postpartum (if it existed) for isoniazid, pyrazinamide and ethambutol, respectively. In case of isoniazid, the exposures values observed in our study were lower than those reported in published studies in pregnancy (Gausi *et al.*, 2020). The observed median C_{max} in our cohort was 1.35 and 1.43 mg/L pre- and -postpartum, respectively, compared to median C_{max} during pregnancy and postpartum of 2.89 vs. 3.69 mg/L, respectively (Gausi *et al.*, 2020). Exposures values reported in the literature in non-pregnant population ranged from 3.0 to 5.5 mg/L for C_{max} and between 10.0 and 22.5 mg·h/L for $AUC_{0\text{-}24h}$ (Choudhri *et al.*, 1997; McIlleron *et al.*, 2006; Chideya *et al.*, 2009; Denti, Jeremiah, *et al.*, 2015; van Oosterhout *et al.*, 2015; Rockwood *et al.*, 2016) while those observed in this study were 1.39 and 1.43 mg/L for prepartum and postpartum in case of C_{max} and 6.88 mg·h/L prepartum and 5.01 mg·h/L postpartum. mg/L, These discrepancies are attributed to different distribution of NAT2 genotype between different population (Sabbagh *et al.*, 2011), or large variability in exposures caused by sampling handling and instability at room temperature (Poole *et al.*, 1960). To best of our knowledge, this is the only available results on pyrazinamide pharmacokinetic during pregnancy in TB/HIV patients.

Pyrazinamide concentrations observed in our study were comparable to previously published studies in TB/HIV adults. The reported exposure values ranged from 30 to 55 mg/L for C_{max} and between 344 to 420 mg·h/L for AUC_{0-24}while those observed in our studies were 35.9 mg/L for prepartum and 34.5 mg/L postpartum in case of C_{max} and for AUC_{0-24} it was 419 and 407 mg·h/L for prepartum and postpartum, respectively. Observed ethambutol exposures in our study were slightly lower than those reported in non-pregnant population. Literature values ranged from 2.11 to 5.0 mg/L and AUC_{0-24h} between 20.0 and 23.0 mg·h/L (Tappero *et al.*, 2005; Tostmann *et al.*, 2013; Denti, Jeremiah, *et al.*, 2015; van Oosterhout *et al.*, 2015) compared to median C_{max} of 1.82, 2.1 mg/L prepartum and postpartum respectively and a median AUC_{0-24h} of 16.5 prepartum and 19.0 mg·h/L. Some of the limitations we faced when analyzing this data is that the samples were collected sparsely and opportunistically with uncertainty in the reported time of the dose impaired a robust estimation population PK parameter. However, incorporation of prior information in popPK modelling stabilized the model parameters. Secondly, the choice of the comparator arm was not optimal as the women were sampled in the late stage of pregnancy and sampled shortly after delivery and the physiological changes occurred during pregnancy have not been back to normal values. Overall, the difference is very moderate and reassuring that pregnant woman are not at risk of inadequate ethambutol exposure. Our findings are unique and reassuring, although based on observational study with limited data. Pregnant women do not need dose adjustment in TB treatment; however, additional studies are needed across different geographic populations and with both first- and second-line anti-TB drugs.

8.2 Pretomanid Pharmacokinetics in the Presence of Rifamycins: Interim Results from a Randomised Trial among Patients with Tuberculosis.

There is an increased need for shorter-duration regimens against TB, as they would decrease burden on patients and improve adherence. The introduction of oral newer drugs against TB

(bedaquiline and delamanid) or the repurposing of old drugs (linezolid and clofazimine) has resulted in shorter MDR-TB treatment duration (from 20 to 9-12 months all-oral regimen) (World Health Organization, 2020b). Also, the latest results from S31/A5349 (NCT02410772) have shown non-inferiority for efficacy of a 4-months Rifapentine-containing TB regimen when compared to the standard 6-month HRZE regimen. Hence, it is imperative to learn how to best use these drugs and achieve shorter and efficacious regimen. Currently, pretomanid 200 mg is only approved by the FDA for the treatment of drug-resistant or extensively-drug resistant tuberculosis, and little information is available on pretomanid exposure when combined with first-line TB drugs. We reported the pharmacokinetic of pretomanid in the presence of rifampicin or rifabutin. We also evaluated the effect of rifamycin on the exposure of pretomanid when given with or without food. We found that the exposure is reduced by 50% in presence of rifampicin. Previously, Pretomanid exposure when given in healthy volunteers with rifampicin were similar to the exposure seen following pretomanid 50mg administration without rifampicin. Furthermore, doses of 50 mg showed decreased bactericidal activity when compared to doses of 100mg or higher (Diacon *et al.*, 2012; Dooley *et al.*, 2014). For these reasons, there were some concerns that co-administration with rifampicin could produce subtherapeutic levels of pretomanid. In this study, patients receiving rifampicin in the APT cohort had 44 % reduction in exposure compared to those receiving rifabutin. Slightly different exposure was observed in the A5306 cohort, 59% reduction in arm receiving rifampicin compared to pretomanid only arm. However, the exposure observed in the APT rifampicin arm is similar to the exposure of pretomanid monotherapy of A5306 cohort and to those seen in trials of the now-registered dose of 200mg and proven robust clinical efficacy, wherein pretomanid was given without a rifamycin (Diacon *et al.*, 2010, 2012). A possible explanation for the comparable exposure of pretomanid

seen in the APT rifampicin arm and to that seen in A5306 pretomanid only arm or other published efficacy studies is likely driven by the effect of food on pretomanid absorption and bioavailability, as the patients in the APT cohort received the dose with food (Winter, Ginsberg, *et al.*, 2013). Another interesting finding that we observed different rifampicin effect on pretomanid between APT and A5306 cohorts; 44.4% vs 59.4% reduction in pretomanid AUC, respectively. This could be explained by co-administration with food or that the patients in the APT cohort were given FDC, both of which have been reported to affect rifampicin exposure (Saktiawati *et al.*, 2016; Court *et al.*, 2018). Another possible explanation is the effect on the observed pretomanid exposures is driven by some unidentified drug-drug or metabolic effect, either with the companion drug or with rifabutin. Though isoniazid is an inhibitor of some CYP2C/E and CYP3A enzymes (Desta *et al.*, 2001), there is no current evidence to support an interaction between pretomanid and isoniazid.. It is also worth mentioning that the exposure seen in the rifabutin arm of APT cohort was higher than that seen when pretomanid given alone. In our analysis, pretomanid AUC co-administered with rifabutin was 59.5 mg·h/L versus AUC of 36 and 59 mg·h/L when protemaind was given as 200 and 600mg alone on an empty stomach, respectively (Diacon *et al.*, 2010; Lyons, 2018). However, pretomanid clearance is comparable and relatively unchanged between earlier monotherapy trials (4.8 L/h) and the rifabutin-containing arm in APT (3.79 L/h), this could be explained by the food effect. This is also supported by the fact that pretomanid exposures in the presence of rifabutin in APT are quite similar to those observed after a single dose of pretomanid in a fed state. Although, there is no safety data on these higher exposures in the rifabutin arm. The simulations showed that favorable PTA (>90%) can be achieved when pretomanid is co-administered with rifamycins under fed conditions. Pretomanid co-administered with rifabutin achieved a PTA of more than 90% for

1.59-log10 bactericidal activity. Pretomanid given with rifampin achieved a similar PTA for 1-log10 bactericidal activity. However, the PTA simulation should be taken with extra care as MIC's values are usually imprecise, the PK/PD targets are not fully defined in humans and do not describe the complete time course of drug effect on TB microbes. Overall, the observed AUC in APT in a fed state seems comparable to exposures seen with standard 200 mg dose in a fasting state, which produced potent early bactericidal activity in earlier trials.

8.3 Clofazimine population pharmacokinetics and effect on QTc interval in patients with TB

Prior to this work, clofazimine population pharmacokinetics had not been described adequately in TB patients. An abstract by Ganesan et al. (Ganesan *et al.*, 2015) reported a two-compartment disposition model using data from leprosy patients and healthy volunteers with an estimated peripheral volume of around 4,000 L and a half-life of 15 days. Nix et al. (Nix *et al.*, 2004) applied a one-compartment model to describe the effect of food on clofazimine bioavailability in healthy volunteers. The reported volume of distribution was 1,470 L, and they were not able to characterize the terminal elimination phase due to limited assay sensitivity. Clofazimine has been associated with QT interval prolongation (Diacon *et al.*, 2015; Pontali *et al.*, 2017; Cohen *et al.*, 2019). However, there has been no quantitative exposure-safety analysis of clofazimine effect on QT prolongation. We applied nonlinear mixed-effecting modelling on data from observational study in XDR-TB patients and EBA study to characterize clofazimine population pharmacokinetic and characterize the exposure-QTc relationship in TB patients following established and optimized dosing regimen. We described clofazimine disposition using a three-compartment disposition model. We characterized a large peripheral volume (~10,000 L) that acts as a reservoir as the drug accumulates and long terminal half-life (~30 days). These findings are consistent with what is known about the drug (Barry *et al.*, 1965; O'connor *et al.*, 1995;

Cholo *et al.*, 2012). One of the keys findings of this work that clofazimine disposition is highly affected by fat fraction.

We optimized alternative dosing regimen to achieve therapeutic drug concentrations above the *M. tuberculosis* wild type MIC value (0.25 mg/L). We simulated dosing scenarios that strike a balance between the rapid attainment of concentration above therapeutic target and avoid peak concentration at the end of the loading period substantially higher than average steady-state peak concentrations to reduce risk of serious QT prolongation.

Following the development of the popPK model of clofazimine, we applied popPK/PD modelling to quantitatively describe clofazimine exposure-safety and assess clofazimine concentration effect on QTc interval following standard dosing and the suggested optimized loading dose regimens (200 mg and 300 mg). We reported a statistically significant QT prolongation driven by clofazimine individual predicted plasma concentrations. The simulated QTcF prolongation following 200 mg or 300 mg daily for two weeks followed by 100 mg daily was not associated with higher prolongation in QTcF or dQTcF compared to the standard daily dosing of 100 mg. A 2-week loading dose may support treatment shortening by enabling more rapid attainment of efficacy targets without comprising safety, although a longer loading periods maybe required in patients with extreme fat fractions.

Further studies are needed on clofazimine in TB patients to better describe concentration-response and investigate its safety when used in combination with other drugs with known QT prolongation effects (e.g., bedaquiline, delamanid, or moxifloxacin) (Guglielmetti *et al.*, 2018; Pontali *et al.*, 2018; Li *et al.*, 2019; Bayer Corporation, 2020).

8.4 Linezolid population pharmacokinetics in South African patients with drug-resistant TB.

We developed a population pharmacokinetic model in South African patients with MDR/XDR tuberculosis. We investigated the effect of covariates on the exposure and disposition of linezolid. Age, HIV status and dose level were not significant covariates. We also evaluated the probability of targets attainment following administration of 300, 600 and 1200 mg once daily Compared to other published population pharmacokinetic models, the reported clearance parameters in this analysis were slightly lower; median clearance in our study was 3.57 compared to the reported range in TB patients of 6.13 to 9.96 L/h (Meagher *et al.*, 2003; McGee *et al.*, 2009; Kamp *et al.*, 2017; Alghamdi *et al.*, 2020). However, our estimates of central volume was similar 40.2 L in our analysis versus 40.6 reported literature median in TB patients (Meagher *et al.*, 2003; McGee *et al.*, 2009; Kamp *et al.*, 2017; Alghamdi *et al.*, 2020). Linezolid has a small therapeutic drug window. There is an urgent need to find the optimal dose that maximizes efficacy without compromising safety. The simulation showed that favourable PTA (> 90%) is achieved following 600 and 1200mg up to MIC of 0.5 mg/L, while the 300 mg daily dosing did not achieve adequate PTA beyond 0.25 mg/L. Alghamdi et al reported slightly lower PTA results (Alghamdi *et al.*, 2020); the standard dosing of 600 mg achieved favourable PTA (>90%) up to MIC of 0.25 mg/L, and the PTA dropped to ~60% at MIC of 0.5 mg/L, while for the 1200 mg dosing, favourable PTA was achieved up to 0.5. The difference in results could be attributed to the reported clearance in the two population; 3.56 mg/L in our study versus 6.32 mg/L. Safety-wise, trough concentrations following the standard 600 mg daily dosing had 54% probability of exceeding the safety threshold of 2 mg/L (Millard *et al.*, 2018), while the 1200 mg dosing regimen had an 82% chance of exceeding the same target. In the NiX-TB trial, linezolid was administered as 1200 mg orally. They reported 90 % improved treatment outcome(98

patients out of 109 had a favourable outcome); they also reported a high rate of linezolid related adverse events (81% of patients suffered peripheral neuropathy and 48% suffered myelosuppression) with most of the patients undergoing dose reduction (Conradie *et al.*, 2020). On the other hand, 300 mg had a 16.5 % chance of achieving trough concentrations beyond 2 mg/L, although. The results from this analysis support continued use of 600 mg daily dosing while monitoring the patients for possible side effect and subsequent reduction to lower dose level. However, further research is needed to optimize an effective dosing regimen without putting patients at higher risk of toxicity.

8.5 Overall summary and Pharmacometrics research priorities and optimisation of TB treatment

8.5.1 Summary

In summary, this thesis addressed some of the open questions in TB treatment and management. For the exposure of TB drugs in pregnancy and whether a dose adjustment is required, we characterized the population pharmacokinetic of first-line TB drugs in pregnancy (isoniazid, pyrazinamide and ethambutol) and evaluated the effect of pregnancy on the exposure of these drugs. Reassuringly, we reported that no dose adjustment is required for these drugs in pregnancy. For pretomanid, a novel anti-tubercular agent, it was unknown how the exposure will differ when administered with rifampicin or rifabutin in TB patients, and the current label recommends that pretomanid not to be administered with rifampicin. We evaluated the effect of rifampicin and rifabutin on the exposure of pretomanid in TB patients. We reported similar exposures to those observed when pretomanid is given alone at the currently approved 200 mg dose, likely driven by food effect in our study. This might permit the administration of pretomanid with rifampicin, although these results need to be replicated in other clinical trials. For clofazimine and linezolid, the developed population pharmacokinetic/pharmacodynamic

model could be used to optimize dosing regimen and inform exposure-efficacy and safety analysis in TB patients.

8.5.2 Limitations

There are several limitations in the analyses performed in this thesis. First, there was uncertainty in the time of the dose and the level of adherence to treatment, as some of the analyses were done opportunistically as in Chapter 3, or the time of the dose was self-reported by the patients especially in sparse pharmacokinetic visits as the case in Chapters 4, 5, and 7. However, the impact of this uncertainty on PK parameters was mitigated by utilizing different tools in the framework of population modelling, such as inclusion of between occasion variability for each sampling visit or development of population models using the intensive data then assessing the impact of the uncertainty in the sparse data on model parameters. Finally, some of the analyses assessed the attainment of stipulated targets for PK/PD indexes. These targets were mostly based on non-clinical data or derived from hollow fibre models which might not fully mimic drug dynamics especially at site of action. Furthermore, PK/PD targets utilizing MIC values fails to consider the large uncertainty associated with MIC measurements, kinetics of drug-protein interaction, and proportions of free drug in various tissues (Ahmad *et al.*, 2011). Additionally, PK/PD targets based on MICs provide very limited information on the rate of bactericidal activity and impact of increasing drug concentration on this rate. Lastly, MIC-based PK/PD targets represent thresholds, thus implying an all-or-nothing exposure-effect relationship: all exposure values below (or above) the PK/PD targets are treated equally with no quantitative distinction.(Mueller *et al.*, 2004) Ideally, research in this field could employ a popPK/PD modelling approach utilising time-kill curves and move past shortcomings and limitations of using MIC-based “threshold” PK/PD targets.

8.5.3 Role of modelling and simulation

Considering the limited number of resources available for TB research and how expensive clinical trials are, we believe that it is imperative that state-of-the-art analysis techniques, such as model-based approaches, be used for both the design and interpretation of such trials

There remain many open research questions in TB, some of which can only be answered with data from new clinical trials. Modelling and simulation could be applied to existing data to provide insights on drug efficacy, safety and dose optimization. Furthermore, modelling and simulation can decrease cost of conducting clinical trials especially in countries with limited resources by optimally designing sampling collection, addressing studies objective with fewer patients, utilizing sparse samples, determining likelihood of pharmacological success, target attainment, or pooling dataset across different studies. In the case of neglected populations, such as pregnant women or children, modelling and simulation can effectively be applied to perform opportunistic analyses. Another aspect of TB research in which modelling and simulation can play a role is the interpretation of treatment outcome data. Traditionally, TB research relies on outcomes such proportion of patients with culture conversion at 2 months, or at most time to culture conversion. These are poor and require very large sample sizes to detect an effect. Quantitative markers for bacterial load are available, such as colony forming unit or time to positivity in Mycobacteria growth indicator tube (MGIT), but they are noisy and inherently variable, making it particularly challenging to separate signal from noise, but with the use of modelling and simulation and analyzing repeated samples collected longitudinally we can quantify signal-to-noise ratio and describe the efficacy of TB drugs. Lastly, modelling and simulation can effectively address limitations associated with optimizing dosing regimen based on MICs by use of population models based on time-kill curves. These models can provide

detailed assessment of PK/PD relationship and allow comparison of different concentration profile rather than crude use of MICs. (Mueller *et al.*, 2004)

8.5.4 Research priorities and optimisation of TB treatment

TB treatment and management is complicated by long treatment duration (standard first-line therapy is for 6 months), poor tolerability, and high risk of drug-drug interaction with rifamycins. Such complications have significant impacts on TB control and WHO End TB goals. Co-infection with HIV further complicates these limitations. Thus, there is increased need to develop efficacious, well-tolerated and safe regimen that can shorten TB treatment, especially with the discovery of new drugs against TB (bedaquiline, delamanid and pretomanid). Population PK/PD modelling could be employed to optimize dosing regimen of these drugs to achieve efficacious therapeutic drug levels.

Tuberculosis meningitis is the most lethal form of TB, with mortality rate approaching 60% in HIV patients. TBM is high burden in Southern African countries. The current treatment recommendations for TBM are based on treatment regimen for pulmonary TB with 6 months HRZE regimen. However, these recommendations do not take into account the different ability of these drugs to pass blood-brain barrier resulting in sub-optimal cerebrospinal fluid exposure. Thus, there is urgent need for intervention and treatment recommendations that improve outcomes in HIV-associated TBM.

As we hope we have shown in this thesis, population modelling can be applied to inform decision-making, maximize the use of collected information, inform on dose selection, and drive evidence-based policy recommendations on the treatment and care of patients with TB.

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Appendix 1:NONMEM scripts

1.1 Final NONMEM scripts for results presented in chapter 3

1.1.1 Isoniazid

```
$SIZES      MAXFCN=10000000
$PROBLEM    TB-HIV pregnancy INH Rory
$INPUT      ID ID_PK=DROP ID_SC=DROP OCC VISIT PKVIS=DROP WHAT=DROP
        DAT2=DROP TIME TSOD SS=DROP II=DROP MDV EVID WT HT
        ARV_TREAT=DROP ARV FORM DOB=DROP AGE RIF_START=DROP
        DAYS_RIF DATE_DELIV=DROP DAYS_DELIV PROBLEM BOTH
        COMMENTS=DROP NAT2 NAT2D=DROP RIF=DROP RIF_DOSE=DROP
        RIF_DV=DROP RIF_BLQ=DROP INH=DROP AMT DV BLQ EMB=DROP
        EMB_DOSE=DROP EMB_DV=DROP EMB_BLQ=DROP PZA=DROP
        PZA_DOSE=DROP PZA_DV=DROP PZA_BLQ OCC1=DROP
;                           TIM2=DROP TIMO=DROP TIMM=DROP
        ORDER1=DROP ORDER2=DROP
$DATA       /home/mahmoud/Projects/Paolo.RO/INH/INH_26.11.2018.csv
        IGNORE=#
$ABBREVIATED COMRES=2
$SUBROUTINE ADVAN13 TRANS1 TOL=9
;PRIOR----------------------------------------------------

;Sim_start
$PRIOR      NWPRI NPEXP=1 PLEV=0.9999
;Sim_end
$MODEL      NCOMPARTMENTS=3 COMP=(ABSORB DEFDOSE)
        COMP=(CENTRAL DEFOBSERVATION) COMP=(PERI)
$THETA  (-1,2.52496,5) ; 1 Q L/h[log]
$THETA  (-1,3.35084,4) ; 2 V3 h [log]
$THETA  (-1,2.07716,5) ; 3 NN [log]
$THETA  (-2,0.192598,5) ; 4 MTT [log]
$THETA  (0,0,20) FIX ; 5 DUMMY KA
$THETA  (0,97.187) ; 6 CL FAST[L/h]
$THETA  (0,130.334,200) ; 7 VOL [L]
```

```
$THETA  (0,0.222409,0.5) ; 8 PROP []
$THETA  (0.0224,0.0444422,1) ; 9 ADD [mg/L]; at least 20% of LLQ
$THETA  (0,1,50) FIX ; 10 BIO []
$THETA  (0,28.9672) ; 11 CL SLOW [L/h]
$THETA  (0,0,10) FIX ; 12 dummy []
$THETA  (-0.99,0,2) FIX ; 13 EFV CL []
$THETA  (-0.99,0,2) FIX ; 14 PREG CL []
$THETA  (-0.99,0,2) FIX ; 15 PREG BIO []
$THETA  (-0.99,0,2) FIX ; 16 PREG V []
$THETA  0.125 FIX ; 17 % FAST
$THETA  0.448 FIX ; 18 % SLOW 50
$THETA  (0,75.6432) ; 19 CL INT [L/h]
;**********DONE
; PRIORS FOR KA AND ALAG1
;Sim_start logQ                          ; LOGVP                         ; LOGNN
          ; LOGMTT
$THETAP  2.80336 FIX
 2.778819 FIX
 1.004 FIX
 -0.079 FIX
;Sim_end
$OMEGA  0.0159906  ;   1 BSV CL
$OMEGA  0  FIX  ;    2 BSV V
$OMEGA  0  FIX  ;   3 BSV KA
$OMEGA  0  FIX  ;  4 BSV BIO
$OMEGA  0  FIX  ;  5 BSV MTT
$OMEGA  BLOCK(1) FIX
 0  ;   6 B0V CL
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) FIX
 0  ;  10 B0V KA
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1)
 0.134415  ; 14 B0V BIO
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1)
 0.320527  ; 18 B0V MTT
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
```

```
$OMEGA  0  FIX  ;    22 BSVQ
$OMEGA  0  FIX  ;   23 BSVVP
;-------------------------------------
; UNCERTAINTY IN PRIORS DATA FOR THETAS Q AND VP
;Sim_start
$THETAPV  BLOCK(4) FIX
 0.25  ;         Q
 0 0.25  ;        VP
 0 0 0.25  ;        NN
 0 0 0 0.25  ;       MTT
;Sim_end
$SIGMA  BLOCK(1) FIX
 1
;*********************************************************************DONE
$PK

MXSTEP=50000

;******** DOSE **************DONE

IF(AMT.GT.0) THEN
        DOSE = AMT
ENDIF
;******** PREG **************DONE

PREGNANT=0
IF (DAYS_DELIV<2) PREGNANT=1

;******** Allometric scaling **************DONE
; Standard formula and ratios for lean

; They are all female
SEXM=0

; This formulas require WT in KG and HT in m !!!
IF (SEXM.EQ.0) THEN  ; female
        WHSMAX=37.99
        WHS50=35.98
ELSE       ;males
        WHSMAX=42.92
        WHS50=30.93
ENDIF

HTM2 = HT**2
FFM = (WHSMAX*HTM2*WT)/(WHS50*HTM2+WT)
FAT=WT-FFM
```

```
TVFFM=41
TVWT=66
TVFAT=25

ALLMCLWT=(WT/TVWT)**0.75
ALLMVWT=WT/TVWT

ALLMCLFFM=(FFM/TVFFM)**0.75
ALLMVFFM=FFM/TVFFM

ALLMCLFAT=(FAT/TVFAT)**0.75
ALLMVFAT=FAT/TVFAT


;******** OCCASIONS **************DONE
; DEFAULT OCCASION 1

BOVCL= ETA(6)
BOVKA= ETA(10)
BOVBIO= ETA(14)
BOVMTT= ETA(18)
IF (OCC==2) THEN
        BOVCL= ETA(7)
        BOVKA= ETA(11)
        BOVBIO= ETA(15)
        BOVMTT= ETA(19)
ENDIF
IF (OCC==3) THEN
        BOVCL= ETA(8)
        BOVKA= ETA(12)
        BOVBIO= ETA(16)
        BOVMTT= ETA(20)
ENDIF
IF (OCC==4) THEN
        BOVCL= ETA(9)
        BOVKA= ETA(13)
        BOVBIO= ETA(17)
        BOVMTT= ETA(21)
ENDIF


BSVCL   = ETA(1)
BSVV2   = ETA(2)
BSVKA   = ETA(3)
BSVBIO  = ETA(4)
BSVMTT  = ETA(5)
```

```
BSVQ    = ETA(22)
BSVVP   = ETA(23)


;******** EFV ************ DONE

EFV_CL = 1
IF (ARV==1) EFV_CL = 1+THETA(13)

;******** PREGNANCY ************ DONE

PREG_CL=1
IF (PREGNANT==1) PREG_CL=1+THETA(14)

PREG_BIO=1
IF (PREGNANT==1) PREG_BIO=1+THETA(15)

PREG_V=1
IF (PREGNANT==1) PREG_V=1+THETA(16)



;********  GENO **************DONE

; Imputing missing value
GENO_NAT2=NAT2
IF (GENO_NAT2.LT.1.AND.MIXNUM.EQ.1) GENO_NAT2=1 ; Fast
IF (GENO_NAT2.LT.1.AND.MIXNUM.EQ.2) GENO_NAT2=2 ; Inter
IF (GENO_NAT2.LT.1.AND.MIXNUM.EQ.3) GENO_NAT2=3 ; Slow

SUBPOP = MIXEST
PPOP = MIXP

NAT2_CL=THETA(6) ; NAT2==0 FAST or inter
IF (GENO_NAT2==3) NAT2_CL=THETA(11)  ; NAT2==0 SLOW
IF (GENO_NAT2==2) NAT2_CL=THETA(19)  ; NAT2==0 SLOW



;********  Typical  **************DONE
TVQ = EXP(THETA(1))*ALLMCLWT
TVVP = EXP(THETA(2))*ALLMVWT
TVNN =EXP(THETA(3))
TVMTT=EXP(THETA(4))
;-----------------------------------
TVKA=THETA(5)
```

```
TVCL=NAT2_CL*PREG_CL*ALLMCLFFM*EFV_CL
TVV2=THETA(7)*PREG_V*ALLMVWT
;8 PROP
;9 ADD
TVBIO=THETA(10)*PREG_BIO
;-------------------------------------
CL    = TVCL * EXP(BSVCL+BOVCL)
V     = TVV2 * EXP(BSVV2)
Q   = TVQ*EXP(BSVQ)
VP  = TVVP*EXP(BSVVP)
MTT = TVMTT * EXP(BSVMTT+BOVMTT)
NN = TVNN
BIO   = TVBIO * EXP(BSVBIO+BOVBIO)
K = CL/V
K23 = Q/V
K32 = Q/VP

;******** RESET code for Cmax Tmax **************DONE
IF (NEWIND/=2.OR.EVID>=3) THEN
        COM(1)=0
        COM(2)=0
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
ENDIF

;******** Transit **************DONE

F1=0 ; I need to set bioavailability in compartment 1 to 0

KTR = (NN+1)/MTT
KA = KTR

IF (NEWIND/=2.OR.EVID>=3) THEN ; new individual, or reset event
   ; The values read here will be stored in TDOS and PD in this very PK call.
        TNXD=TIME ; Time of the dose
        PNXD=AMT ; Amount. If it's zero, the DE is deactivated.
ENDIF

TDOS=TNXD ; This will either save here the temporary values if it's a new individual...
PD=PNXD ; ...or the values which were read one record ahead during the execution of the
previous record.
IF(AMT.GT.0) THEN ; This reads one record ahead and stores the data to be used when running
the following record
; IF(AMT.GT.0.AND.ALAG1.EQ.0) THEN ; Use this instead if there is ALAG, as it will also
checks if the ALAG is not 0
        TNXD=TIME
```

```
        PNXD=AMT
ENDIF

; Uncomment this if you have ALAG or if you use ADDL
; IF (DOSTIM.GT.0) THEN ; This will account for the ADDL or lagged doses. It will overwrite the time, if it a non-event record
;       TNXD=DOSTIM
;       PNXD=AMT
; ENDIF
PIZZA = LOG(BIO*PD*KTR + 0.00001) - GAMLN(NN+1)
$MIX

 ; Probabilities to take a guess at the undetermined Nat2 genotype
NSPOP=3
P(1)=THETA(17)  ; Probability of FAST
P(2)=THETA(18)  ; Probability of INTERMEDIATE
P(3)=1-P(1)-P(2) ; Probability of SLOW

;**********************************************************DONE
$DES

TEMPO = T-TDOS ; this is time after dose for the transit, it should always be >= 0

KTT = 0
DADT(1) = -KA*A(1)

IF(PD.GT.0.AND.TEMPO.GT.0) THEN ; This happens only if PD>0, so only if a dose has been detected
        KTT = KTR*(TEMPO)
        DADT(1) = EXP(PIZZA+NN*LOG(KTT)-KTT) -KA*A(1)
ENDIF
DADT(2)=KA*A(1)-K*A(2)-K23*A(2)+K32*A(3)
DADT(3)=K23*A(2)-K32*A(3)
; For Cmax Tmax
TIMEATERDOSE=T-TIMEDOSE
CONCENTR = A(2)/V               ; plasma concentration
IF (CONCENTR.GE.COM(1)) THEN
        COM(1) = CONCENTR           ; CMAX
        COM(2) = TIMEATERDOSE       ; TIME OF CMAX
ENDIF
;**********************************************************DONE

$ERROR

IPRED=A(2)/V
```

```
PROP=IPRED*THETA(8)
ADD=THETA(9)

IMPUTED_BLQ=0.0575

IF (ICALL/=4.AND.BLQ==2) THEN
        PROP=0
        ADD=100000000
ENDIF

W = SQRT(ADD**2+PROP**2)

IF (W.LE.0.000001) W=0.000001

IRES=DV-IPRED
IWRES=IRES/W

Y = IPRED + W*ERR(1)

IF (ICALL==4.AND.Y<=IMPUTED_BLQ*2) THEN
        Y=IMPUTED_BLQ ; For the BLQ values in simulation (VPC)
ENDIF

; For Cmax Tmax
C_MAX = COM(1) ; CMAX
T_MAX = COM(2) ; TIME OF CMAX

IF(AMT.GT.0) THEN
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
; Reset CMAX code when a new dose is given
        COM(1)=0
        COM(2)=0
ENDIF

TAD=TIME-TIMEDOSE

AUC_INF=AMOUNTDOSE*BIO/CL

VARAUC=BOVBIO-BSVCL-BOVCL


;Sim_start
$ESTIMATION METHOD=1 INTERACTION MAXEVAL=0 MCETA=1000
RANMETHOD=4P
$ESTIMATION MSFO=run001b_INH.msf MAXEVAL=99999 PRINT=1 METHOD=1 INTER
```

```
        NOABORT NSIG=3 SIGL=9 ATOL=9 MCETA=500 RANMETHOD=4P
        SADDLE_RESET=1
$COVARIANCE PRECOND=1 PRINT=E MATRIX=R
;$SIMULATION (12345) ONLYSIMULATION
$TABLE      FILE=sdtab001b_INH.csv ID OCC TIME TAD TSOD Y DV PRED RES
        WRES IPRED IRES IWRES CWRES CWRESI OBJI WRESCHOL NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=patab001b_INH.csv ID TSOD OCC KA CL V K VP Q BIO MTT
        NN NAT2 GENO_NAT2 BSVCL BSVV2 BSVKA BSVBIO BOVCL BOVKA
        BOVBIO BOVMTT VARAUC NOPRINT NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=cotab001b_INH.csv ID OCC VISIT AGE HT WT FFM FAT
        PREG_CL PREG_V PREG_BIO EFV_CL DAYS_DELIV DAYS_RIF NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=catab001b_INH.csv ID OCC DOSE ARV FORM NAT2 GENO_NAT2
        VISIT PREGNANT NOPRINT NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=mytab001b_INH.csv ID OCC VISIT TIME TAD TSOD Y DV
        PRED IPRED WRES IWRES KA CL V K VP Q BIO MTT NN BSVCL
        BSVV2 BSVKA SUBPOP PPOP BSVBIO NAT2 GENO_NAT2 BOVCL BOVKA
        BOVBIO BOVMTT VARAUC AGE HT WT FFM FAT PREG_CL PREG_V
        PREG_BIO EFV_CL DAYS_DELIV DAYS_RIF ARV FORM PREGNANT
        C_MAX T_MAX AUC_INF NOPRINT NOAPPEND ONEHEADER FORMAT=,
```

1.1.2 Pyrazinamide NONMEM control stream

```
;; 1. Based on: 014_PZA
; Model desc:final model
;*******************************************************************
$SIZES      PD=-1000 LVR=-150 LTH=-200 MAXFCN=10000000 LNP4=-150000
$PROBLEM    TB-HIV pregnancy INH Rory
$INPUT      ID ID_PK=DROP ID_SC=DROP OCC VISIT PKVIS=DROP WHAT=DROP
        DAT2=DROP TIME TSOD SS=DROP II=DROP MDV EVID WT HT
        ARV_TREAT=DROP ARV FORM DOB=DROP AGE RIF_START=DROP
        DAYS_RIF DATE_DELIV=DROP DAYS_DELIV PROBLEM BOTH
        COMMENTS=DROP NAT2 NAT2D=DROP RIF=DROP RIF_DOSE=DROP
        RIF_DV=DROP RIF_BLQ=DROP INH=DROP INH_DOSE=DROP
        INH_DV=DROP INH_BLQ=DROP EMB=DROP EMB_DOSE=DROP
        EMB_DV=DROP EMB_BLQ=DROP PZA=DROP AMT DV BLQ OCC1=DROP
        ORDER1=DROP ORDER2=DROP
$DATA       PZA_26.11.2018.csv IGNORE=# IGNOR=(PROBLEM.GT.0)
$ABBREVIATED COMRES=2
$SUBROUTINE ADVAN13 TRANS1 TOL=9
;*******************************************************************DONE
$MODEL      NCOMPARTMENTS=2 COMP=(ABSORB DEFDOSE)
        COMP=(CENTRAL DEFOBSERVATION)
;*********************DONE

;Sim_start
$PRIOR      NWPRI NPEXP=1 PLEV=0.9999
;Sim_end
$THETA  (-2,-0.0676348,5) ; 1 MTT [LOG]
$THETA  (-2,1.3262,5) ; 2 NN [LOG]
;-------------------------------------------
$THETA  (0,3.38548,50) ; 3 CL [L/h]
$THETA  (0,43.7717,100) ; 4 VOL [L]
$THETA  (0,0,10) FIX ; 5 DUMMY KA
$THETA  (0,0.0917933,0.5) ; 6 PROP []
$THETA  (0,0.0111283,0.5) ; 7 ADD [mg/L];
$THETA  (0,1,50) FIX ; 8 BIO []
$THETA  (0,0,50) FIX ; 9 dummy []
$THETA  (0,0,2) FIX ; 10 dummy [L/h]
$THETA  (0,0,2) FIX ; 11 dummy [L]
$THETA  (0,0,2) FIX ; 12 dummy []
$THETA  (-0.99,0,2) FIX ; 13 EFV CL []
$THETA  (-0.99,0,2) FIX ; 14 PREG CL []
$THETA  (-0.99,0,2) FIX ; 15 PREG BIO []
$THETA  (-0.99,0,2) FIX ; 16 PREG V []
$THETA  (0,0,2) FIX ; 17 dummy []
$THETA  (0,0,2) FIX ; 18 dummy []
$THETA  (0,0,70) FIX ; 19 dummy []
```

```
; PRIORS FOR KA AND ALAG1
;Sim_start
$THETAP  -0.17 FIX ; log MTT
 0.956 FIX ; log NN
;Sim_end
;**********DONE
$OMEGA  0.0644809  ;   1 BSV CL
$OMEGA  0  FIX  ;    2 BSV V
$OMEGA  0  FIX  ;   3 BSV KA
$OMEGA  0  FIX  ;  4 BSV BIO
$OMEGA  0  FIX  ;  5 BSV MTT
;BOVCL
$OMEGA  BLOCK(1) FIX
 0  ;   6 B0V CL
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;BOVKA
$OMEGA  BLOCK(1) FIX
 0  ;  10 B0V KA
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;BOVBIO/BOVMTT
$OMEGA  BLOCK(2)
 0.51808  ; 14 B0V MTT
 0 0.0183931  ; 18 B0V BIO
$OMEGA  BLOCK(2) SAME
$OMEGA  BLOCK(2) SAME
$OMEGA  BLOCK(2) SAME
; UNCERTAINTY IN PRIORS DATA FOR THETAS Q AND VP
;Sim_start
$THETAPV  BLOCK(2) FIX
 0.1  ;       MTT
 0 0.25  ;        NN
;Sim_end
$SIGMA  BLOCK(1) FIX
 1
;**********************************************************************DONE
$PK
MXSTEP=50000
;******** DOSE **************DONE

IF(AMT.GT.0) THEN
        DOSE = AMT
ENDIF
```

```
;******** PREG **************DONE

PREGNANT=0
IF (DAYS_DELIV<2) PREGNANT=1

;******** Allometric scaling **************DONE
; Standard formula and ratios for lean

; They are all female
SEXM=0

; This formulas require WT in KG and HT in m !!!
IF (SEXM.EQ.0) THEN  ; female
        WHSMAX=37.99
        WHS50=35.98
ELSE       ;males
        WHSMAX=42.92
        WHS50=30.93
ENDIF

HTM2 = HT**2
FFM = (WHSMAX*HTM2*WT)/(WHS50*HTM2+WT)
FAT=WT-FFM
;-----------------------------------
TVFFM=41
TVWT=66
TVFAT=25
;------------------------------
ALLMCLWT=(WT/TVWT)**0.75
ALLMVWT=WT/TVWT

ALLMCLFFM=(FFM/TVFFM)**0.75
ALLMVFFM=FFM/TVFFM

ALLMCLFAT=(FAT/TVFAT)**0.75
ALLMVFAT=FAT/TVFAT

;******** OCCASIONS **************DONE
; DEFAULT OCCASION 1

OCC1 = 0
OCC2 = 0
OCC3 = 0
OCC4 = 0
IF(OCC.EQ.1) OCC1 = 1
```

```
IF(OCC.EQ.2) OCC2 = 1
IF(OCC.EQ.3) OCC3 = 1
IF(OCC.EQ.4) OCC4 = 1
;-----------------------------------
BOVCL  = ETA(6)*OCC1  + ETA(7)*OCC2  + ETA(8)*OCC3 + ETA(9)*OCC4
BOVKA  = ETA(10)*OCC1 + ETA(11)*OCC2 + ETA(12)*OCC3 + ETA(13)*OCC4
BOVMTT = ETA(14)*OCC1 + ETA(16)*OCC2 + ETA(18)*OCC3 + ETA(20)*OCC4
BOVBIO = ETA(15)*OCC1 + ETA(17)*OCC2 + ETA(19)*OCC3 + ETA(21)*OCC4
;BETWEEN SUBJECT VARIABILITY
BSVCL   = ETA(1)
BSVV2   = ETA(2)
BSVKA   = ETA(3)
BSVBIO  = ETA(4)
BSVMTT  = ETA(5)


;******** EFV ************* DONE
EFV_CL = 1
IF (ARV==1) EFV_CL = 1+THETA(13)
;******** PREGNANCY ************* DONE

PREG_CL=1
IF (PREGNANT==1) PREG_CL=1+THETA(14)

PREG_BIO=1
IF (PREGNANT==1) PREG_BIO=1+THETA(15)

PREG_V=1
IF (PREGNANT==1) PREG_V=1+THETA(16)
;********  Typical  **************DONE
TVMTT=EXP(THETA(1))
TVNN =EXP(THETA(2))
;--------------------------------------------
TVCL=THETA(3)*PREG_CL*ALLMCLFFM*EFV_CL
TVV2=THETA(4)*PREG_V*ALLMVWT
;THETA(5)
;PROP
;ADD
TVBIO=THETA(8)*PREG_BIO
;----------------------------------
CL    = TVCL * EXP(BSVCL+BOVCL)
V     = TVV2 * EXP(BSVV2)
MTT = TVMTT * EXP(BSVMTT+BOVMTT)
NN = TVNN
BIO   = TVBIO * EXP(BSVBIO+BOVBIO)
K = CL/V
```

```
;******** RESET code for Cmax Tmax **************DONE
IF (NEWIND/=2.OR.EVID>=3) THEN
        COM(1)=0
        COM(2)=0
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
ENDIF
;******** Transit **************DONE

F1=0 ; I need to set bioavailability in compartment 1 to 0

KTR = (NN+1)/MTT
KA    = KTR ;TVKA * EXP(BSVKA+BOVKA)

IF (NEWIND/=2.OR.EVID>=3) THEN ; new individual, or reset event
   ; The values read here will be stored in TDOS and PD in this very PK call.
        TNXD=TIME ; Time of the dose
        PNXD=AMT ; Amount. If it's zero, the DE is deactivated.
ENDIF

TDOS=TNXD ; This will either save here the temporary values if it's a new individual...
PD=PNXD ; ...or the values which were read one record ahead during the execution of the
previous record.
IF(AMT.GT.0) THEN ; This reads one record ahead and stores the data to be used when running
the following record
; IF(AMT.GT.0.AND.ALAG1.EQ.0) THEN ; Use this instead if there is ALAG, as it will also
checks if the ALAG is not 0
        TNXD=TIME
        PNXD=AMT
ENDIF

; Uncomment this if you have ALAG or if you use ADDL
; IF (DOSTIM.GT.0) THEN ; This will account for the ADDL or lagged doses. It will overwrite
the time, if it a non-event record
;       TNXD=DOSTIM
;       PNXD=AMT
; ENDIF
PIZZA = LOG(BIO*PD*KTR + 0.00001) - GAMLN(NN+1)
$DES
TEMPO = T-TDOS ; this is time after dose for the transit, it should always be >= 0

KTT = 0
DADT(1) = -KA*A(1)

IF(PD.GT.0.AND.TEMPO.GT.0) THEN ; This happens only if PD>0, so only if a dose has been
detected
```

```
        KTT = KTR*(TEMPO)
        DADT(1) = EXP(PIZZA+NN*LOG(KTT)-KTT) -KA*A(1)
ENDIF
DADT(2)=KA*A(1)-K*A(2)


; For Cmax Tmax
TIMEATERDOSE=T-TIMEDOSE
CONCENTR = A(2)/V               ; plasma concentration
IF (CONCENTR.GE.COM(1)) THEN
        COM(1) = CONCENTR           ; CMAX
        COM(2) = TIMEATERDOSE       ; TIME OF CMAX
ENDIF
;*********************************************************DONE

$ERROR

IPRED=A(2)/V

PROP=IPRED*THETA(6)
ADD=THETA(7)

IMPUTED_BLQ=0.0575

;IF (ICALL/=4.AND.BLQ==1) THEN
;       PROP=0
;       ADD=ADD + EXTRA_ERR
;ENDIF

IF (ICALL/=4.AND.BLQ==2) THEN
        PROP=0
        ADD=100000000
ENDIF

W = SQRT(ADD**2+PROP**2)

IF (W.LE.0.000001) W=0.000001

IRES=DV-IPRED
IWRES=IRES/W

Y = IPRED + W*ERR(1)

IF (ICALL==4.AND.Y<=IMPUTED_BLQ*2) THEN
        Y=IMPUTED_BLQ ; For the BLQ values in simulation (VPC)
ENDIF
```

```
; For Cmax Tmax
C_MAX = COM(1) ; CMAX
T_MAX = COM(2) ; TIME OF CMAX

IF(AMT.GT.0) THEN
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
; Reset CMAX code when a new dose is given
        COM(1)=0
        COM(2)=0
ENDIF

TAD=TIME-TIMEDOSE

AUC_INF=AMOUNTDOSE*BIO/CL

VARAUC=BOVBIO-BSVCL-BOVCL

;*************************************************************DONE
;Sim_start
$ESTIMATION METHOD=1 INTERACTION MAXEVAL=0 MCETA=1000
RANMETHOD=4P
$ESTIMATION MSFO=run014a_PZA.msf MAXEVAL=99999 PRINT=1 METHOD=1
        MCETA=500 RANMETHOD=4P INTER NOABORT NSIG=3 SIGL=9 ATOL=9
        REPEAT SADDLE_RESET=1
$COVARIANCE PRECOND=1 PRINT=E MATRIX=R
;$SIMULATION (12345) ONLYSIMULATION

;Sim_end

;*************************************************************
$TABLE     FILE=sdtab014a_PZA.csv ID OCC TIME TAD TSOD Y DV PRED RES WRES
        IPRED IRES IWRES CWRES CWRESI OBJI WRESCHOL NOPRINT
;ESAMPLE=1000 NPDE
        NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=patab014a_PZA.csv ID OCC KA CL V K BIO MTT NN BSVCL
        BSVV2 BSVKA BSVBIO BOVCL BOVKA BOVBIO BOVMTT VARAUC
        NOPRINT NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=cotab014a_PZA.csv ID OCC VISIT AGE HT WT FFM FAT
        PREG_CL PREG_V PREG_BIO EFV_CL DAYS_DELIV DAYS_RIF NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=catab014a_PZA.csv ID OCC DOSE ARV FORM VISIT PREGNANT
        NOPRINT NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=mytab014a_PZA.csv ID OCC VISIT TIME TAD TSOD Y DV PRED
        IPRED WRES IWRES KA CL V K BIO MTT NN BSVCL BSVV2 BSVKA
```

BSVBIO BOVCL BOVKA BOVBIO BOVMTT VARAUC AGE HT WT FFM FAT PREG_CL PREG_V PREG_BIO EFV_CL DAYS_DELIV DAYS_RIF ARV FORM PREGNANT C_MAX T_MAX AUC_INF NOPRINT NOAPPEND ONEHEADER FORMAT=,

1.1.3 Ethambutl NONMEM control stream

```
$SIZES      PD=-1000 LVR=-150 LTH=-200 MAXFCN=10000000 LNP4=-150000
$PROBLEM    TB-HIV pregnancy INH Rory
$INPUT      ID ID_PK=DROP ID_SC=DROP OCC VISIT PKVIS=DROP WHAT=DROP
        DAT2=DROP TIME TSOD SS=DROP II=DROP MDV EVID WT HT
        ARV_TREAT=DROP ARV FORM DOB=DROP AGE RIF_START=DROP
        DAYS_RIF DATE_DELIV=DROP DAYS_DELIV PROBLEM BOTH
        COMMENTS=DROP NAT2 NAT2D=DROP RIF=DROP RIF_DOSE=DROP
        RIF_DV=DROP RIF_BLQ=DROP INH=DROP INH_DOSE=DROP
        INH_DV=DROP INH_BLQ=DROP EMB=DROP AMT DV BLQ PZA=DROP
        PZA_DOSE=DROP PZA_DV=DROP PZA_BLQ OCC1=DROP ORDER1=DROP
        ORDER2=DROP
$DATA      EMB_26.11.2018.csv IGNORE=# IGNORE=(PROBLEM.GT.0)
$ABBREVIATED COMRES=2
$SUBROUTINE ADVAN13 TRANS1 TOL=9
;*********************************************************************DONE

;PRIOR----------------------------------------------

;Sim_start
$PRIOR      NWPRI NPEXP=1 PLEV=0.9999
;Sim_end

;-----------------------------------------
$MODEL      NCOMPARTMENTS=3 COMP=(ABSORB DEFDOSE)
        COMP=(CENTRAL DEFOBSERVATION) COMP=(PERI)
;**********************DONE
$THETA  (-2,5.04498,10) ; 1 Q L/h[log]
$THETA  (-2,5.77578,10) ; 2 V3 L [log]
$THETA  (-2,1.80918,10) ; 3 NN [log]
$THETA  (-2,0.762704,10) ; 4 MTT h [log]
$THETA  (-2,5.62352,10) ; 5 VOL L [log]
;-----------------------------------------
$THETA  (0,0,10) FIX ; 6 DUMMY KA [1/h]
$THETA  (0,60.1713) ; 7 CL [L/h]
$THETA  (0,0.232186,0.5) ; 8 PROP []
$THETA  (0,0.03,1) FIX ; 9 ADD [mg/L]; at least 20% of LLQ
$THETA  (0,1,50) FIX ; 10 BIO []
$THETA  (0,0,50) FIX ; 11 dummy []
$THETA  (0,0,2) FIX ; 12 dummy []
$THETA  (-0.99,0,2) FIX ; 13 EFV CL []
$THETA  (-0.99,0,2) FIX ; 14 PREG CL []
$THETA  (-0.99,0,2) FIX ; 15 PREG BIO []
$THETA  (-0.99,0,2) FIX ; 16 PREG V []
$THETA  (0,0,2) FIX ; 17 dummy []
```

```
$THETA  (0,0,2) FIX ; 18 dummy []
$THETA  (0,0,70) FIX ; 19 dummy []
; PRIORS
;Sim_start
$THETAP  4.87 FIX ; logQ
 6.77 FIX ; LOGVP
 2.41 FIX ; LOGNN
 0.9321 FIX ; LOGMTT
 5.82 FIX ; LOGVC
;Sim_end
$OMEGA  0.3  ;   1 BSV CL
$OMEGA  0  FIX  ;    2 BSV V
$OMEGA  0  FIX  ;   3 BSV KA
$OMEGA  0  FIX  ;  4 BSV BIO
$OMEGA  0  FIX  ;  5 BSV MTT
$OMEGA  BLOCK(1) FIX
 0  ;   6 B0V CL
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) FIX
 0  ;  10 B0V KA
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1)
 0.0436551  ; 14 B0V BIO
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1)
 0.0588298  ; 18 B0V MTT
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  0  FIX  ;    22 BSVQ
$OMEGA  0  FIX  ;   23 BSVVP
; UNCERTAINTY IN PRIORS DATA FOR THETAS Q AND VP
;Sim_start
$THETAPV  BLOCK(5) FIX
 0.25  ;         Q
 0 0.25  ;        VP
 0 0 0.25  ;        NN
 0 0 0 0.25  ;       MTT
 0 0 0 0 0.25  ;        VC
;Sim_end
```

```
$SIGMA  BLOCK(1) FIX
 1
;**********************************************************************DONE
$PK
MXSTEP=50000

;******** DOSE **************DONE

IF(AMT.GT.0) THEN
        DOSE = AMT
ENDIF


;******** PREG **************DONE

PREGNANT=0
IF (DAYS_DELIV<2) PREGNANT=1

;******** Allometric scaling **************DONE
; Standard formula and ratios for lean

; They are all female
SEXM=0

; This formulas require WT in KG and HT in m !!!
IF (SEXM.EQ.0) THEN  ; female
        WHSMAX=37.99
        WHS50=35.98
ELSE       ;males
        WHSMAX=42.92
        WHS50=30.93
ENDIF

HTM2 = HT**2
FFM = (WHSMAX*HTM2*WT)/(WHS50*HTM2+WT)
FAT=WT-FFM


TVFFM=41
TVWT=66
TVFAT=25

ALLMCLWT=(WT/TVWT)**0.75
ALLMVWT=WT/TVWT

ALLMCLFFM=(FFM/TVFFM)**0.75
```

```
ALLMVFFM=FFM/TVFFM

ALLMCLFAT=(FAT/TVFAT)**0.75
ALLMVFAT=FAT/TVFAT


;******** OCCASIONS **************DONE
; DEFAULT OCCASION 1


BOVCL= ETA(6)
BOVKA= ETA(10)
BOVBIO= ETA(14)
BOVMTT= ETA(18)
IF (OCC==2) THEN
        BOVCL= ETA(7)
        BOVKA= ETA(11)
        BOVBIO= ETA(15)
        BOVMTT= ETA(19)
ENDIF
IF (OCC==3) THEN
        BOVCL= ETA(8)
        BOVKA= ETA(12)
        BOVBIO= ETA(16)
        BOVMTT= ETA(20)
ENDIF
IF (OCC==4) THEN
        BOVCL= ETA(9)
        BOVKA= ETA(13)
        BOVBIO= ETA(17)
        BOVMTT= ETA(21)
ENDIF


BSVCL   = ETA(1)
BSVV2   = ETA(2)
BSVKA   = ETA(3)
BSVBIO  = ETA(4)
BSVMTT  = ETA(5)
BSVQ    = ETA(22)
BSVVP   = ETA(23)


;******** EFV ************* DONE

EFV_CL = 1
```

```
IF (ARV==1) EFV_CL = 1+THETA(13)

;******** PREGNANCY ************* DONE

PREG_CL=1
IF (PREGNANT==1) PREG_CL=1+THETA(14)

PREG_BIO=1
IF (PREGNANT==1) PREG_BIO=1+THETA(15)

PREG_V=1
IF (PREGNANT==1) PREG_V=1+THETA(16)

;********  Typical  **************DONE

TVQ =           EXP(THETA(1))*ALLMCLWT
TVVP =  EXP(THETA(2))*ALLMVWT
TVNN =          EXP(THETA(3))
TVMTT=          EXP(THETA(4))
TVV2=           EXP(THETA(5))*PREG_V*ALLMVWT
;---------------------------------------
;TVKA=THETA(6)
TVCL=THETA(7)*PREG_CL*ALLMCLFFM*EFV_CL
;THETA(8) PROP
;THETA(9) ADD
TVBIO=THETA(10)*PREG_BIO
;THETA(11)
;THETA(12)

CL    = TVCL * EXP(BSVCL+BOVCL)
V     = TVV2 * EXP(BSVV2)
Q   = TVQ*EXP(BSVQ)
VP  = TVVP*EXP(BSVVP)
MTT = TVMTT * EXP(BSVMTT+BOVMTT)
NN = TVNN
BIO   = TVBIO * EXP(BSVBIO+BOVBIO)
K = CL/V
K23 = Q/V
K32 = Q/VP

;******** RESET code for Cmax Tmax **************DONE

IF (NEWIND/=2.OR.EVID>=3) THEN
          COM(1)=0
          COM(2)=0
          TIMEDOSE = TIME
```

```
        AMOUNTDOSE = AMT
ENDIF


;******** Transit **************DONE

F1=0 ; I need to set bioavailability in compartment 1 to 0

KTR = (NN+1)/MTT
KA = KTR ;KA    = TVKA * EXP(BSVKA+BOVKA)

IF (NEWIND/=2.OR.EVID>=3) THEN ; new individual, or reset event
   ; The values read here will be stored in TDOS and PD in this very PK call.
        TNXD=TIME ; Time of the dose
        PNXD=AMT ; Amount. If it's zero, the DE is deactivated.
ENDIF

TDOS=TNXD ; This will either save here the temporary values if it's a new individual...
PD=PNXD ; ...or the values which were read one record ahead during the execution of the
previous record.

IF(AMT.GT.0) THEN ; This reads one record ahead and stores the data to be used when running
the following record
; IF(AMT.GT.0.AND.ALAG1.EQ.0) THEN ; Use this instead if there is ALAG, as it will also
checks if the ALAG is not 0
        TNXD=TIME
        PNXD=AMT
ENDIF

; Uncomment this if you have ALAG or if you use ADDL
; IF (DOSTIM.GT.0) THEN ; This will account for the ADDL or lagged doses. It will overwrite
the time, if it a non-event record
;       TNXD=DOSTIM
;       PNXD=AMT
; ENDIF

PIZZA = LOG(BIO*PD*KTR + 0.00001) - GAMLN(NN+1)


;*********************************************************DONE
$DES
; TIME
TEMPO=T-TDOS ; this is time after dose, it should always be >= 0
KTT=0
; Eqautions
DADT(1) = -KA*A(1)
```

```
IF(PD.GT.0.AND.TEMPO.GT.0) THEN ; This happens only id PD>0, so only if a dose has been
detected
        KTT=KTR*(TEMPO)
        DADT(1)=EXP(PIZZA+NN*LOG(KTT)-KTT)-KA*A(1)
ENDIF
DADT(2)=KA*A(1)-K*A(2)-K23*A(2)+K32*A(3)
DADT(3)=K23*A(2)-K32*A(3)


; For Cmax Tmax
TIMEATERDOSE=T-TIMEDOSE
CONCENTR = A(2)/V               ; plasma concentration
IF (CONCENTR.GE.COM(1)) THEN
        COM(1) = CONCENTR           ; CMAX
        COM(2) = TIMEATERDOSE       ; TIME OF CMAX
ENDIF



;*******************************************************DONE

$ERROR

IPRED=A(2)/V

PROP=IPRED*THETA(8)
ADD=THETA(9)

IMPUTED_BLQ=0.0575

;IF (ICALL/=4.AND.BLQ==1) THEN
;       PROP=0
;       ADD=ADD + EXTRA_ERR
;ENDIF

IF (ICALL/=4.AND.BLQ==2) THEN
        PROP=0
        ADD=100000000
ENDIF

W = SQRT(ADD**2+PROP**2)

IF (W.LE.0.000001) W=0.000001

IRES=DV-IPRED
IWRES=IRES/W
```

```
Y = IPRED + W*ERR(1)

IF (ICALL==4.AND.Y<=IMPUTED_BLQ*2) THEN
        Y=IMPUTED_BLQ ; For the BLQ values in simulation (VPC)
ENDIF

; For Cmax Tmax
C_MAX = COM(1) ; CMAX
T_MAX = COM(2) ; TIME OF CMAX

IF(AMT.GT.0) THEN
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
; Reset CMAX code when a new dose is given
        COM(1)=0
        COM(2)=0
ENDIF

TAD=TIME-TIMEDOSE

AUC_INF=AMOUNTDOSE*BIO/CL

VARAUC=BOVBIO-BSVCL-BOVCL

;Sim_start
$ESTIMATION METHOD=1 INTERACTION MAXEVAL=0 MCETA=1000
RANMETHOD=4P
$ESTIMATION MSFO=run010_EMB.msf MAXEVAL=99999 PRINT=1 METHOD=1
        MCETA=500 RANMETHOD INTER NOABORT NSIG=3 SIGL=9 ATOL=9
        REPEAT SADDLE_RESET=1
$COVARIANCE PRECOND=1 PRINT=E MATRIX=R
;$SIMULATION (12345) ONLYSIMULATION
$TABLE     FILE=sdtab010_EMB.csv ID OCC TIME TAD TSOD Y DV PRED RES
        WRES IPRED IRES IWRES CWRES CWRESI OBJI WRESCHOL NOPRINT
;ESAMPLE=1000 NPDE
        NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=patab010_EMB.csv ID OCC KA CL V K VP Q BIO MTT NN
        BSVCL BSVV2 BSVKA BSVBIO BOVCL BOVKA BOVBIO BOVMTT VARAUC
        NOPRINT NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=cotab010_EMB.csv ID OCC VISIT AGE HT WT FFM FAT
        PREG_CL PREG_V PREG_BIO EFV_CL DAYS_DELIV DAYS_RIF NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=catab010_EMB.csv ID OCC DOSE ARV FORM VISIT PREGNANT
        NOPRINT NOAPPEND ONEHEADER FORMAT=,
$TABLE     FILE=mytab010_EMB.csv ID OCC VISIT TIME TAD TSOD Y DV PRED
```

IPRED WRES IWRES KA CL V K VP Q BIO MTT NN BSVCL BSVV2
BSVKA BSVBIO BOVCL BOVKA BOVBIO BOVMTT VARAUC AGE HT WT
FFM FAT PREG_CL PREG_V PREG_BIO EFV_CL DAYS_DELIV DAYS_RIF
ARV FORM PREGNANT C_MAX T_MAX AUC_INF NOPRINT NOAPPEND
ONEHEADER FORMAT=,

1.2 Final NONMEM scripts for results presented in chapter 4

```
;; 1. Based on: 240
; Model desc:
; Settings for the memory of NONMEM
$SIZES      PD=-1000 LVR=-150 LTH=-200 MAXFCN=10000000 LNP4=-150000
;-------------------------------------------------------------------------
$PROBLEM    (POOLED DATA) REMOVE ALB
;-------------------------------------------------------------------------------
$INPUT      ID_STUDY DAT2=DROP TIME DATE_TIME=DROP WHAT=DROP DAYS
            PKVIS DV BLQ LLOQ CMTX=DROP AMT MDV II EVID OCC SS TAD
            TSOD TIME_DAT RIF PA_ALONE LPV EFV ARM_WHAT AGE SEX RACE
            HT HIV CAVITY HB ALB ALT WT CREAT CREAT_W12 ALT_W12 HB_W12
            DAT_TYPE PROB PROB_EVID COMMENTS=DROP STUDY SEX_WHAT=DROP
            ID
;-------------------------------------------------------------------------------
$DATA       ../../POOLED_PA_NONMEM_DAT_2020_09_12.csv IGNORE=@
            IGNORE=(PROB>0) IGNORE=(PROB_EVID>0) IGNORE=(BLQ.GT.0)
            IGNORE=(EFV.EQ.1) IGNORE=(LPV.EQ.1)

;; IGNORE=(DAT_TYPE.EQ.0)

;-----------------------------------------------------------------
;;$ETAS       FILE=run239.phi
$ESTIMATION METHOD=1 INTERACTION MAXEVAL=0 MCETA=1000
RANMETHOD=4P
$ESTIMATION METHOD=1 INTER MAXEVAL=99999 PRINT=1 NOABORT NSIG=3
SIGL=6
                            MCETA=50 RANMETHOD=4P
            NONINFETA=1 ETASTYPE=1
;SADDLE_RESET=1

;REPEAT
$COVARIANCE PRINT=E PRECOND=1
;-----------------------------------------------------------------

; $ABBREVIATED REPLACE ETA(PKVIS_CL)=ETA(,6 to 9 by 1)

; $ABBREVIATED REPLACE ETA(OCC_KA)=ETA(,10 to 17 by 1)

; $ABBREVIATED REPLACE ETA(OCC_MTT)=ETA(,18 to 25 by 1)

; $ABBREVIATED REPLACE ETA(OCC_BIO)=ETA(,26 to 33 by 1)

;-----------------------------------------------------------------
```

```
$SUBROUTINE ADVAN5 TRANS1 ;;TOL=9 SSTOL=3 SSATOL=3

;-----------------------------------------------------------

;CODE BLOCK THAT DEFINE THE MODEL
$MODEL      NCOMPS=9 ; NUMBER OF COMPARTMENTS (ABSORPTION
COMPATMENT (DEFINED AS FIRST ONE) AND CENTRAL COMPARTMENT DEFIEND
AS 2ND COMPARTMENT
          COMP=(TRANSIT1,DEFDOSE) ;1 GUT TRANIST 1
          COMP=(TRANSIT2) ;2 GUT TRANIST 2
          COMP=(TRANSIT3) ;3 GUT TRANIST 3
          COMP=(TRANSIT4) ;4 GUT TRANIST 4
          COMP=(TRANSIT5) ;5 GUT TRANIST 5
          COMP=(TRANSIT6) ;6 GUT TRANIST 6
          COMP=(TRANSIT7) ;7 GUT TRANIST 7
          COMP=(ABS) ;8 GUT ABS
          COMP=("CENTRAL",DEFOBS) ;9 CENTRAL CMT
$ABBREVIATED COMRES=2
;-------------------------------------------------------------------------------

;initializing population parameters
$THETA  (0,3.89499) ; 1 TVCL (L/hr)
$THETA  (0,90.2299) ; 2 TVV (L)
$THETA  (0,0.594115) ; 3 TVKA (1/hr)
$THETA  (0,1.1557) ; 4 MTT (hr)
$THETA  6 FIX ; 5 NN ()
$THETA  1 FIX ; 6 BIO
$THETA  (1E-12,0.0784723,1) ; 7 PROP
$THETA  (1E-12,0.0366074) ; 8 ADD         (mg/L)
$THETA  (1E-12,1.78504,10) ; 9 RIF_APT_CL
$THETA  (1E-12,1,10) FIX ; 10 FEMALE_CL
$THETA  (1E-12,1) FIX ; 11 PRE_DOSE_BOVBIO_SCALE
$THETA  0 FIX ;(-0.1,0.0109213,0.07692) ; 12 ALB PER UNIT CHANGE
$THETA  1 FIX ; 13 NO_RIFAMYC_CL
$THETA  (1E-12,1) FIX ; 14 ACTG_KA
$THETA  (1E-12,1) FIX ; 15 ACTG_MTT
$THETA  (1E-12,0.578015) ; 16 ACTG_BIO
$THETA  (1E-12,2.4587,10) ; 17 ACTG_RIF_CL
$THETA  1 FIX ; 18 RIF_CL
$THETA  (1E-12,1.52914) ; 19 ACTG KA MTT
;-----------------------------------------------------
;BSV INITIAL VALUE
$OMEGA  0.03574  ;    1 BSVCL
$OMEGA  0  FIX  ;     2 BSVV
$OMEGA  0  FIX  ;    3 BSVKA
$OMEGA  0  FIX  ;  4 BSV MTT
```

```
$OMEGA  0.0132767  ;  5 BSV BIO
;-----------------------------------------------------
;BOV INITAL VALUES-----------------------------------
;-----------------------------------------------------
$OMEGA  BLOCK(1)
 0.0132097  ;    6 BOVCL
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;---------------------------------------------
$OMEGA  BLOCK(1)
 0.322556  ;  10 BOVMTT
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;-----------------------------------------------------
$OMEGA  BLOCK(1)
 0.158372  ;   18 BOVKA
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;-----------------------------------------------------
$OMEGA  BLOCK(1)
 0.0382157  ;  26 BOVBIO
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;-----------------------------------------------------------
$SIGMA  1  FIX
;-----------------------------------------------------------
$PK

SEX_M = 1 ;Male
ARM = RIF ; RIF IN ACTG DATA
```

```
IF(SEX.EQ.0) SEX_M = 0 ; Female

;Adding allometric scalling using UCT_MODEL_TEMPLATE
HTM = HT/100 ;rescaling HT to m units
;SEX_M = 0 --> female
;SEX_M = 1 --> male
IF (SEX_M.EQ.0) THEN
        WHSMAX=37.99
        WHS50=35.98
ELSE      ;males
        WHSMAX=42.92
        WHS50=30.93
ENDIF
;-----------------------------------------------------------
HTM2 = HTM**2
FFM = (WHSMAX*HTM2*WT)/(WHS50*HTM2+WT)
FAT = WT-FFM
FAT_PER = (FAT/WT)*100

ARM_SEX  = ARM*10 + SEX_M
ARM_DAT = ARM*10 + DAT_TYPE
ARM_VIS = ARM*10 + PKVIS
ARM_VIS_SEX = ARM*100 +  PKVIS*10 + SEX_M
STUDY_ARM = STUDY*10+ARM
STUDY_ARM_SEX = STUDY*100+ARM*10 + SEX
STUDY_ARM_VIS = STUDY*100+ARM*10 + PKVIS
STUDY_ARM_VIS_SEX = STUDY*1000+ARM*100 + PKVIS*10 + SEX




;-------Typical values of covariates
TVWT = 58 ;median wt from the data set
TVFAT = 12
TVFFM = 46
;---------Allometric scaling and covariates
ALLMCL_WT = (WT/TVWT)**0.75
ALLMV_WT = (WT/TVWT)

ALLMCL_FAT = (FAT/TVFAT)**0.75
ALLMV_FAT = (FAT/TVFAT)

ALLMCL_FFM = (FFM/TVFFM)**0.75
ALLMV_FFM = (FFM/TVFFM)
```

```
CREATIMP = CREAT
IF(CREAT.EQ.-99) CREATIMP = 56

ALBIMP = ALB
IF(ALB.EQ.-99) ALBIMP = 37

CREAT_12IMP = CREAT_W12
IF(CREAT_W12.EQ.-99) CREAT_12IMP = 63

ALT_12IMP = ALT_W12
IF(ALT_W12.EQ.-99) ALT_12IMP = 19.5

DELTA_CREAT = CREAT_12IMP - CREATIMP

DELTA_ALT = ALT_12IMP - ALT


ACTG_FAST = 0
IF(STUDY.EQ.1.AND.OCC.EQ.2) ACTG_FAST = 1
IF(STUDY.EQ.1.AND.OCC.EQ.4) ACTG_FAST = 1


ACTGO_PREDOSE = 0
IF(STUDY.EQ.1.AND.OCC.EQ.1) ACTGO_PREDOSE = 1
IF(STUDY.EQ.1.AND.OCC.EQ.3) ACTGO_PREDOSE = 1


;ARM 1 : RIF
;ARM 2 : RIFB
;ARM 0 : PA ALONE
;STUDY 1 : ACTG (FAST)
;STUDY 2 : APT (FED)
RIF_APT_CL = 1 ; RIF is 1, 0 or 2 is NO RIF or RFB
RIF_ACTG_CL = 1
NO_RIFA_CL = 1
RIF_CL = 1
;-------------------------------------------------------------
IF (ARM.EQ.1.AND.STUDY.EQ.2)  RIF_APT_CL = THETA(9)   ; RIF_APT
IF (ARM.EQ.1.AND.STUDY.EQ.1)  RIF_ACTG_CL = THETA(17)         ; RIF_ACTG
IF (ARM.EQ.0)  NO_RIFA_CL =  THETA(13)                                  ; RIFB
IF (ARM.EQ.1)  RIF_CL =  THETA(18)                                      ;
RIFAMPICIN
;-------------------------------------------------------------
SEX_EFF = 1
IF (SEX_M.EQ.0)  SEX_EFF = THETA(10)
```

```
;-------------------------------------------------------------
ACTG_KA = 1
IF (STUDY.EQ.1) ACTG_KA = THETA(14)
;-------------------------------------------------------------
ACTG_MTT = 1
IF (STUDY.EQ.1) ACTG_MTT = THETA(15)
;-------------------------------------------------------------

ACTG_KA_MTT = 1
IF (STUDY.EQ.1) ACTG_KA_MTT = THETA(19)


;-------------------------------------------------------------
ACTG_BIO = 1
;IF (STUDY.EQ.2)                    APT_BIO = THETA(16)
IF (ACTG_FAST.EQ.1)        ACTG_BIO = THETA(16)


;---------------------------------------------
ALB_COV = (1 + THETA(12)*(ALBIMP-37))

;Population parameters
TVCL =
THETA(1)*RIF_APT_CL*RIF_ACTG_CL*NO_RIFA_CL*ALLMCL_FFM*SEX_EFF*RIF_
CL
TVV = THETA(2)*ALLMV_WT
TVKA = THETA(3)*ACTG_KA*ACTG_KA_MTT
TVMTT = THETA(4)*ACTG_MTT*(1/ACTG_KA_MTT)
TVNN = THETA(5)
TVBIO = THETA(6)*ALB_COV*ACTG_BIO
;-------------------------------------------------------------------------
;Defining Between subjects' ETA's
BSVCL          = ETA(1)
BSVV = ETA(2)
BSVKA          = ETA(3)
BSVMTT  = ETA(4)
BSVBIO         = ETA(5)
;-------------------------------------------------------------------------
;Defining Between OCC variability;
BOVCL          = 0
BOVKA          = 0
BOVMTT  = 0
BOVBIO  = 0
;Between Visit variablity in CL
PKVIS1 = 0
PKVIS2 = 0
```

```
PKVIS3 = 0
PKVIS4 = 0
;-------------------------------------------------------------------------
OCC1  = 0
OCC2  = 0
OCC3  = 0
OCC4  = 0
OCC5  = 0
OCC6  = 0
OCC7  = 0
OCC8  = 0
;-------------------------------------------------------------------------
IF (PKVIS==1) PKVIS1 = 1
IF (PKVIS==2) PKVIS2 = 1
IF (PKVIS==3) PKVIS3 = 1
IF (PKVIS==4) PKVIS4 = 1
;-------------------------------------------------------------------------
IF (OCC==1) OCC1 = 1
IF (OCC==2) OCC2 = 1
IF (OCC==3) OCC3 = 1
IF (OCC==4) OCC4 = 1
IF (OCC==5) OCC5 = 1
IF (OCC==6) OCC6 = 1
IF (OCC==7) OCC7 = 1
IF (OCC==8) OCC8 = 1
;-------------------------------------------------------------------------------------------------------------------
-------------------------------------
BOVCL         = PKVIS1*ETA(6) + PKVIS2*ETA(7) + PKVIS3*ETA(8) + PKVIS4*ETA(9)
;-------------------------------------------------------------------------------------------------------------------
-------------------------------------
BOVMTT       = OCC1*ETA(10) + OCC2*ETA(11) + OCC3*ETA(12) + OCC4*ETA(13)  +
OCC5*ETA(14)  + OCC6*ETA(15)  + OCC7*ETA(16)  + OCC8*ETA(17)
;-------------------------------------------------------------------------------------------------------------------
-------------------------------------
BOVKA         = OCC1*ETA(18) + OCC2*ETA(19) + OCC3*ETA(20) + OCC4*ETA(21)  +
OCC5*ETA(22)  + OCC6*ETA(23)  + OCC7*ETA(24)  + OCC8*ETA(25)
;-------------------------------------------------------------------------------------------------------------------
-------------------------------------
BOVBIO        = OCC1*ETA(26) + OCC2*ETA(27) + OCC3*ETA(28) + OCC4*ETA(29)  +
OCC5*ETA(30)  + OCC6*ETA(31)  + OCC7*ETA(32)  + OCC8*ETA(33)
;-------------------------------------------------------------------------------------------------------------------
-------------------------------------
;scale un-obs doses
IF (OCC==1.OR.OCC==3.OR.OCC==5.OR.OCC==7) BOVBIO = THETA(11)*BOVBIO

;PARAMETERS
```

```
CL = TVCL*EXP(BSVCL+BOVCL)
V9 = TVV*EXP(BSVV)
MTT = TVMTT*EXP(BSVMTT + BOVMTT)
BIO = TVBIO*EXP(BSVBIO + BOVBIO)
KA = TVKA *EXP(BSVKA + BOVKA)
NN = TVNN ;NUMBER-OF-TRANSIT-COMPARTMENT
KTR = (NN+1)/MTT ;FOR-DERIVATION-OF-TRANSIT-COMPARTMENT-CONSTANT-
FOLLOWING-ESTIMATION-OF-NN-&-MTT

;-------------------------------------------------------------------------
F1       = BIO
KTR = (NN+1)/MTT                          ;FOR-DERIVATION-OF-TRANSIT-
COMPARTMENT-CONSTANT-FOLLOWING-ESTIMATION-OF-NN-&-MTT
K12    =        KTR
K23    =        KTR
K34    =        KTR
K45    =        KTR
K56    =        KTR
K67    =        KTR
K78    =        KTR
K89    =        KA
K90    =  CL/V9
S9  =   V9                                                ;CENETRAL COMPARTMENT
SCALAR
;---------------------------------------------------------------
A_0(1) = 0.0001
A_0(2) = 0.0001
A_0(3) = 0.0001
A_0(4) = 0.0001
A_0(5) = 0.0001
A_0(6) = 0.0001
A_0(7) = 0.0001
A_0(8) = 0.0001
A_0(9) = 0.0001

$ERROR
IPRED  = A(9)/V9
IRES   = DV - IPRED
PROP = THETA(7)*IPRED
ADD = THETA(8)
 W=SQRT(PROP**2 + ADD**2)      ;using add + prop error model
IF (W.LE.0.000001) W=0.000001
  IWRES  = IRES/W
  Y      = IPRED + W*EPS(1)
 ;---------------------------------------------------------------
```

```
 IF(AMT>0) THEN
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
ENDIF

TAD2 = TIME-TIMEDOSE


; For Cmax Tmax
C_MAX = COM(1) ; CMAX
T_MAX = COM(2) ; TIME OF CMAX

IF(AMT.GT.0) THEN
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
; Reset CMAX code when a new dose is given
        COM(1)=0
        COM(2)=0
ENDIF

;;AUC = A(3)
AUC_INF=AMOUNTDOSE*BIO/CL


 ; To prevent simulation (ICALL==4) of negative values. It set a positive lower bound for Y, so
that VPCs in the log-scale can be plotted
IF (ICALL==4.AND.Y<=0.01) Y=0.005
;-------------------------------------------------------------------------------
VARCL = BSVCL + BOVCL
VARBIO = BSVBIO + BOVBIO
VARAUC = BSVBIO + BOVBIO - BSVCL - BOVCL
AMOUNT_ABS = A(8) ;drug amount at central compartment
AMOUNT_CENT = A(9) ;drug amount at abs compartment
;-------------------------------------------------------------------------------

$TABLE      WRESCHOL ID OCC TIME TAD TAD2 TSOD DV PRED RES WRES IPRED
        IRES IWRES CWRESI CWRES OBJI NOPRINT NOAPPEND ONEHEADER
        FORMAT=, FILE=sdtab241.csv
;-------------------------------------------------------------------------------
$TABLE      ID OCC CL V9 KA BIO MTT BSVCL BSVV BSVKA BSVMTT BSVBIO
        BOVCL BOVMTT BOVKA BOVBIO VARCL VARBIO VARAUC NOPRINT
        NOAPPEND ONEHEADER FORMAT=, FILE=patab241.csv
;-------------------------------------------------------------------------------
$TABLE      ID WT HT AGE FFM FAT CREAT CREATIMP CREAT_12IMP ALB ALBIMP
        ALT ALT_12IMP DELTA_CREAT DELTA_ALT CAVITY NOPRINT
        NOAPPEND ONEHEADER FORMAT=, FILE=cotab241.csv
```

```
;-------------------------------------------------------------------------------
$TABLE      ID OCC SEX ARM RACE HIV STUDY PKVIS ARM_SEX ARM_VIS
            ARM_VIS_SEX STUDY_ARM STUDY_ARM_SEX STUDY_ARM_VIS
            STUDY_ARM_VIS_SEX NOPRINT NOAPPEND ONEHEADER FORMAT=,
            FILE=catab241.csv
;-------------------------------------------------------------------------------
$TABLE      ID ID_STUDY OCC TIME TAD TSOD TAD2 C_MAX T_MAX AUC_INF DV
            PRED IPRED AMOUNT_ABS AMOUNT_CENT EVID MDV AMT RES WRES
            IRES IWRES CWRES CWRESI OBJI CL V9 KA BIO MTT BSVCL BSVV
            BSVKA BSVMTT BSVBIO BOVMTT BOVKA BOVBIO VARCL VARBIO
            VARAUC WT FFM FAT FAT_PER HT AGE CREAT CREATIMP ARM SEX
            SEX_M CREAT_12IMP ALB ALBIMP ALT ALT_12IMP DELTA_CREAT
            STUDY DELTA_ALT CAVITY HIV NOPRINT NOAPPEND ONEHEADER
            FORMAT=, FILE=mytab241.csv
;-------------------------------------------------------------------------------
```

1.3 Final NONMEM scripts for results presented in chapter 5

```
;; 1. Based on: 518
;Model desc:
;Settings for the memory of NONMEM
$SIZES      PD=-1000 LVR=-150 LTH=-200 MAXFCN=10000000 LNP4=-150000
;-----------------------------------------------------------------------
$PROBLEM     Final Model CFZ popPK
;-----------------------------------------------------------------------
$INPUT      ID DAT2=DROP TIME WHAT=DROP PK_VIS VISIT=DROP BDQ_DZ=DROP
        LZD_DZ=DROP LZD_FOOD=DROP BDQ_FOOD=DROP LZD_MISSED=DROP
        CFZ_DZ CFZ_FOOD BDQ_FLAG=DROP LZD_FLAG=DROP DV_BDQ=DROP
        DV_M2=DROP BLQ_BDQ=DROP BLQ_M2=DROP LAB_ID_BDQ=DROP
        LAB_SAMPLE_DATE_BDQ=DROP BDQ_SAMPLE=DROP DV_LZD=DROP
        BLQ_LZD=DROP LAB_ID_LZD=DROP LAB_SAMPLE_DATE_LZD=DROP
        LZD_SAMPLE=DROP DV BLQ LAB_ID_CFZ=DROP
        LAB_SAMPLE_DATE_CFZ=DROP CLOFA LZD=DROP BDQ=DROP
        INDEX_START_CFZ=DROP INDEX_START_BDQ=DROP DUR_CFZ DUR_BDQ
        CMT AMT EVID MDV II OCC SS=DROP ADDL AMT_BDQ=DROP
        EVID_BDQ=DROP MDV_BDQ=DROP II_BDQ=DROP OCC_BDQ=DROP
        SS_BDQ=DROP ADDL_BDQ=DROP AMT_LZD=DROP EVID_LZD=DROP
        MDV_LZD=DROP II_LZD=DROP OCC_LZD=DROP SS_LZD=DROP
        INDEX_DOSE_TAD_CFZ=DROP TAD_CFZ INDEX_DOSE_TAD_BDQ=DROP
        TAD_BDQ=DROP INDEX_DOSE_TAD_LZD=DROP TAD_LZD=DROP
        INDEX_DOSE_CFZ=DROP TSOD_CFZ INDEX_DOSE_BDQ=DROP
        TSOD_BDQ=DROP INDEX_DOSE_TSOD_LZD=DROP TSOD_LZD=DROP
        BDQ_HIST_TT=DROP PROB PROB_LZD=DROP PROB_CFZ PROB_BDQ=DROP
        WHAT_CHANGED=DROP SEX RACE GFR BMI VOMIT DAT_TYPE ARV TENO
        EMTRI NEVI ALUVIA AZT LMV EFV ABC HEART DIABETES
        KIDNEY_DIZ LIVER_DIZ TB_MISSED_DOSES_WEEK=DROP
        IMPUTED_LZD=DROP INDEX_START_LZD=DROP DUR_LZD=DROP
        LLOQ_CFZ ARM HIV PI_ART WT HT AGE CREAT RESIS
        VISIT_DAY=DROP DOZ_WHAT=DROP VISITNUM=DROP
        ACTUAL_VISIT=DROP ARM_WHAT=DROP AVISIT=DROP ADY=DROP ALT
        AST INDEX_START=DROP
$DATA      ../../POOLED_CFZ_NONMEM_2019_11_28.csv IGNORE=#
        IGNORE=(CLOFA<1) IGNORE=(PROB>0) IGNORE=(PROB_CFZ>0)
        IGNORE=(BLQ>0)
$ABBREVIATED COMRES=2
$SUBROUTINE ADVAN13 TRANS1 TOL=9 ATOL=9 SSTOL=6 SSATOL=6
$MODEL      NCOMPARTMENTS=5 COMP=(ABSORB DEFDOSE)
        COMP=(CENTRAL DEFOBSERVATION) COMP=(PERI) COMP=(PERI2)
        COMP=("AUC",INITIALOFF)
;initializing population parameters
$THETA  (-2,9.25537,100) ; 1 V3 L[LOG]
;----------------------------------------
$THETA  (-2,4.02681,10) ; 2 Q(L/hr) [LOG]
```

```
$THETA  (0,0.20932) ; 3 TVKA 1/hr
$THETA  (0,0.498223,1) ; 4 BIO
$THETA  (0,0.114037,1) ; 5 PROP
$THETA  0.00156 FIX ; 6 ADD (mcq/ml)
$THETA  (0,1.4056) ; 7 MTT (hr)
$THETA  (0,11.484) ; 8 TVCL(L/hr)
$THETA  (0,261.85) ; 9 TVV L
$THETA  1 FIX ; 10  SCALAR
$THETA  (1,4.74808) ; 11 NN
$THETA  (0.0000001,0.0905273) ; 12 SPARSE ADD ERROR
$THETA  0 FIX ; (-0.99,0.0849611); 13 DOZ ON BIO
$THETA  (0,86.0271) ; 14 Q2
$THETA  (0,888.737) ; 15 V4
$THETA  1 FIX ; (0,0.002,1); 16 BIOSS
$THETA  (0,1.44415) ; 17 IND HALF
;--Omega---------------------------------
$OMEGA  BLOCK(1)
 0.0652958  ;   1 BSV CL
$OMEGA  BLOCK(1)
 0.0554437  ;    2 BSV V
$OMEGA  BLOCK(1)
 0.0875504  ;    3 BSVVP
$OMEGA  BLOCK(1) FIX
 0  ;    4 BSV Q
$OMEGA  BLOCK(1)
 0.297691  ;  5 BSVVP_2
$OMEGA  BLOCK(1) FIX
 0  ;   6 BSV Q2
;---------------------------------
$OMEGA  BLOCK(1) FIX
 0  ;   7 BSV KA
$OMEGA  BLOCK(1)
 0.0905985  ;  8 BSV BIO
$OMEGA  BLOCK(1) FIX
 0  ;  9 BSV MTT
;BOV--------------------------------------
$OMEGA  BLOCK(1) FIX
 0  ;  10 BOV CL
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;-------------------------------------------------------
$OMEGA  BLOCK(1)
 0.106494  ;  15 BOV KA
$OMEGA  BLOCK(1) SAME
```

```
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;----------------------------------------------------
$OMEGA  BLOCK(1)
 0.217212  ; 24 BOV MTT
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;----------------------------------------------------
$OMEGA  BLOCK(1)
 0.124779  ; 33 BOV BIO
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;----------------------------------------------------
$SIGMA  1  FIX  ;     SIGMA
;*************************************************************DONE
$PK
IF (NEWIND.NE.2) B_DUR = DUR_CFZ
        DELTA_DUR = DUR_CFZ - B_DUR
;ADDING DOSE VARIABLE
IF (CFZ_DZ.EQ.100) THEN
        DOZ = 0
ELSE
        DOZ = 1
ENDIF
IF (OCC==30.OR.OCC==40.OR.OCC==50) FIRST_STR = 1
IF (OCC==600.OR.OCC==60) FIRST_STR = 2
IF (OCC==700.OR.OCC==70) FIRST_STR = 3

;ARM FIRST 3 DOSES
```

```
ARM_FIRST = ARM*10 + FIRST_STR

FIRST_ARM = FIRST_STR*10 + ARM

STUDY_STR = 1
IF (DAT_TYPE.EQ.3) STUDY_STR  = 2

STUDY_SEX = 1
IF (DAT_TYPE.NE.3.AND.SEX.EQ.1) STUDY_SEX = 2
IF (DAT_TYPE.EQ.3.AND.SEX.EQ.1) STUDY_SEX = 3
IF (DAT_TYPE.EQ.3.AND.SEX.EQ.2) STUDY_SEX = 4



;defining VIS ID FOR TB ALLIANCE
STR_VIS = 0
IF (OCC==30) STR_VIS = 1
IF (OCC==40) STR_VIS = 2
IF (OCC==50) STR_VIS = 3
IF (OCC==600.OR.OCC==60) STR_VIS = 4
IF (OCC==700.OR.OCC==70) STR_VIS = 5

;ARM VIS

ARM_VIS = ARM*10 + STR_VIS


VIS_ARM = 0

IF (STR_VIS==1.AND.ARM==1) VIS_ARM = 11
IF (STR_VIS==2.AND.ARM==1) VIS_ARM = 21
IF (STR_VIS==3.AND.ARM==1) VIS_ARM = 31
IF (STR_VIS==4.AND.ARM==1) VIS_ARM = 41
IF (STR_VIS==5.AND.ARM==1) VIS_ARM = 51

IF (STR_VIS==1.AND.ARM==3) VIS_ARM = 13
IF (STR_VIS==2.AND.ARM==3) VIS_ARM = 23
IF (STR_VIS==3.AND.ARM==3) VIS_ARM = 33
IF (STR_VIS==4.AND.ARM==3) VIS_ARM = 43
IF (STR_VIS==5.AND.ARM==3) VIS_ARM = 53

IF (STR_VIS==1.AND.ARM==4) VIS_ARM = 14
IF (STR_VIS==2.AND.ARM==4) VIS_ARM = 24
IF (STR_VIS==3.AND.ARM==4) VIS_ARM = 34
IF (STR_VIS==4.AND.ARM==4) VIS_ARM = 44
IF (STR_VIS==5.AND.ARM==4) VIS_ARM = 54
```

```
IF (STR_VIS==1.AND.ARM==6) VIS_ARM = 16
IF (STR_VIS==2.AND.ARM==6) VIS_ARM = 26
IF (STR_VIS==3.AND.ARM==6) VIS_ARM = 36
IF (STR_VIS==4.AND.ARM==6) VIS_ARM = 46
IF (STR_VIS==5.AND.ARM==6) VIS_ARM = 56

STR = 0
IF(SEX.EQ.1.AND.DAT_TYPE.EQ.0) STR=1
IF(SEX.EQ.1.AND.DAT_TYPE.EQ.1) STR=1

IF(SEX.EQ.2.AND.DAT_TYPE.EQ.0) STR=2
IF(SEX.EQ.2.AND.DAT_TYPE.EQ.1) STR=2

IF(SEX.EQ.1.AND.DAT_TYPE.EQ.3) STR=3
IF(SEX.EQ.2.AND.DAT_TYPE.EQ.3) STR=4
;------------ADDING DUR CATEGORY
SEX_DUR = 0

IF(SEX.EQ.1.AND.DUR_CFZ.LE.55) SEX_DUR= 1
;MALE & SPARSE
IF(SEX.EQ.1.AND.DUR_CFZ.GT.55.AND.DUR_CFZ.LE.110) SEX_DUR=2

IF(SEX.EQ.1.AND.DUR_CFZ.GT.110) SEX_DUR=3

;FEMALE & INTENSIVE
IF(SEX.EQ.2.AND.DUR_CFZ.LE.55) SEX_DUR= 4
;MALE & SPARSE
IF(SEX.EQ.2.AND.DUR_CFZ.GT.55.AND.DUR_CFZ.LE.110) SEX_DUR= 5

IF(SEX.EQ.2.AND.DUR_CFZ.GT.110) SEX_DUR= 6
;DUR_CFZ
IF(DUR_CFZ.LE.55) DUR= 1
;MALE & SPARSE
IF(DUR_CFZ.GT.55.AND.DUR_CFZ.LE.110) DUR=2

IF(DUR_CFZ.GT.110) DUR=3

;Adding allometric scalling using UCT_MODEL_TEMPLATE
HTM = HT/100 ;rescaling HT to m units
;Female has value of sex 2 and male value of sex 1
IF (SEX.EQ.2) THEN
        WHSMAX=37.99
        WHS50=35.98
        ELSE       ;males
        WHSMAX=42.92
```

```
        WHS50=30.93
ENDIF


;-----------------------------------------------------
HTM2 = HTM**2
FFM = (WHSMAX*HTM2*WT)/(WHS50*HTM2+WT)
FAT = WT-FFM
FAT_PER = (FAT/WT)*100
;-------Typical values of covariates
TVWT = 55 ;median wt from the data set
TVFAT = 13
TVFFM = 42
;---------Allometric scaling and covariates
ALLMCL_WT = (WT/TVWT)**0.75
ALLMV_WT = (WT/TVWT)

ALLMCL_FAT = (FAT/TVFAT)**0.75
ALLMV_FAT = (FAT/TVFAT)

ALLMCL_FFM = (FFM/TVFFM)**0.75
ALLMV_FFM = (FFM/TVFFM)
;---------------------------------
GFR_MED = 115
CREAT_MED = 65
AGE_MED = 33

BIO_DOZ = 1
IF (DOZ.EQ.1) BIO_DOZ = 1 + THETA(13)


BIOBS=THETA(4)         ; BIO STRAT1=0
BIOSS=THETA(16)         ; BIO STEADY STATE
IND50=THETA(17)        ;  HALF LIFE




;Population parameters
TVV3 = EXP(THETA(1))*ALLMV_FAT
TVQ = EXP(THETA(2))*ALLMCL_WT
;-----------------------------------
TVKA = THETA(3)

IF (DAT_TYPE.EQ.3) THEN
```

```
                TVBIO = (BIOBS+(BIOSS-BIOBS)*(1- EXP(-
LOG(2)*DELTA_DUR/IND50)))*BIO_DOZ
        ELSE
                TVBIO = BIOSS
ENDIF
;THETA(5) ; PROPR ERROR
;THETA(6) ; ADD ERROR
TVMTT = THETA(7)
TVCL = THETA(8)*ALLMCL_WT
TVV = THETA(9)*ALLMV_FFM
TVNN = THETA(11)

TVQ2 = THETA(14)*ALLMCL_WT
TVV4 = THETA(15)*ALLMV_WT
;-------------------------------------------------------------------------
;Defining Between subjects' ETA's
BSVCL       = ETA(1)
BSVV                = ETA(2)
BSVVP               = ETA(3)
BSVQ        = ETA(4)
BSVVP_2     = ETA(5)
BSVQ2               = ETA(6)

BSVKA       = ETA(7)
BSVBIO      = ETA(8)
BSVMTT      = ETA(9)

;BETWEEN VISIT VAR ON CL
BOVCL = 0
IF  (OCC==30)                           BOVCL = ETA(10)
IF      (OCC==40)                       BOVCL = ETA(11)
IF      (OCC==50)                       BOVCL = ETA(12)
IF      (OCC==600.OR.OCC==60)  BOVCL = ETA(13)
IF      (OCC==700.OR.OCC==70)  BOVCL = ETA(14)
;-------------------------------------------------------------------------

BOVKA = 0
BOVMTT = 0
BOVBIO = 0
;Defining Between OCC variability;
;OCCASION 1-------------------------------------------------------------
IF (OCC==1.OR.OCC==30) THEN
        BOVKA = ETA(15)
        BOVMTT = ETA(24)
        BOVBIO = ETA(33)
ENDIF
```

```
;OCCASION 2----------------------------------------------------------------
IF (OCC==2.OR.OCC==40) THEN
        BOVKA = ETA(16)
        BOVMTT = ETA(25)
        BOVBIO = ETA(34)
ENDIF
;OCCASION 3----------------------------------------------------------------
IF (OCC==3.OR.OCC==50) THEN
        BOVKA = ETA(17)
        BOVMTT = ETA(26)
        BOVBIO = ETA(35)
ENDIF
;-----------------------------------
;OCCASION 10 INTENSIVE- PRE DOSE-------------------------------------------------------------
----
IF (OCC==10) THEN
        BOVKA = ETA(18)
        BOVMTT = ETA(27)
        BOVBIO = ETA(36)
ENDIF
;OCCASION 20 INTENSIVE- INTENSIVE SAMPLES----------------------------------------------
-------------------
IF (OCC==20) THEN
        BOVKA = ETA(19)
        BOVMTT = ETA(28)
        BOVBIO = ETA(37)
ENDIF

IF (OCC==600) THEN
        BOVKA = ETA(20)
        BOVMTT = ETA(29)
        BOVBIO = ETA(38)
ENDIF

IF (OCC==60) THEN
        BOVKA = ETA(21)
        BOVMTT = ETA(30)
        BOVBIO = ETA(39)
ENDIF
IF (OCC==700) THEN
        BOVKA = ETA(22)
        BOVMTT = ETA(31)
        BOVBIO = ETA(40)
ENDIF
IF (OCC==70) THEN
        BOVKA = ETA(23)
```

```
        BOVMTT = ETA(32)
        BOVBIO = ETA(41)
ENDIF



;-----------------------------------
SCALAR_FLAG = 0
IF (DAT_TYPE.EQ.1 ) THEN
        BOVBIO = THETA(10)*BOVBIO
   SCALAR_FLAG = 1
ENDIF
;-----------------------------------
;PARAMETERS
CL  = TVCL*EXP(BSVCL+BOVCL)                     ;CLEARANCE
V   = TVV*EXP(BSVV)                             ;CENTRAL VOL.

BIO = TVBIO*EXP(BSVBIO+BOVBIO)                  ;BIOAVAILABILITY
MTT =TVMTT*EXP(BSVMTT + BOVMTT)                 ;MTT TIME

V3 = TVV3*EXP(BSVVP)                            ;PERIPH VOL
Q = TVQ*EXP(BSVQ)                                       ;INTER COMPT CL
V4 = TVV4*EXP(BSVVP_2)
Q2 = TVQ2
NN = TVNN
;-----------------------------------------------------------------------------------------------------------------------
---------------------------------
;re-parameterization
K   = CL/V ;(rate constant of elimination)
K23 = Q/V   ;(rate constant from central to peripheral 1)
K32 = Q/V3 ;(rate constant from peripheral 1 to central)
K24 = Q2/V   ;(rate constant from central to peripheral 1)
K42 = Q2/V4 ;(rate constant from peripheral 1 to central)
S2 = V

F1 =    0 ; I need to set bioavailability in compartment 1 to 0

KTR = (NN+1)/MTT
KA  = TVKA*EXP(BSVKA+BOVKA) ;ABS. RATE CONSTANT


IF (NEWIND/=2.OR.EVID>=3) THEN ; new individual, or reset event
   ; The values read here will be stored in TDOS and PD in this very PK call.
        TNXD=TIME ; Time of the dose
        PNXD=AMT ; Amount. If it's zero, the DE is deactivated.
        COM(1)=0
```

```
        COM(2)=0
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
ENDIF

TDOS=TNXD ; This will either save here the temporary values if it's a new individual...
PD=PNXD ; ...or the values which were read one record ahead during the execution of the
previous record.

IF(AMT.GT.0) THEN ; This reads one record ahead and stores the data to be used when running
the following record
; IF(AMT.GT.0.AND.ALAG1.EQ.0) THEN ; Use this instead if there is ALAG, as it will also
checks if the ALAG is not 0
        TNXD=TIME
        PNXD=AMT
ENDIF

; Uncomment this if you have ALAG or if you use ADDL
IF (DOSTIM.GT.0) THEN ; This will account for the ADDL or lagged doses. It will overwrite
the time, if it a non-event record
TNXD=DOSTIM
PNXD=AMT
ENDIF

PIZZA = LOG(BIO*PD*KTR + 0.00001) - GAMLN(NN+1)
A_0(1) = 0.0001
A_0(2) = 0.0001
A_0(3) = 0.0001
A_0(4) = 0.0001

;-------------------------------------------------------------------------------
$DES

TEMPO = T-TDOS ; this is time after dose for the transit, it should always be >= 0

KTT = 0

DADT(1) = -KA*A(1)

IF(PD.GT.0.AND.TEMPO.GT.0) THEN ; This happens only if PD>0, so only if a dose has been
detected
        KTT = KTR*(TEMPO)
        DADT(1) = EXP(PIZZA+NN*LOG(KTT)-KTT) -KA*A(1)
ENDIF

DADT(2)=KA*A(1)-K*A(2)-K23*A(2)+K32*A(3) -K24*A(2)+K42*A(4)
```

```
DADT(3)=K23*A(2)-K32*A(3)
DADT(4)=K24*A(2)-K42*A(4)
; For Cmax Tmax
TIMEATERDOSE=T-TIMEDOSE
CONCENTR = A(2)/V               ; plasma concentration
IF (CONCENTR.GE.COM(1)) THEN
        COM(1) = CONCENTR           ; CMAX
        COM(2) = TIMEATERDOSE       ; TIME OF CMAX
ENDIF
DADT(5) = CONCENTR

$ERROR
IPRED = A(2)/V
IRES = DV-IPRED
PROP = IPRED*THETA(5)

ADD = THETA(6)

IF(DAT_TYPE.EQ.1) THEN
        ADD = THETA(12)
ENDIF

W = SQRT(ADD**2+PROP**2)
IF (W.LE.0.000001) W=0.000001
IWRES = IRES/W
Y = IPRED + W*ERR(1)
;-----------------------------------------------------------------
 IF(AMT>0) THEN
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
ENDIF

TAD2 = TIME-TIMEDOSE

; For Cmax Tmax
C_MAX = COM(1) ; CMAX
T_MAX = COM(2) ; TIME OF CMAX

IF(AMT.GT.0) THEN
        TIMEDOSE = TIME
        AMOUNTDOSE = AMT
; Reset CMAX code when a new dose is given
        COM(1)=0
        COM(2)=0
ENDIF
```

```
AUC_24 = A(5)
AUC_INF=AMOUNTDOSE*BIO/CL
  ;To prevent simulation (ICALL==4) of negative values. It set a positive lower bound for Y, so
that VPCs in the log-scale can be plotted
IF (ICALL==4.AND.Y<=0.00781) Y=0.003905
;-------------------------------------------------------------------------------
VARCL = BSVCL + BOVCL
VARBIO = BSVBIO + BOVBIO
VARAUC = BSVBIO + BOVBIO - BSVCL - BOVCL

AMOUNT_1 = A(1) ;drug amount at abs compartment
AMOUNT_2 = A(2) ;drug amount at central compartment
AMOUNT_3 = A(3) ;drug amount at PERIPH CMT
AMOUNT_4 = A(4) ;drug amount at PERIPH 2 CMT
;-------------------------------------------------------------------
;$ESTIMATION METHOD=1 INTERACTION MAXEVAL=0 MCETA=1000
RANMETHOD=4P
$ESTIMATION METHOD=1 INTER MAXEVAL=99999 PRINT=1 NOABORT
;MCETA=500 RANMETHOD=4P SADDLE_RESET=1 REPEAT
        NSIG=3 SIGL=6 ; RULES for precision SIGL=<TOL AND NSIG=<SIGL/3
        NONINFETA=1 ETASTYPE=1
;$COVARIANCE PRECOND=1 PRINT=E MATRIX=R
$TABLE      WRESCHOL FILE=sdtab519.csv ID OCC TIME TAD_CFZ TSOD_CFZ DV
        PRED RES WRES IPRED IRES IWRES CWRESI CWRES OBJI NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=patab519.csv ID OCC CL AUC_INF AUC_24 V V3 Q KA BIO
        MTT BSVCL BSVQ BSVV BSVVP BSVVP_2 BSVKA BSVMTT BSVBIO
        BOVMTT BOVCL BOVKA BOVBIO VARCL VARBIO VARAUC NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=cotab519.csv ID WT HT AGE BMI FFM FAT FAT_PER CREAT
        GFR DUR_CFZ NOPRINT NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=catab519.csv ID OCC SEX RESIS CFZ_FOOD CFZ_DZ DOZ ARM
        STR_VIS VIS_ARM ARM_VIS RACE HIV PI_ART ARV TENO EMTRI
        NEVI ALUVIA AZT LMV EFV ABC DAT_TYPE NOPRINT NOAPPEND
        ONEHEADER FORMAT=,
$TABLE      FILE=mytab519.csv ID OCC TIME TAD_CFZ CMT TAD2 TSOD_CFZ DV
        RESIS PRED IPRED PK_VIS AMOUNT_1 AMOUNT_2 AMOUNT_3 EVID
        MDV AMT TNXD RES WRES IRES IWRES CWRES CWRESI OBJI CL
        AUC_INF AUC_24 C_MAX T_MAX V V3 Q KA BIO MTT BSVCL BSVQ
        BSVV BSVVP BSVVP_2 BSVKA BSVMTT BSVBIO BOVMTT BOVCL BOVKA
        BOVBIO VARCL VARBIO VARAUC WT HT AGE RACE CFZ_DZ DOZ ARM
        GFR CREAT FFM FAT FAT_PER HIV BMI DAT_TYPE NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
$TABLE      FILE=mytab_519.csv ID OCC TIME TAD_CFZ TSOD_CFZ Y DV PRED
        IPRED CL V KA AMOUNT_1 AMOUNT_2 BIO MTT SCALAR_FLAG
        NOPRINT NOAPPEND ONEHEADER FORMAT=,
```

1.4 Final NONMEM scripts for results presented in chapter 6

```
;; 1. Based on: 420
;Model desc:
;Settings for the memory of NONMEM
$SIZES      PD=-1000 LVR=-150 LTH=-200 MAXFCN=10000000 LNP4=-150000
;-----------------------------------------------------------------------
$PROBLEM    final popPD model
;-------------------------------------------------

$INPUT      ID PATID VISIT_DAY DAT2=DROP DATE_TIME=DROP TIME CFZ_dz
        WHAT=DROP DV_OBS CMT AMT EVID MDV II_CFZ=DROP SS_CFZ=DROP
        ADDL_CFZ=DROP PROB PK_VIS DUR_CFZ DAT_TYPE QTCB DV PRMEAN
        QRSDUR QT_RAW RRMEAN HRMEAN BASE_QTCB BASE_QTCF
        BASE_PRMEAN BASE_QRSDUR BASE_QTMEAN BASE_RRMEAN
        BASE_HRMEAN dBASE_QTCB dBASE_QTCf dBASE_PRMEAN
        dBASE_QRSDUR dBASE_QTMEAN dBASE_RRMEAN dBASE_HRMEAN
        COMMENT=DROP OCC AGE SEX RACE ARM_WHAT=DROP ARM HT WT BMI
        HIV ALT ALB ALP AMYLASE AST CALC COV_VAL_CL=DROP CK CREAT
        BILI_DIR HCT HGB BILI_IND LDH PHOS K_POT PROTEIN SODIUM
        LIPASE URATE UREA DV_BDQ DV_M2 EVID_BDQ
        INDEX_DOSE_TAD_CFZ=DROP TAD_CFZ TSOD_CFZ RTIME DV_PRED
        DV_IPRED AMOUNT_1=DROP AMOUNT_2=DROP AMOUNT_3=DROP AUC_INF
        AUC_24 C_MAX T_MAX CL_MOD V_MOD V3_MOD Q_MOD Q2_MOD V4_MOD
        KA_MOD NN_MOD BIO_MOD MTT_MOD BSVCL_MOD BSVQ_MOD
BSVV_MOD
        BSVVP_MOD BSVVP_2_MOD BSVKA_MOD BSVMTT_MOD BSVBIO_MOD
        BOVMTT_MOD BOVCL_MOD BOVKA_MOD BOVBIO_MOD VARCL_MOD
        VARBIO_MOD VARAUC_MOD FFMX=DROP FATX=DROP FAT_PERX=DROP
        TAD_DVID BTIME CLOCK_TIME ARM_IGNORE BASE_FLG ARM_FLG
        CFZ_FLG TRT_FLG DRUG_ARM
;=======================================================================
=========
$DATA      ..\QTC_CFZ_BOOT_2020_10_02.csv IGNORE=@
        IGNORE=(DAT_TYPE.EQ.0) IGNORE=(CFZ_FLG.NE.1)

;;$ABB PROTECT

; INCLUDE ONLY BASELINE FROM ALL TRT ARMS
$PRED
DAYS = DUR_CFZ
;adfadf
IF(PROB.EQ.2) DAYS=0

TAD_VPC = TAD_CFZ
IF(PK_VIS.EQ.-1) TAD_VPC = RTIME
```

```
TSOD_VPC = TSOD_CFZ
IF(PK_VIS.EQ.-1) TSOD_VPC = RTIME

VIS = VISIT_DAY
IF(VISIT_DAY.LT.0) VIS = -1

STR_VIS = 0
IF(PK_VIS.EQ.-1) STR_VIS = -1
IF(OCC.EQ.30.AND.PROB.NE.2) STR_VIS = 1
IF(OCC.EQ.40) STR_VIS = 2
IF(OCC.EQ.50) STR_VIS = 3
IF(OCC.EQ.600.OR.OCC.EQ.60) STR_VIS = 4
IF(OCC.EQ.700.OR.OCC.EQ.70) STR_VIS = 5

STR_SEX=STR_VIS*10+SEX

RR_SEC = RRMEAN/1000
;Adding allometric scalling using UCT_MODEL_TEMPLATE
HTM = HT/100 ;rescaling HT to m units
;Female has value of sex 2 and male value of sex 1
IF (SEX.EQ.2) THEN
    WHSMAX=37.99
    WHS50=35.98
    ELSE       ;males
    WHSMAX=42.92
    WHS50=30.93
ENDIF


;-----------------------------------------------------------
HTM2 = HTM**2
FFM = (WHSMAX*HTM2*WT)/(WHS50*HTM2+WT)
FAT = WT-FFM
FAT_PER = (FAT/WT)*100
;-------Typical values of covariates
TVWT = 55 ;median wt from the data set
TVFAT = 13
TVFFM = 42
;---------Allometric scaling and covariates
ALLMCL_WT = (WT/TVWT)**0.75
ALLMV_WT = (WT/TVWT)

ALLMCL_FAT = (FAT/TVFAT)**0.75
ALLMV_FAT = (FAT/TVFAT)

ALLMCL_FFM = (FFM/TVFFM)**0.75
```

```
ALLMV_FFM = (FFM/TVFFM)



;OVER ALL MEAN FOR EACH SAMPLE SAMPLE POINT
QTCF_0 = 391.34 ; median is 393.33
QTCF_5 = 389.59 ; median is 391.5
QTCF_10 = 390.88 ; median is 390.17

BL_QTCF = BASE_QTCF
CONC = DV_IPRED

QTCF_BAR = 0
IF(TAD_DVID.EQ.0) QTCF_BAR = QTCF_0
IF(TAD_DVID.EQ.5) QTCF_BAR = QTCF_5
IF(TAD_DVID.EQ.10) QTCF_BAR = QTCF_10

;-------------------------------
TVQTCF = THETA(1)
TVAMP  = EXP(THETA(2))
TVPIK  = EXP(THETA(3))
TVAMP2 = EXP(THETA(4))
TVPIK2 = EXP(THETA(5))
TVAMP3 = EXP(THETA(6))
TVPIK3 = EXP(THETA(7))
TVAMP4 = THETA(8)
TVPIK4 = THETA(9)
TVSL   = THETA(10)
;---------------------------
; Unscheduled/early withdrawl visits were attributed to baseline predose value
; TIME AFTER DOSE EFFECT
; time effect AT PREDOSE AND Unscheduled/early withdrawl visits were attributed to baseline
predose value
; ------------------------------------------------------------------------------

;ADD = THETA (11)
;PROP = THETA(12)
TVEMAX = EXP(THETA(13))
RATIO = EXP(THETA(14))
TVEC50 = TVEMAX*RATIO
TVGAM  = EXP(THETA(15))
;---------------------------
TVALPHA = THETA(16)
;-------------------------
BSV_BASE = ETA(1)
BSV_AMP1 = ETA(2)
```

```
BSV_AMP2 = ETA(3)
BSV_AMP3 = ETA(4)
;--------------------
BSVSLP = ETA(5)
;------------------------
BSV_PIK1 = ETA(6)
BSV_PIK2 = ETA(7)
BSV_PIK3 = ETA(8)
;------------------------------
BSV_EMAX = ETA(9)
BSV_EC50 = ETA(10)
BSV_GAM  = ETA(11)
;------------------------------
BSV_AMP4 = ETA(12)
BSV_PIK4  = ETA(13)
;----------------------------
BSV_ALPHA  = ETA(14)
;----------------------------
BOVEC50 = 0
IF (OCC.EQ.30.AND.PROB.NE.2)      BOVEC50 = ETA(15)
IF (OCC.EQ.35)                                BOVEC50 = ETA(16)
IF (OCC.EQ.40)                                BOVEC50 = ETA(17)
IF (OCC.EQ.45)                                BOVEC50 = ETA(18)
IF (OCC.EQ.50)                                BOVEC50 = ETA(19)
IF (OCC.EQ.600)                          BOVEC50 = ETA(20)
IF (OCC.EQ.60)                                BOVEC50 = ETA(21)
IF (OCC.EQ.700)                          BOVEC50 = ETA(22)
IF (OCC.EQ.70)                                BOVEC50 = ETA(23)
;-------------------------------------------------
QTCF_BASE=TVQTCF*EXP(BSV_BASE)
AMP=TVAMP*EXP(BSV_AMP1)
AMP2=TVAMP2*EXP(BSV_AMP2)
AMP3=TVAMP3*EXP(BSV_AMP3)
AMP4=TVAMP4*EXP(BSV_AMP4)
PIK=TVPIK+(BSV_PIK1)
PIK2=TVPIK2+(BSV_PIK2)
PIK3=TVPIK3+(BSV_PIK3)
PIK4=TVPIK4*EXP(BSV_PIK4)
ALPHA=TVALPHA*EXP(BSV_ALPHA)
;---------------------------
SL = TVSL+BSVSLP     ;Slope of CONC vs.DQcF relationship
;-----------------------------------
EC50=TVEC50*EXP(BSV_EC50+BOVEC50)
EMAX=TVEMAX*EXP(BSV_EMAX)
GAM = TVGAM*EXP(BSV_GAM)
LOG_CONC = LOG(CONC+ 1E-10)
```

```
;-------------------------------------------------
DRUG_EFF = EXP(LOG(EMAX)+LOG(CONC) - LOG(EC50 + CONC + 1E-12 ))
;-------------------------------------------------
CIRC_1 = AMP*(COS(2*3.1416*(CLOCK_TIME-PIK)/24))
TV_CIRC_1 = TVAMP*(COS(2*3.1416*(CLOCK_TIME-TVPIK)/24))
CIRC_2 = AMP2*(COS(2*3.1416*(CLOCK_TIME-PIK2)/12))
TV_CIRC_2 = TVAMP2*(COS(2*3.1416*(CLOCK_TIME-TVPIK2)/12))
CIRC_3 = AMP3*(COS(2*3.1416*(CLOCK_TIME-PIK3)/6))
TV_CIRC_3 = TVAMP3*(COS(2*3.1416*(CLOCK_TIME-TVPIK3)/6))
CIRC_4 = AMP4*(COS(2*3.1416*(CLOCK_TIME-PIK4)/4))
;-------------------------------------------------
CIRC = CIRC_1 + CIRC_2 + CIRC_3 + CIRC_4
TVCIRC = TV_CIRC_1 + TV_CIRC_2 + TV_CIRC_3
QTCF_TVCIRC = TVQTCF*(1+ TVCIRC)

QTCF_CIRC = QTCF_BASE*(1+ CIRC)
QTCF_EMAX = QTCF_BASE + DRUG_EFF
TVQTCF_EMAX = TVQTCF + DRUG_EFF

;-----------------------------------------
; Basline including circadian cosine function
QTCF = QTCF_BASE*(1 + CIRC  ) + DRUG_EFF
;-----------------------------------
;ERROR MODEL
IPRED = QTCF
;-----------------------------------
ADD_QTcF = THETA(11)
PROP_QTcF = IPRED*THETA(12) ; IPRED_CFU * THETA(x)
W = SQRT((ADD_QTcF)**2 + (PROP_QTcF)**2)

IRES = DV-IPRED
IF (W.LE.0.000001) W=0.000001
IWRES = IRES/W

Y = IPRED + W*EPS(1)

$THETA  (0,391.177,1000) ; 1 QTCF BASE
$THETA  (-10,-4.01647,1E-12) ; 2 AMP [log]
$THETA  (-10,1.60802,3.178054) ; 3 PIK [log]
$THETA  (-10,-4.88474,1E-12) ; 4  AMP2 [log]
$THETA  (-10,1.32406,3.178054) ; 5 PIK2 [log]
$THETA  (-10,-4.66655,1E-12) ; 6  AMP3 [log]
$THETA  (-10,1.7788,3.178054) ; 7 PIK3[log]
$THETA  0 FIX ; 8 AMP4
$THETA  0 FIX ; 9 PIK4
$THETA  0 FIX ; 10 SL
```

```
$THETA  (0,8.34708,100) ; 11 ADD ERROR
$THETA  0 FIX ; 12 PROP  ERROR
$THETA  (-10,3.29361,10) ; 13 EMAX[log]
$THETA  (-10,-4.64654,1E-12) ; 14 RATIO [log]
$THETA  0 FIX ; 15 GAMMA [log]
$THETA  0 FIX ; 16 ALPHA
;----------------------------------
$OMEGA  BLOCK(1) 0.00141274  ; 1  BSV QTC
$OMEGA  BLOCK(1) FIX 0  ; 2  BSV AMP 1
$OMEGA  BLOCK(1) 0.854185  ; 3  BSV AMP 2
$OMEGA  BLOCK(1) FIX 0  ; 4   BSV AMP3
$OMEGA  BLOCK(1) FIX 0  ; 5    BSV SLP
$OMEGA  BLOCK(1) FIX 0  ; 6   BSV PIK1
$OMEGA  BLOCK(1) FIX 0  ; 7   BSV PIK2
$OMEGA  BLOCK(1) FIX 0  ; 8   BSV PIK3
$OMEGA  BLOCK(1) FIX 0  ; 9   BSV emxx
$OMEGA  BLOCK(1) FIX 0  ; 10   BSV ec50
$OMEGA  BLOCK(1) FIX 0  ; 11   BSV_GAM
$OMEGA  BLOCK(1) FIX 0  ; 12   BSV_AMP4
$OMEGA  BLOCK(1) FIX 0  ; 13   BSV_PIK4
$OMEGA  BLOCK(1) FIX 0  ; 14   BSV_ALPHA
;-----------------------------------------------
$OMEGA  BLOCK(1) FIX 0  ; 15   BOV EC50
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;-------------------------------------------------------
$SIGMA  1  FIX
;-------------------------------------------------
;-------------------------------------------------
$ESTIMATION METH=SAEM AUTO=1 NOABORT PRINT=1 GRD=TS(11) NITER=10000
$ESTIMATION METHOD=IMP INTER EONLY=1 NITER=30 ISAMPLE=5000 PRINT=1
;;GRD=TS(7,8)
$COVARIANCE PRINT=E PRECOND=1
$TABLE      WRESCHOL FILE=sdtab421.csv ID DV OCC TIME RTIME CLOCK_TIME
            TAD_CFZ TSOD_CFZ PRED RES WRES IPRED IRES IWRES CWRESI
            CWRES OBJI NOPRINT NOAPPEND ONEHEADER FORMAT=,
;------------------------------------------------------------------------
$TABLE      FILE=patab421.csv ID OCC QTCF_BASE QTCF ALPHA SL AMP AMP2
            AMP3 PIK PIK2 PIK3 EC50 EMAX GAM BSV_ALPHA BSV_BASE
            BSV_AMP1 BSV_AMP2 BSV_AMP3 BSVSLP BSV_PIK1 BSV_PIK2
```

```
        BSV_PIK3 BSV_EC50 BOVEC50 BSV_EMAX BSV_GAM NOPRINT
        NOAPPEND ONEHEADER FORMAT=,
;-----------------------------------------------------------------------
$TABLE      FILE=cotab421.csv ID RTIME CLOCK_TIME DUR_CFZ DV_PRED
        RR_SEC QTCB PRMEAN QRSDUR RRMEAN HRMEAN BASE_QTCB
        BASE_QTCF BASE_PRMEAN BASE_QRSDUR BASE_QTMEAN BASE_RRMEAN
        BASE_HRMEAN dBASE_QTCB dBASE_QTCf dBASE_PRMEAN
        dBASE_QRSDUR dBASE_QTMEAN dBASE_RRMEAN dBASE_HRMEAN
        DV_IPRED AUC_INF AUC_24 C_MAX T_MAX WT HT AGE BMI FFM FAT
        FAT_PER CREAT ALT ALB AST DUR_CFZ CK HCT HGB K_POT PROTEIN
        SODIUM NOPRINT NOAPPEND ONEHEADER FORMAT=,
;-----------------------------------------------------------------------
$TABLE      FILE=catab421.csv ID OCC PK_VIS SEX CFZ_DZ ARM RACE HIV
        TAD_DVID NOPRINT NOAPPEND ONEHEADER FORMAT=,
;-----------------------------------------------------------------------
$TABLE      FILE=mytab421.csv ID PATID OCC DV TIME RTIME BTIME VIS
        CLOCK_TIME TAD_CFZ TSOD_CFZ CMT EVID MDV AMT PRED IPRED
        QTCF QTCF_BASE QTCB RRMEAN RR_SEC SL AMP AMP2 AMP3 PIK
        QTCF_CIRC QTCF_EMAX PIK2 PIK3 EC50 EMAX GAM BSV_BASE
        BSV_AMP1 BSV_AMP2 BSV_AMP3 BSV_PIK1 BSV_PIK2 BSV_PIK3
        BSVSLP BSV_EC50 BOVEC50 BSV_EMAX BSV_GAM DV_PRED DV_IPRED
        PRMEAN QRSDUR HRMEAN BASE_QTCB BASE_QTCF BASE_PRMEAN
        BASE_QRSDUR BASE_QTMEAN BASE_RRMEAN BASE_HRMEAN
dBASE_QTCB
        dBASE_QTCf dBASE_PRMEAN dBASE_QRSDUR dBASE_QTMEAN
        dBASE_RRMEAN dBASE_HRMEAN FFM FAT FAT_PER CREAT ALT ALB
        ALP AMYLASE AST CALC DUR_CFZ CK BILI_DIR HCT HGB BILI_IND
        K_POT PROTEIN SODIUM LIPASE URATE UREA PHOS CFZ_DZ ARM
        PK_VIS RACE HIV TAD_DVID DAT_TYPE SEX TVCIRC QTCF_TVCIRC
        DRUG_EFF TVQTCF_EMAX DRUG_ARM NOPRINT NOAPPEND ONEHEADER
        FORMAT=,
```

1.5 Final NONMEM scripts for results presented in chapter 7

```
;; 1. Based on: 593
;Model desc:
;Settings for the memory of NONMEM
$SIZES      PD=-1000 LVR=-150 LTH=-200 MAXFCN=10000000 LNP4=-150000
        DIMTMP=1000
;-------------------------------------------------------------------------
$PROBLEM    Final model popPK
;-------------------------------------------------------------------------
$INPUT      ID DATXX=DROP DAT2=DROP TIME TIME_24=DROP DATE_TIME=DROP
        DATE_TIME_24=DROP WHAT=DROP PK_VIS LZD_DZ LZD_FOOD DV BLQ
        CMT_LZD AMT EVID MDV II_XX=DROP OCC SS_DX=DROP TAD_LZD
        TAD_LZD_24 TSOD_LZD TSOD_LZD_24 PROB PROB_LZD PROB_VIS
        PROB_CMT DAT_TYPE WBC HB PLATLET KA_ELC ALB ALT ALP
        TOTAL_BIL TSH LACTATE QT=DROP QT_2=DROP QT_3=DROP RR=DROP
        RR_2=DROP RR_3=DROP QTCF=DROP QTCF_2=DROP QTCF_3=DROP SEX
        RACE ARV EFV ALUVIA ATAZ_RITO BMI HIV PI_ART WT HT AGE
        CREAT LZD WHAT_PROB=DROP
;-------------------------------------------------------------------------
$DATA      ../../probex_lzd_2020_11_17.csv IGNORE=@ IGNORE=(LZD<1)
        IGNORE=(PROB>0) IGNORE=(PROB_LZD>0) IGNORE=(PROB_CMT>0)
        IGNORE=(PROB_VIS>0) IGNORE=(BLQ>0) IGNORE=(TSOD_LZD.GT.35)

;;IGNORE=(DAT_TYPE.EQ.0)

;-------------------------------------------------------------------------
$ABBREVIATED COMRES=2
;-------------------------------------------------------------------------

;$ABBREVIATED DECLARE INTEGER NDOSE INTEGER MAX_ACCUM_DOSES

;-------------------------------------------------------------------------

; This defines protect functions for /0, LOG(0), etc. Advised to use
$ABBREVIATED PROTECT
;-------------------------------------------------------------------------

;-------------------------------------------------------------------------
$SUBROUTINE ADVAN5 TRANS1 ;TOL=9 ATOL=9 SSTOL=6 SSATOL=6

;-------------------------------------------------------------------------
$MODEL      NCOMPS=7 ; NUMBER OF COMPARTMENTS (ABSORPTION
COMPATMENT (DEFINED AS FIRST ONE) AND CENTRAL COMPARTMENT DEFIEND
AS 2ND COMPARTMENT
        COMP=(TRANSIT1,DEFDOSE) ;1 GUT TRANIST 1
        COMP=(TRANSIT2) ;2 GUT TRANIST 2
```

```
      COMP=(TRANSIT3) ;3 GUT TRANIST 3
      COMP=(TRANSIT4) ;4 GUT TRANIST 4
      COMP=(TRANSIT5) ;5 GUT TRANIST 5
      COMP=(ABS) ;6 GUT ABS
      COMP=("CENTRAL",DEFOBS) ;7 CENTRAL CMT

;COMP=("AUC",INITIALOFF)       ;8 DUMMY CMT (AUC)

;initialization-of-theta(S)-from the previous run
$THETA  (0,3.53407,10) ; 1 TVCL (L/H)
$THETA  (0,39.8889,100) ; 2 TVV (L)
$THETA  (0,1.24497,3) ; 3 TVKA (1/H)
$THETA  (0,0.354648,3) ; 4 MTT (H)
$THETA  1 FIX ; 5 BIO()
$THETA  (0.0001,5) FIX ; 6 NN ()
$THETA  (0.01,0.0923303,1) ; 7 PROP (%)
$THETA  (1e-5,0.05) FIX ; 8 ADD (mg/L)
$THETA  24 FIX ; 9 Sparse Lag (H)
$THETA  (1e-5,0.589981) ; 10 predose-add error
$THETA  0 FIX ; 11 Food on bio
$THETA  1 FIX ; (1e-5,0.74594); 12 scale bovbio
;-----------------------------------------------
$OMEGA  BLOCK(1)
 0.117282  ;    1 BSVCL
$OMEGA  BLOCK(1) FIX
 0  ;     2 BSVV
$OMEGA  BLOCK(1) FIX
 0  ;    3 BSVKA
$OMEGA  BLOCK(1) FIX
 0  ;   4 BSVMTT
$OMEGA  BLOCK(1) 0 FIX  ;   5 BSVBIO
;---------------------------------------
$OMEGA  BLOCK(1)
 0.1  ;    6 BOVKA
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;---------------------------------------
$OMEGA  BLOCK(1)
 0.1  ;  11 BOVMTT
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;---------------------------------------
```

```
$OMEGA  BLOCK(1)
 0.1  ;  16 BOVBIO
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;----------------------------------------
$OMEGA  BLOCK(1) FIX
 0.5  ;  21 BOVLAG
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;----------------------------------------
$OMEGA  BLOCK(1) FIX
 0  ;   24 BSVNN
;-------------------------------------
$OMEGA  BLOCK(1) FIX
 0  ;  25 BSVLAG
;----------------------------------------
$OMEGA  BLOCK(1) FIX
 0  ;   26 BOVCL
$OMEGA  BLOCK(1) SAME
$OMEGA  BLOCK(1) SAME
;--------------------------------
$SIGMA  1  FIX
;----------------------------------------
$PK ;;CALLFL = -2



;Adding Dose as covriate
IF(AMT.GT.0) DOZ = AMT
 ;DEFINING_PK_PARAMTERS

;----ADDING-ALLOMETRIC-SCALLING-

;Adding allometric scalling using UCT_MODEL_TEMPLATE
HTM = HT/100 ;rescaling HT to m units
;Female has value of sex 2 and male value of sex 1
IF (SEX.EQ.2) THEN
        WHSMAX=37.99
        WHS50=35.98
        ELSE       ;males
        WHSMAX=42.92
        WHS50=30.93
ENDIF
;-----------------------------------------------------
```

```
HTM2 = HTM**2
FFM = (WHSMAX*HTM2*WT)/(WHS50*HTM2+WT)
FAT = WT-FFM
FAT_PER = (FAT/WT)*100
;-------Typical values of covariates
TVWT = 56 ;median wt from the data set
TVFAT = 13
TVFFM = 43
;---------Allometric scaling and covariates
ALLMCL_WT = (WT/TVWT)**0.75
ALLMV_WT = (WT/TVWT)
;-----------------------------------------------------
ALLMCL_FAT = (FAT/TVFAT)**0.75
ALLMV_FAT = (FAT/TVFAT)
;-----------------------------------------------------
ALLMCL_FFM = (FFM/TVFFM)**0.75
ALLMV_FFM = (FFM/TVFFM)
;-------------------------------------------------------------------------------------------
;-------------------------------------------------------------------------------------------
;CREATININE CLEARANCE - COCKCROFT AND GAULT

SCR = CREAT  ; SERUM CREATININE mm3/L
IF(CREAT==-99) SCR = 58 ; MEDIAN SCR

AGESCR = AGE
IF(AGE < 18) AGESCR = 33 ; MEDIAN AGE

IF(SEX==1) CRCLSTD=1.23*(140-AGESCR)*TVWT/SCR  ; CLcr for MALE, WT=47
IF(SEX==2) CRCLSTD=1.04*(140-AGESCR)*TVWT/SCR  ; FEMALES

TV_CRCLSTD=100  ; ML/MIN

RF = CRCLSTD/TV_CRCLSTD

FOOD_BIO = 1
IF(LZD_FOOD.EQ.1) FOOD_BIO = 1 + THETA(11)
;PARAMTERS
TVCL  = THETA(1)*ALLMCL_WT          ; Clearance Typical Value WITH ALLOMETRIC
SCALING
TVV   = THETA(2)*ALLMV_WT  ; Volume Typical Value WITH ALLOMETRIC
SCALLING
TVKA          = THETA(3)                        ; First Order oral abs Typical Value
TVMTT         = THETA(4)                        ; Typical-VALUE-FOR-MTT
TVBIO         = THETA(5)*FOOD_BIO                       ; Typical BIO value
TVNN          = THETA(6)                        ; NUMBER-OF-TRANSIT-COMPS
;-------------------------------------------------------------------------------------------
```

```
;Defining ETA's
;BETWEEN SUBJETS VARIABILITY---------------------------------------------------------------
BSVCL                   = ETA(1)
BSVV            = ETA(2)
BSVKA                   = ETA(3)
BSVMTT                  = ETA(4)
BSVBIO                  = ETA(5)
;-------------------------------------------------------------------
BSVNN                   = ETA(24)
BSVLAG                  = ETA(25)
;Defining Between OCC VARIABILITY-----------------------------------
BOVCL = 0
BOVKA = 0
BOVMTT = 0
BOVBIO = 0
BOVLAG  = 0

;Defining Between OCC variability;
;OCCASION 1---------------------------------------------------------
IF (OCC==1) THEN
        BOVKA = ETA(6)
        BOVMTT = ETA(11)
        BOVBIO = ETA(16)
ENDIF
;OCCASION 2---------------------------------------------------------
IF (OCC==2) THEN
        BOVKA = ETA(7)
        BOVMTT = ETA(12)
        BOVBIO = ETA(17)
ENDIF
;OCCASION 3---------------------------------------------------------
IF (OCC==3) THEN
        BOVKA = ETA(8)
        BOVMTT = ETA(13)
        BOVBIO = ETA(18)
ENDIF
;-----------------------------------
;OCCASION 10 INTENSIVE- PRE DOSE-------------------------------------------------------------
----
IF (OCC==10) THEN
        BOVKA = ETA(9)
        BOVMTT = ETA(14)
        BOVBIO = ETA(19)
ENDIF
;OCCASION 20 INTENSIVE- INTENSIVE SAMPLES----------------------------------------------------
--------------------
```

```
IF (OCC==20) THEN
        BOVKA = ETA(10)
        BOVMTT = ETA(15)
        BOVBIO = ETA(20)
ENDIF

;-------------------------------------------------
OCC1   =   0
OCC2   =   0
OCC3   =   0
;-------------------------------------------------
VIS1   =   0
VIS2   =   0
VIS3   =   0
; CREATE INDICATOR VARIABLES FOR OCCASION
IF(PK_VIS.EQ.1)   VIS1   =   1     ;SPARSE VISIT MONTH 1
IF(PK_VIS.EQ.2)   VIS2   =   1    ;SPARSE VISIT MONTH 2
IF(PK_VIS.EQ.3)   VIS3   =   1    ;SPARSE VISIT MONTH 6
; CREATE INDICATOR VARIABLES FOR OCCASION
IF(OCC.EQ.1)   OCC1   =   1     ;SPARSE VISIT MONTH 1
IF(OCC.EQ.2)   OCC2   =   1    ;SPARSE VISIT MONTH 2
IF(OCC.EQ.3)   OCC3   =   1    ;SPARSE VISIT MONTH 6
;-------------------------------------------------------------------------
BOVLAG = OCC1*ETA(21)+ OCC2*ETA(22)+OCC3*ETA(23)
;-------------------------------------------------------------------------
BOVCL = VIS1*ETA(26)+ VIS2*ETA(27)+VIS3*ETA(28)
;-------------------------------------------------------------------------
TVLAG = THETA(9)*DAT_TYPE ; APPLY ONLY TO SPARSE DATA
BOVLAG = BOVLAG*DAT_TYPE

IF (DAT_TYPE==1) THEN
        BOVBIO=THETA(12)*BOVBIO
ENDIF
;-----------------------------------------------------------------------------
MU_1 = LOG(TVCL)
MU_2 = LOG(TVV)
MU_3 = LOG(TVKA)
MU_4 = LOG(TVMTT)
MU_5 = LOG(TVBIO)
; MU_24 = LOG(TVNN)
;MU_25 = LOG(TVLAG)
;PARAMETERS

CL              = EXP(MU_1 + BSVCL)*EXP(BOVCL)
V7              = EXP(MU_2 + BSVV)
KA              = EXP(MU_3 + BSVKA)*EXP(BOVKA)
```

```
MTT   = EXP(MU_4 + BSVMTT)*EXP(BOVMTT)
BIO    = EXP(MU_5 + BSVBIO)*EXP(BOVBIO)
NN              = TVNN*EXP(BSVNN)
LAG    = TVLAG + BSVLAG + BOVLAG

ALAG1   =  LAG
TLAG = LAG

;-------------------------------------------------------------------------
F1      = BIO
KTR = (NN+1)/MTT                        ;FOR-DERIVATION-OF-TRANSIT-
COMPARTMENT-CONSTANT-FOLLOWING-ESTIMATION-OF-NN-&-MTT
K12    =        KTR
K23    =        KTR
K34    =        KTR
K45    =        KTR
K56    =        KTR
K67 =  KA
K70    =  CL/V7
S7  =   V7                                              ;CENETRAL COMPARTMENT
SCALAR

;;;-------------------------------------------------------------
A_0(1) = 0.0001
A_0(2) = 0.0001
A_0(3) = 0.0001
A_0(4) = 0.0001
A_0(5) = 0.0001
A_0(6) = 0.0001
A_0(7) = 0.0001


$ERROR
LLOQ_LZD=0.1
IPRED  = A(7)/V7
IRES   = DV - IPRED
PROP = THETA(7)*IPRED
;0.2*LLOQ_LZD +
ADD =  THETA(8)

IF(ICALL.NE.4.AND.BLQ==1) ADD = ADD + (LLOQ_LZD/2)

IF(ICALL.NE.4.AND.BLQ==2) THEN
        PROP = 0
        ADD = 100000000
ENDIF
```

```
 IF(OCC.EQ.10.OR.DAT_TYPE.EQ.1)  ADD = THETA(10)

W=SQRT(PROP**2 + ADD**2)       ;using add + prop error model
IF (W.LE.0.000001) W=0.000001
IWRES  = IRES/W
Y = IPRED + W*EPS(1)
IF (ICALL==4.AND.Y<=0.1) Y=0.05 ;HALF THE VALUE OF LLOQ (FOR LZD IS = 0.1)
;----------------------------------------------------------------------
 IF(AMT>0) THEN
          TIMEDOSE = TIME
          AMOUNTDOSE = AMT
ENDIF

TAD2 = TIME-TIMEDOSE
;----------------------------------------------------------------------
TSOD_NON = TSOD_LZD
IF(DAT_TYPE.EQ.1.AND.TAD2.GT.20) THEN
                    TSOD_NON = TAD2 - 24
          ;;ELSEIF(DAT_TYPE.EQ.1.AND.TAD2.LT.20) THEN
          ;;         TSOD_NON = TAD2 + 24
ENDIF
;----------------------------------------------------------------------
IF(TSOD_NON.GT.40) TSOD_NON = TSOD_NON - 24

AUC_INF=AMOUNTDOSE*BIO/CL
  ;To prevent simulation (ICALL==4) of negative values. It set a positive lower bound for Y, so
that VPCs in the log-scale can be plotted
;------------------------------------------------------------------------------
VARCL = BSVCL + BOVCL
VARBIO = BSVBIO + BOVBIO
VARAUC = BSVBIO + BOVBIO - BSVCL - BOVCL

AMOUNT_6 = A(6) ; ABS CMT
AMOUNT_7 = A(7) ; CENTRAL CMT
CONC_MOD = A(7)/V7
;-------------------------------------------------------------------------------

$PHIS      FILE=run593.phi TBLN=2
$ESTIMATION METHOD=SAEM AUTO=1 NOABORT PRINT=1 GRD=TS(7,8,10)
$ESTIMATION METHOD=IMP ISAMPLE=1000 INTERACTION NITER=50 MAPITER=51
          SIG=3 PRINT=1 SIGL=6 EONLY=1 NOHABORT
; $ESTIMATION METHOD=1 INTER MAXEVAL=0 PRINT=1 NOABORT NSIG=3 SIGL=6

; ;MCETA=500 RANMETHOD=4P
```

```
; NONINFETA=1 ETASTYPE=1 FAST

;-----------------------------------------------------------------------------
$COVARIANCE PRINT=E MATRIX=R UNCONDITIONAL
;-----------------------------------------------------------------------------
$TABLE      WRESCHOL FILE=sdtab599.csv ID OCC TIME TAD_LZD TSOD_NON
            TAD_LZD_24 TSOD_LZD TSOD_LZD_24 DV PRED RES WRES IPRED
            IRES IWRES CWRESI CWRES OBJI NOPRINT NOAPPEND ONEHEADER
            FORMAT=,
;-----------------------------------------------------------------------------
$TABLE      ID OCC CL AUC_INF V7 KA BIO MTT BSVCL TLAG BOVLAG BSVV
            BSVKA BSVMTT BSVBIO BOVMTT BOVCL BOVKA BOVBIO VARCL VARBIO
            VARAUC NOPRINT NOAPPEND ONEHEADER FORMAT=,
            FILE=patab599.csv
;-----------------------------------------------------------------------------
$TABLE      ID WT HT CRCLSTD SCR RF AGE BMI FFM FAT FAT_PER CREAT
            NOPRINT NOAPPEND ONEHEADER FORMAT=, FILE=cotab599.csv
;-----------------------------------------------------------------------------
$TABLE      ID OCC SEX LZd_FOOD DOZ RACE HIV ARV ALUVIA EFV DAT_TYPE
            PI_ART NOPRINT NOAPPEND ONEHEADER FORMAT=,
            FILE=catab599.csv
;-----------------------------------------------------------------------------
$TABLE      ID OCC TIME TAD_LZD TSOD_NON CMT_LZD TAD2 TSOD_LZD DV
PRED
            CONC_MOD IPRED PK_VIS AMOUNT_6 AMOUNT_7 EVID MDV AMT RES
            WRES IRES IWRES CWRES CWRESI OBJI CL AUC_INF V7 KA BIO MTT
            TLAG BOVLAG BSVCL BSVV BSVKA BSVMTT BSVBIO BOVMTT BOVCL
            BOVKA BOVBIO VARCL VARBIO VARAUC WT HT AGE RACE LZD_DZ DOZ
            CREAT FFM FAT FAT_PER HIV PI_ART BMI DAT_TYPE NOPRINT
            NOAPPEND ONEHEADER FORMAT=, FILE=mytab599.csv
;-----------------------------------------------------------------------------
```