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Severe acute malnutrition results in lower lumefantrine exposure in children treated with artemether-lumefantrine for uncomplicated malaria

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CONFLICT OF INTEREST

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Running title: Malnutrition results in low lumefantrine exposure

ABSTRACT

Severe acute malnutrition (SAM) has been reported to be associated with increased malaria morbidity in Sub-Saharan African children and may affect the pharmacology of antimalarial drugs. This population pharmacokinetic-pharmacodynamic study included 131 SAM and 266 non-SAM children administered artemether-lumefantrine twice daily for 3 days. Lumefantrine capillary plasma concentrations were adequately described by two transit-absorption compartments followed by two distribution compartments. Allometrically scaled body weight and an enzymatic maturation effect were included in the pharmacokinetic model. Mid-upper arm circumference (MUAC) was associated with decreased absorption of lumefantrine (25.4% decrease per 1 cm reduction). Risk of recurrent malaria episodes (i.e. reinfection) were characterised by an interval-censored time-to-event model with a sigmoid E_{MAX}-model describing the effect of lumefantrine. SAM children were at risk of under-exposure to lumefantrine and an increased risk of malaria reinfection compared to well-nourished children. Research on optimised regimens should be considered for malaria treatment in malnourished children.

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INTRODUCTION

Young children (<5 years of age) are especially vulnerable to malaria and around 61% of all malaria deaths worldwide occurs in this population (1). This is of even greater concern in malnourished children, who are at a higher risk of contracting malaria and dying from the disease compared to well-nourished children (2). The World Health Organization (WHO) defines severe acute malnutrition (SAM) by weight-for-height z-score (WHZ; < -3), mid-upper arm circumferences (MUAC; < 115 mm), or presence of nutritional oedema (3). Slower parasite clearance and higher parasite densities have been observed in malnourished children (4). Altered physiological properties in malnourished children might change pharmacokinetic properties, e.g. reduced drug absorption, smaller volume of distribution, reduced plasma concentrations, altered metabolism due to hepatic dysfunction, and reduced drug-protein binding due to hypoalbuminaemia (5, 6).

Most clinical studies exclude severely malnourished children resulting in limited evidence on the pharmacokinetics of drugs in this population, and the few studies available report contradictory results as illustrated in a recent systematic review (7). One study showed a faster quinine clearance, shorter half-life, and lower quinine concentration 12 hours after dosing with a higher proportion of the metabolite, hydroxyquinine, in global protein-energy malnourished children when compared to normally-nourished children (8). However, another study investigating the pharmacokinetics of quinine after intravenous infusion did not find a significant difference between global protein-energy malnourished children and well-nourished children (4). Another pharmacokinetic study of orally administered quinine showed lower maximum concentration, longer absorption half-life, slower clearance, and a longer elimination half-life in children with kwashiorkor (9). For chloroquine, a small study (7 normal and 8 undernourished children) did not find any pharmacokinetic differences in the malnourished children (10). However, a single dose study in children with kwashiorkor found

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decreased chloroquine absorption, lower chloroquine exposure, and lower peak plasma desethylchloroquine concentration compared to adequately-nourished children (11).

Artemether-Lumefantrine (Coartem®) is one of the artemisinin-based combination therapies recommended by the WHO for the treatment of malaria, and it is the most common antimalarial drug used worldwide (12). Artemether is an artemisinin derivative and it is metabolised rapidly with a terminal half-life of 2-3 hours to form its active metabolite dihydroartemisinin (13). Lumefantrine is eliminated more slowly with a terminal half-life of 3-6 days and it is metabolised to desbutyl-lumefantrine. Both lumefantrine and desbutyl-lumefantrine possess an *in vitro* antimalarial activity with geometric mean 50% inhibitory concentrations (IC_{50}) of 65.2 nM (95% CI: 42.3, 100.8 nM) and 9.0 nM (95% CI: 5.7, 14.4 nM), respectively (14). Lumefantrine capillary blood concentrations and venous plasma concentrations are highly correlated with no substantial differences in observed *in vivo* concentrations (15-17). Lumefantrine is highly lipophilic and its bioavailability increases by 57% (90% CI: 29%, 56%) when administered together with fat (18), and as little as 1.2 g of fat has been shown to maximise the absorption of lumefantrine (19). Therefore, artemether-lumefantrine is recommended to be administered with a fat-containing meal or a drink (e.g. milk). Irrespectively of drug administration with or without fat, lumefantrine exposure has been reported to be lower in children compared with adults when receiving standard treatment against malaria (20). A recently published large pooled pharmacokinetic-pharmacodynamic meta-analysis of artemether-lumefantrine reported that the dose-adjusted day-7 lumefantrine concentrations in malnourished young children (aged <3 years with WHZ <-2) was 23% (95% CI: 1%, 41%) lower than adequately-nourished children of the same age, and 53% (95% CI: 37%, 65%) lower than in adults, resulting in increased risk of treatment failure (21). The pharmacokinetic and pharmacodynamic properties of lumefantrine have been poorly defined in malnourished children, and its population pharmacokinetic properties have not been studied previously in SAM children. This is the first study

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aimed to investigate the population pharmacokinetic-pharmacodynamic properties of lumefantrine in SAM children.

RESULTS

This clinical trial was an open-labelled comparative intervention study of artemether-lumefantrine in 131 SAM and 266 non-SAM children with uncomplicated *falciparum* malaria, aged between 6 to 59 months. Only 160 out of 266 non-SAM children provided blood samples and these children were included in the pharmacokinetic analysis. Full demographic characteristics of study participants are presented in the Table 1.

Pharmacokinetic model

Lumefantrine capillary plasma concentrations were transformed into their natural logarithms and modelled using nonlinear mixed-effects modelling. The pharmacokinetic properties of lumefantrine were described best by a two-compartment disposition model (ΔOFV = -753, compared to a one-compartment disposition model, supplementary figure 1). Adding an extra disposition compartment did not improve the model fit significantly (ΔOFV = -5.37). A transit-absorption model with two transit-compartments was superior to all other absorption models (ΔOFV = -6.94, compared to first-order absorption). The absorption rate constant (K_a) and the transit rate constant (K_{tr}) were assumed to be equal, thus resulting in no degree of freedom difference to the traditionally used first-order absorption model. The relative bioavailability of lumefantrine was fixed to unity for the population, but allowing for inter-individual variability in this parameter improved the model fit substantially (ΔOFV = -262; Box-Cox transformed distribution provided the best implementation).

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The fraction of observed concentrations below the LLOQ were low (84 out of 1,341 sample; 6.26%), but evaluated using M1, M3, and M6 methods to avoid possible bias on account of censored data (22). Omitting LLOQ data (M1) or using a maximum likelihood approach for LLOQ data (M3) resulted in misspecifications in the fraction of observed LLOQ data. Imputing the first LLOQ data within a patient to be half of the LLOQ value (M6) resulted in a good predictive performance (Figure 1) and was implemented in the final model.

Covariate model

Implementation of body weight as a fixed allometric function on all clearance and volume parameters did not improve the model fit (ΔOFV = 66.1), but it was retained in the final model due to the strong biological prior evidence and previously published results (16, 20, 23, 24). Other implementations of body weight as a covariate were evaluated (i.e. linear, estimating the exponent in the allometric function, estimating different exponents in the allometric function for SAM and non-SAM children, and allowing malnutrition measurements to influence the exponent in the allometric function), but none of these demonstrated a substantially improved model fit compared to the fixed allometric function. An enzyme maturation effect on clearance improved the model fit significantly. All investigated indicators of malnutrition (i.e. MUAC, WHZ, and weight-for-age z-score (WAZ)) had a significant impact on the relative bioavailability, irrespectively of the assumed parameter distribution of the relative bioavailability. Of these three malnutrition covariates, the mid-upper arm circumferences (MUAC) had the largest drop in objective function value (ΔOFV = -64.4) and was retained in the final pharmacokinetic model. Addition of any other indicators associated with malnutrition together with MUAC did not result in any additional improvement in model fit. Impact of malnutrition-associated indicators were further investigated using a full-covariate approach. The median bioavailability was 38.6% (95% CI: 74.5%, 27.4%) lower in SAM children compared with non-SAM children, and the median bioavailability was reduced by 21.0% (95% CI:

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19.5%, 29.3%) per 1 cm reduction of MUAC, or 15.5% (95% CI: 3.07%, 33.2%) per 1 unit WAZ reduction. Impact of the malnutrition-associated indicators on other pharmacokinetic parameters were not statistically significant (Figure 2).

The final model showed a satisfactory goodness-of-fit (Supplementary Figure 1) with a good predictive performance (Figure 1). Inter-individual variability of clearance and volume parameters were estimated close to zero and therefore removed in the final model. Eta shrinkages were generally low except for the mean absorption transit time (i.e. 53.2% for mean absorption transit time, 13.2% for bioavailability, and 24.4% for inter-compartmental clearance), and epsilon shrinkage was 18.0%. A numerical predictive check (n = 2,000) resulted in 1.85% (95% CI: 1.39%, 3.79%) and 3.01% (95% CI: 1.62%, 3.48%) of lumefantrine observations being below and above the simulated 95% prediction interval, respectively. Bootstrapping (1,000 re-sampled datasets) indicated a robust pharmacokinetic model with high precision in parameter estimates. Final primary and secondary pharmacokinetic parameter estimates of lumefantrine are summarised in Table 2 and Table 3, respectively.

Pharmacodynamic model

Observed parasite density at any of the weekly follow-up visits was back-extrapolated to the previous malaria-free visit, assuming an exponential parasite growth. The overall parasite growth rate was estimated to an 11-fold increase per asexual life cycle (48 hours). Thus, observed recurrent malaria was back-extrapolated to the starting interval of the blood stage infection (i.e. when parasites emerge from the liver). Children in the PK-PD arm and PD arm were combined and used for the development of the pharmacodynamic model. Weekly malaria screening identified 95 patients with a reinfection of malaria (median parasitaemia: 4,360 [95% CI: 80.0, 146,000]) who were

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included in the pharmacodynamic modelling. Four children with recrudescent malaria, 3 children with *P. vivax* infections, and 12 children lost to follow-up or with unidentifiable malaria species were excluded from the pharmacodynamic analysis. Thus, the pharmacodynamic analysis was based on 380 children. The final pharmacokinetic model and individual parameter estimates were fixed and added into the interval-censoring time-to-event model describing the risk of having a reinfection. A sigmoid E_{MAX}-function of the predicted lumefantrine concentrations improved the model fit significantly when compared to a model without antimalarial drug effect (ΔOFV = -62.3). No other covariates were found to have a significant impact in the pharmacodynamic model. A visual predictive plot of the interval-censoring time-to-event model exhibited an appropriate predictive performance of time to parasite breakthrough during a malaria reinfection, time to malaria detection, and the recurrent parasite density (Figure 3). Bootstrapping showed robust parameter estimates with acceptable relative standard errors (Table 2).

The *in vivo* minimum inhibitory concentration (MIC) of lumefantrine was estimated based on the predicted lumefantrine concentration at the start of new blood stage infection, using the same back-extrapolation methodology as described above. The 95th percentile of these predicted lumefantrine concentrations was assumed to be the highest possible concentrations which still allowed parasite replication. In the patients with recurrent malaria, the predicted MIC values were between 164 ng/mL and 182 ng/mL, based on the start and the end of the likely time period of new infection emerging from the liver (supplementary figure 3).

In silico lumefantrine dose optimisation

SAM children had on average 19.2% lower exposure to lumefantrine compared to non-SAM children in this study, and all children had substantially lower drug exposure compared to adults in previously reported literature (20). Based on the final population pharmacokinetic-pharmacodynamic model

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developed here, we proposed and evaluated three alternative dosing regimens (i.e. increased, intensified, and extended dosing regimens).

Pharmacokinetic exposure parameters (AUC, C_{MAX}, day-7 concentration) of the increased dose regimen were approximately equivalent to standard dosing, because of a relatively lower bioavailability of the increased dose (i.e. approximately half of that seen in children receiving standard dose). However, both the intensified and extended dosing regimens were able to increase the exposure to lumefantrine in SAM children to similar levels as that seen in non-SAM children receiving standard dosing (figure 4, supplementary figure 4). Nevertheless, lumefantrine exposure was overall low in children compared with adults, resulting in 98.4% of SAM children and 94.7% of non-SAM children having lower exposure than the reported median exposure in adult patients (20). The increased dose regimen exhibited negligible improvement in children because of dose-limited absorption. The intensified and extended dosing regimens resulted in 76.9% and 69.1%, respectively, of non-SAM children having a predicted exposure below median values reported in adults. A smaller improvement was seen in SAM children after intensified and extended dosing, resulting in 92.7% and 89.3%, respectively, of children having a predicted lower exposure compared to median values reported in adults.

Therapeutic efficacy could not be evaluated since only four patients presented recrudescent malaria in either groups during the 42 days of follow-up. However, time above MIC should be highly correlated to the risk of therapeutic efficacy since residual lumefantrine concentrations above the MIC value eliminate residual parasites to avoid recrudescent infections. Time above MIC was 8.05 (95% CI: 5.62, 28.9) days and 9.33 (95% CI: 6.60, 39.3) days for SAM and non-SAM children, respectively, after standard dosing. Time above MIC in SAM children could be expanded to 9.81 (95%

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CI: 6.67, 50.8) days and 12.3 (95% CI: 8.10, 52.0) days after the intensified and extended dosing regimens, respectively.

Pharmacodynamic protective efficacy of different dosing regimens was evaluated by the simulating the total incidence of malaria re-infections during the 42 days of follow-up (supplementary figure 5). Pharmacodynamic simulations using standard dosing predicted similar protective efficacy towards re-infections after artemether-lumefantrine treatment in SAM and non-SAM children (64.5% (95% CI: 57.7%, 71.5%) versus 67.3% (95% CI: 59.2%, 74.3%), respectively, being malaria free at day 42). The increased dose regimen did not improve the protective efficacy of artemether-lumefantrine because of similar exposure to lumefantrine. A moderate improvement in protective efficacy could be seen with an intensified and extended dosing regimens (supplementary table 1).

DISCUSSION

Comorbidity of malaria and malnutrition is common, reaching high prevalence in the Sahel region where acute malnutrition episodes among children under 5 years of age occur frequently during the malaria season. The review of the literature does not provide a clear picture of the effect of malnutrition on the malaria risk, but some studies show that malnutrition increases mortality due to malaria in children under 5 years of age (7). To our knowledge, this study comparing the pharmacokinetics and pharmacodynamics of lumefantrine in a population of malnourished and none-malnourished children under 5 years of age is the largest cohort reported in the literature to date. We demonstrated that drug exposure in children correlated with risk of reinfection. All investigated indicators of severe acute malnutrition (i.e. MUAC, WHZ, and WAZ) had a significant impact on the absorption of lumefantrine. MUAC was significantly associated with decreased relative bioavailability of lumefantrine (23.8% decrease per 1 cm reduction).

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The pharmacokinetic properties of lumefantrine were explained by a two-distribution compartment model, which is similar to what has been reported previously (24). Delayed lumefantrine absorption has been reported previously (25, 26), and the present data was best described by a two-transit compartment absorption model to mimic this delay in drug absorption along the gastrointestinal tract (20, 27). The absolute bioavailability cannot be estimated using oral data alone, but it allows for estimating the relative difference in bioavailability between patients (i.e. inter-individual variability). A Box-Cox transformed distribution of the relative bioavailability was implemented in the final model, which is identical to previously published findings (20). The estimated negative shape parameter of the Box-Cox distribution indicated a left-skewed distribution of the absorption parameter, which is likely to be explained by the dose limited absorption of lumefantrine (19, 20). Several pharmacokinetic studies have characterised the pharmacokinetic properties of both the lumefantrine and the metabolite desbutyl-lumefantrine (23, 25, 27, 28). However, in the present study the metabolite was not measured and only the pharmacokinetics of the parent drug were analysed.

Even though only 6.26% of samples were below LLOQ, different methods were evaluated to incorporate these samples (29). LLOQ data were omitted (M1 method) in a previous publication, but we evaluated the M1, M3, and M6 methods in the present analysis to avoid any potential censoring bias. Indeed, the predicted fraction of samples below the LLOQ was under-predicted using both the M1 and the M3 method. However, the M6 method showed a good predictive performance as illustrated in figure 1 and was used in the final model.

Allometrically scaled body weight on all clearance and volume parameters, and an enzyme maturation effect were included in the final model due to prior knowledge and a strong biological

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support (20, 30). Covariates associated with severe acute malnutrition (MUAC, WHZ) and severe underweight (WAZ) were investigated both with a stepwise approach and a full covariate approach. All three of these were highly correlated and affected the pharmacokinetic parameters in the same direction (figure 2), both in the stepwise approach and in the full covariate approach, probably due to the strong correlation between these covariates (Supplementary Figure 2). Both of these analyses suggested that the bioavailability is reduced with an increase in malnutrition severity. The stepwise covariate modelling showed that MUAC (on the relative bioavailability) was the most significant covariate and was retained in the final model. Artemether-lumefantrine was administered together with milk (2.5 g of fat) for non-SAM children and together with ready-to-used therapeutic food (RUTF, 32.9 g of fat) to SAM children, and a small amount of fat (1.2 g) has been shown to enhance the exposure of lumefantrine up to 90% compared to when administered to fasting subjects (19). Thus, the administered fat content should maximise the absorption of lumefantrine in both SAM and non-SAM children. Therefore, the co-administration of RUTF to SAM children should guarantee an optimal absorption and excludes this as an explanation why SAM children had a lower bioavailability. Several reasons could explain lower bioavailability in SAM children and several physiological changes have been identified in the gastrointestinal tract in malnourished individuals, for example anorexia, vomiting, diarrhoea, hypochlorhydria, mucosal atrophy, delayed gastric emptying, pancreatic dysfunction, and alterations in the intestinal micro-ecology (5, 6).

Re-infections with *P. falciparum* malaria were used as the pharmacodynamic endpoint, in order to describe the protective effect of lumefantrine. Only a few patients showed recrudescent malaria (i.e. treatment failure) and they were therefore excluded from the pharmacodynamic analysis. In addition, *P. vivax* infections have a different mechanism compared to *P. falciparum* infections and these patients were excluded from the analysis. Both the PK-PD and the PD arm were included into the pharmacodynamic data analysis and modelled simultaneously to maximise the amount of data.

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Commonly, time-to-event models are used to describe the time to malaria detection and to quantify the impact of drug concentration by linking the pharmacokinetic model with a pharmacodynamic E_{MAX}-model. However, the estimated IC_{50} in such models will under-predict the true IC_{50} value since the model assumes that the recurrent malaria appears exactly on the day of the follow-up visit. In reality, the blood stage infection started several days before the time of microscopy detection and the parasites have managed to growth through whatever drug concentrations that were present at that time. Bergstrand *et al* (31, 32) suggested that the pharmacodynamic model should be based on the possible starting time interval of the malaria erythrocytic stage by back-extrapolating the measured parasite density at malaria re-infection using the parasite growth rate. The interval censoring time-to-event model should then be able to estimate an IC_{50} closer to the true value. Therefore, the present study took this into account by determining the likely time of the emergence of the blood stage malaria infection and used this time interval as the event time. Observed parasite density at re-infection and the individual microscopic detection limit were used to determine the individual parasite growth rate. However, the average or median of estimated individual growth rates will not represent the true growth rate in the population since an estimated slow parasite growth rate might be a result of a recent infection or a lower parasite density than the individual detection limit at the previous malaria-free visit. Therefore, it is expected that the true population value is skewed towards the higher estimated growth rates. Thus, the overall parasite growth rate in the population was defined by the 95th percentile of individually estimated parasite growth rates, resulting in an 11-fold increase in parasite densities per asexual reproductive cycle (48 hours). This value is close to what would be expected from historical data (33, 34). By modelling the starting time of the erythrocytic stage, the lumefantrine concentrations at the time of the emerging *P. falciparum* parasites were predicted, and thus provided insight into the clinical MIC values in this population. The predicted MIC values were between 164 ng/mL and 182 ng/mL, which is similar to previously reported cut-off day 7 values associated with therapeutic efficacy.

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The visual predictive check of the pharmacokinetic-pharmacodynamic model (figure 4B) supported the interval-censoring time-to-event model and showed a good prediction of the time to malaria detection. The final pharmacodynamic model and parameter estimates, including IC_{50}, from this study were similar with a previous report studying Thai women infected with *P. falciparum* (25). The baseline hazard in the present study was slightly higher, probably because this study was conducted in an area with higher endemicity, while the previous study was conducted in a low transmission area (Thailand). Malnutrition was not a significant covariate in the pharmacodynamic model, probably because it was already incorporated in the pharmacokinetic model.

This study showed that malnourishment had a dramatic effect on the absorption of lumefantrine when given to children. This threatens our ability to treat malaria in this group, as it will result in inadequate exposure to lumefantrine in SAM children. Alternative dosing regimens were evaluated using *in silico* dose optimisation. Due to the dose limited absorption of lumefantrine, an increased dose regimen could not compensate fully for the lower exposure observed in SAM children (20). However, both the intensified regimen (thrice daily for 3 days), and the extended regimen (twice daily for 5 days) of artemether-lumefantrine in SAM children resulted in equivalent exposures in non-SAM and SAM children (figure 4). This resulted in an expanded time above MIC and slightly higher protective efficacy (supplementary figure 4, supplementary table 1).

In conclusion, the population pharmacokinetic properties of lumefantrine in this study was successfully explained by a two-compartment disposition model with two transit-compartments in the absorption phase. Body weight as an allometric function and age as an enzyme maturation effect were included into the pharmacokinetic model. Malnutrition had a significant impact on the absorption of lumefantrine, resulting in substantially lower drug exposure with increasing

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malnutrition. A parasitaemia-corrected time-to-event model was developed to explain the post-treatment prophylactic effect of lumefantrine against malaria reinfections. Research on altered dosing regimens should be considered for optimal treatment of malaria in malnourished children.

METHODS

Study design

An open comparative intervention study was conducted to determine the clinical efficacy and pharmacokinetic-pharmacodynamic properties of lumefantrine in African SAM (N=133) and non-SAM children (N=266). A subset of the whole study was chosen to be part of the pharmacokinetic study (N=131 for SAM children and N=160 for non-SAM children). Details on the study protocol as well as the clinical efficacy and safety have been published previously (35, 36). This study was conducted at two hospitals, the Oulessebougou district hospital, Koulikoro region, Mali, and at the primary healthcare centre on Andoume, Maradi city, Niger. Two identical versions of the protocol were prepared, a French protocol that was approved by the Ethics Committee of the Faculty of Medicine and Odonto-Stomatologie and the Faculty of Pharmacy in Bamako, Mali (number 2O13/93/CE/FMPOS) and Niger National Ethics Committee of the Ministry of Health (number 004/2014/CCNE), and an English version which was approved by MSF Ethical Review Board. The study was registered at Clinicaltrial.gov (registration number: NCT01958905, registration date: 7 October 2013). Only children whose parents or guardians provided a written informed consent was enrolled in this study.

Children aged between 6 to 59 months with uncomplicated *falciparum* malaria were eligible for enrolment in this study. According to WHO criteria of SAM, children with WHZ < -3 and/or MUAC < 115 mm were classified as SAM. Two misclassified children without SAM condition were later

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enrolled to the non-SAM group. Children with kwashiorkor, severe stunting (severe chronic malnutrition, height-for-age z-score; HAZ < -3), severe anaemia, known underlying or chronic diseases, and other complications requiring hospitalization were excluded from the study.

Fixed-dose combination tablets of non-dispersible artemether 20 mg and lumefantrine 120 mg (Coartem® Novartis; Basel, Switzerland) were given according to the weight-based manufacturer recommended dose (1 tablet < 15 kg and 2 tablets 15-25 kg), twice daily for three days. Study drugs were administered with fat, i.e. one glass of milk (approximately 250 mL containing 2.5 g of fat) in the non-SAM group, and ready-to-used therapeutic food (RUTF; Plumpy'Nut®, one bag of 92 g containing 32.9 g of fat) in the SAM group. If the children vomited within 30 minutes of dose administration, a repeat dose was administered. If the children vomited after the second dose, they were given rescue oral medication (artesunate-amodiaquine fixed-dose formulation; ASAQ Winthrop®, Geneva, Switzerland) and were excluded from the study.

Drug quantification

A population-based sparse sampling approach was used to limit the number of PK samples required per child (37). For each child, five capillary blood (50 µL) samples were collected; the first at one of the following randomly allocated times: 6, 12, 24, 36 or 48 hours, the second at hour 60, the third at hour 72, the fourth at day 7, and the fifth at either day 14 or day 21 (randomly allocated) post-treatment initiation. Each blood sample was transferred onto pre-treated (0.75 M tartaric acid) filter paper (Whatman 31 ET Chr). The filter paper spots were left to dry unaided at room temperature and then sealed in individual plastic bags with desiccant and stored at room temperature away from heat and excessive light until sent to the Division of Clinical Pharmacology, University of Cape Town, South Africa, for drug measurement. Dry blood spot concentrations of lumefantrine were measured

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using solid phase extraction followed by liquid chromatography coupled with tandem mass spectrometry. Quality control samples at low, medium and high concentrations (100, 4000 and 8000 ng/mL, respectively) were analysed in duplicate within each batch of study samples to ensure accuracy and precision of the drug assay. The combined accuracy (%Nom) were between 96.2% and 105.3%, and precision (%CV) between 1.8% and 10.6%, for the low, medium, and high quality controls, respectively. The lower limit of quantification (LLOQ) of the assay was set to be 39.1 ng/mL.

Pharmacokinetic-pharmacodynamic analysis

Lumefantrine capillary blood concentrations were transformed into their natural logarithms and analysed using nonlinear mixed-effects modelling in NONMEM version 7.3 (Icon Development Solution, Ellicott City, MD). Pirana version 2.9.0 (38), Perl-speaks-NONMEM version 4.6.0 (PsN) (39), and Xpose version 4.0 (40), were used for automation, model evaluation, and diagnostics during the model building process. The final pharmacokinetic model was fixed and individual estimates imputed into the exposure-response model. Time-to-malaria reinfection during the 42-days of follow-up was described using an interval-censoring time-to-event model. Pharmacodynamic data were modelled using the Laplace estimation method with interactions. Biologically plausible covariates (i.e. SAM status, WAZ, WHZ, HAZ, MUAC, age, BMI, and body weight) were evaluated in the pharmacokinetic and pharmacodynamic models. Details of the data analyses, model diagnostics, and *in silico* lumefantrine dose optimisation can be found in the SI methods.

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STUDY HIGHLIGHTS

What is the current knowledge on the topic?

☑ Artemether-lumefantrine (Coartem®) is the most prescribed antimalarial drug worldwide. However, exposure to lumefantrine is lower in children compared to adults with standard dosing recommendations. Moreover, altered physiological properties in children with severe acute malnutrition (SAM) might reduce drug absorption and further contribute to sub-therapeutic exposures. Hitherto, the pharmacology of lumefantrine has been poorly defined in malnourished children, and its population pharmacokinetic properties have not been studied previously in SAM children. In addition, a lack of pharmacokinetic-pharmacodynamic information on antimalarial drugs, when given to malnourished patients, makes it very difficult to dose these children adequately.

What question did this study address?

☑ What is the population pharmacokinetic and pharmacodynamic properties of lumefantrine in the SAM children?

What does this study add to our knowledge?

☑ This study is the first population pharmacokinetic-pharmacodynamic study of lumefantrine in the SAM children. Evidently, all malnutrition indicators (i.e. mid-upper arm circumference, weight-for-height z-score, and weight-for-age z-score) influenced the pharmacological properties of lumefantrine in a similar way. The mid-upper arm circumference was the most significant covariate, resulting in substantially reduced absorption of lumefantrine with increasing malnourishment (23.8% decreased absorption per 1 cm reduction in mid-upper arm circumference). Lower exposure

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to lumefantrine resulted in an increased risk of acquiring a new *P. falciparum* infection during the follow-up period.

How might this change clinical pharmacology or translational science?

☑ This work allows for an in-depth understanding of the differences in pharmacokinetics and pharmacodynamics between the SAM children and well-nourished children. SAM children achieved a significantly lower exposure to lumefantrine than normal children. Lumefantrine dose optimization is needed urgently in this population.

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We sincerely thank all children and their parent/guardians for their participation in completing this study. We also thank community leader, the managing boards of health facilities, and the diligent staff from the Oulessebougou district hospital in Mali and the primary healthcare centre of Andoume in Niger. We dedicate this publication to the memory of Professor Ogobara Doumbo, founder and leader of the Malaria Research and Training Center in Bamako. He passed away prematurely during the course of this study on June 2018 after devoting his whole life to malaria research.

AUTHOR CONTRIBUTIONS

P.C., R.H., and J.T. wrote the manuscript; L.D.N., E.B., O.G., O.K.D., K.I.B., A.D., and J.F.E. designed the research; L.D.N., E.B., O.G., H.D., O.A., M.S., P.J.G., and O.K.D. performed the research; P.C. and J.T. analyzed the data; L.W. and K.I.B. contributed new reagents/analytical tools.

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FIGURE LEGENDS

Figure 1. Simulation-based diagnostics for the final population pharmacokinetic model of lumefantrine. Prediction-corrected visual predictive check. Open circles represent lumefantrine concentrations in SAM children and open triangles represent lumefantrine concentration in non-SAM children. Solid line represents the 50th percentile of the observations, and dashed lines represent the 5th and 95th percentiles of the observations. Grey areas represent the 95% confidence intervals of the simulated percentiles. Horizontal dashed line represents the lower limit of quantification of lumefantrine (39.1 ng/mL). The bottom panel represents the visual predictive check of the data below the limit of quantification. Dashed line represents the observed proportion of LLOQ samples, and the shaded area represents the simulated 95% prediction interval of the proportion of LLOQ samples.

Figure 2. Effect of malnutrition descriptors on the pharmacokinetic parameters of lumefantrine. The graphs show the relative difference in pharmacokinetic parameter estimates in SAM and non-SAM children (A), and change in pharmacokinetic parameters estimates per 1-cm mid upper arm circumferences (MUAC) reduction (B), and per 1 WAZ reduction (C). Y-axes represent the change (%) in each pharmacokinetic parameter associated with altered malnutrition status, calculated from 1,000 bootstraps of the full covariate models. The shaded areas represent a covariate effect of ±25%, assumed to be clinically insignificant.

Figure 3. Simulation-based diagnostics for the interval-censoring time-to-event model of lumefantrine in SAM and non-SAM children. (A) time-to-blood stage parasitaemia and (B) time-to-malaria diagnostics. Black solid lines represent the observed Kaplan-Meier plots. Shaded areas represent the simulated 95% prediction intervals from the final pharmacodynamic model.

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Figure 4. *In silico* lumefantrine dose optimisation in SAM and non-SAM children.

Boxes and whiskers represent the median with inter-quantile range and the 95% prediction intervals, respectively. Horizontal dashed lines in panel (A) represent the median day 7 lumefantrine concentration after standard dosing regimen in non-pregnant adult patients (801 ng/mL) (20). The dotted (200 ng/mL) and dashed-dotted (175 ng/mL) lines in panel (A) represent the previously defined day 7 lumefantrine concentrations associated with therapeutic efficacy (21, 41). Grey areas in panel (A) represent the predicted clinical MIC value between 164 ng/mL and 182 ng/mL. Horizontal dashed lines in panel (B) and (C) represent the median lumefantrine exposure (AUC; 647,025 hr $\times$ ng/mL) and maximum concentration (C_{max}; 6,731 ng/mL) after standard dosing in non-pregnant adult patients (20).

SUPPLEMENTARY MATERIALS

(Supplemental Material)

Supplemental Material

- **Supplementary methods**
- **Figure S1**
- **Figure S2**
- **Figure S3**
- **Figure S4**
- **Figure S5**
- **Table S1**
- **Supplementary references**

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Table 1 Baseline characteristics of study patients.

	PK-PD arm		PD arm
	SAM	**Non-SAM**	**Non-SAM**
Total no. of children	131	160	108
Total no. of PK samples	642	700	NA
Total dose of artemether (mg/kg)	17.6 (10.8, 23.7)	11.4 (8.06, 17.6)	13.3 (6.57, 19.4)
Total dose of lumefantrine (mg/kg)	105 (64.8, 142)	68.2 (48.3, 106)	80.0 (39.4, 116)
Total no. of *P. falciparum* reinfection cases	34/131 (23.7%)	61/160 (38.1%)	11/108 (10.1%)
Continuous and categorical covariates at admission			
Age (months)	15 (6.3, 39)	27 (8.0, 53)	24 (7.0, 55)
Axillary temperature at admission (ºC)	38.0 (36.8, 39.7)	38.2 (36.8, 39.7)	37.9 (36.2, 40.0)
Number of male patients (%)	50.4% (66/131)	46.9% (75/160)	42.6% (46/108)
Initial parasitaemia (no. of parasite/µL)	11040 (1092, 154820)	10780 (1121, 152878)	12000 (1058, 123825)
Anthropometric characteristics			
Body weight (kg)	6.78 (5.07, 10.5)	10.9 (6.84, 15.9)	9.30 (6.20, 15.7)
Height (cm)	73.2 (64.0, 94.2)	85.0 (67.6, 107)	81.0 (66.9, 103)
Body mass index (kg/m^2)	12.5 (11.0, 13.6)	14.7 (12.8, 17.0)	14.4 (12.3, 17.4)
Weight-for-height z-score (WHZ)	-3.52 (-4.95, -2.60)	-1.07 (-2.58, 0.759)	-1.46 (-3.10, 1.23)
Weight-for-age z-score (WAZ)	-3.40 (-4.46, -2.08)	-1.30 (-3.04, 0.560)	-1.64 (-3.62, 0.308)
Height-for-age z-score (HAZ)	-1.67 (-2.91, 0.815)	-1.27 (-2.99, 1.56)	-1.31 (-3.15, 1.65)
Mid-upper arm circumferences (MUAC, mm)	116 (104, 131)	140 (122, 163)	133 (118, 163)

All values are given as median (95% confidence interval) unless otherwise indicated.

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Table 2 Parameter estimates from the final population pharmacokinetic and pharmacodynamic model of lumefantrine in children with severe acute malnutrition.

	[a] Population estimates ([c] %RSE)	[b] Bootstrapping median (95% CI)	[a] %CV of BSV ([c] %RSE)	[b] Bootstrapping median (95% CI) for BSV
Pharmacokinetic parameters				
F (%)	1 (fixed)	NA	64.0% (7.08%)	63.9% (52.2%, 76.9%)
Box-Cox on F	-0.373 (54.5%)	-0.373 (-0.742, 0.205)	NA	NA
MTT (h)	3.48 (11.7%)	3.48 (2.52, 4.35)	192% (8.88%)	192% (104%, 259%)
CL/F (L/h)	2.34 (6.25%)	2.34 (2.20, 2.81)	NA	NA
V_C/F (L)	110 (4.46%)	110 (101, 123)	NA	NA
Q_P/F (L/h)	1.10 (8.10%)	1.10 (0.942, 1.33)	67.8% (7.69%)	67.8% (54.0%, 82.2%)
V_P/F (L)	872 (13.9%)	872 (635, 1200)	NA	NA
σ	0.339 (5.20)	0.339 (0.265, 0.426)	NA	NA
Covariates				
TM_{50} (months)	2.91 (31.5%)	2.91 (2.86, 5.98)	NA	NA
α	1 (fixed)	NA	NA	NA
MUAC on F (% per 1 cm)	25.4% (5.24%)	25.4% (21.3%, 27.1%)	NA	NA
Pharmacodynamic parameters				
BASE (reinfections per year)	5.25 (11.8%)	5.58 (4.19, 6.85)	NA	NA
IC_{50} (ng/mL)	156 (12.1%)	156 (141, 214)	NA	NA
γ	4.77 (38.8%)	4.90 (2.30, 9.78)	NA	NA

Abbreviations: F, relative bioavailability; Box-Cox on F, Box-Cox transformation value of F; MTT, mean transit time; CL/F, oral clearance; V_C/F, apparent volume of distribution of the central compartment; Q_P/F, inter-compartment clearance; V_P/F, apparent volume of distribution of the peripheral compartment; σ, residual error variance of lumefantrine concentrations; TM_{50}, enzyme maturation half-life; α, slope factor for enzyme maturation effect; MUAC, mid-upper arm circumferences; BASE, baseline hazard rate; IC_{50}, lumefantrine 50% inhibitory concentration; and γ, slope-factor for the drug effect.[a] Computed population mean parameter estimates from NONMEM were calculated for a typical individual with a body weight of 9.62 kg. The coefficient of variation (%CV) for the between-subject variability was calculated as $100 \times \sqrt{(\omega^2) - 1}$.

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[b] Computed from 1,000 nonparametric bootstraps and presented as 2.5th to 97.5th percentiles of estimates.

[c] Calculated as $100 \times \frac{\text{standard deviation}}{\text{mean value}}$

Table 3 Secondary parameter estimates of lumefantrine in SAM and non-SAM children.

	[a] SAM children (n=131)	[a] Non-SAM children (n=160)	[b] p-value
C_{MAX} (ng/mL)	2900 (592, 7180)	3360 (1120, 7750)	0.0007
T_{MAX} (h)	5.69 (3.91, 13.1)	5.69 (3.79, 14.4)	0.9214
$t_{1/2}$ (days)	3.10 (1.92, 6.43)	3.54 (1.97, 6.78)	0.0006
Day-7 concentrations (ng/mL)	222 (51.8, 730)	300 (67.5, 798)	<0.0001
$AUC_{0\text{-}28\ days}$ (h×µg/mL)	262 (54.4, 661)	316 (78.7, 756)	0.0003

Abbreviations: SAM, severe acute malnutrition; C_{MAX}, maximum concentration; T_{MAX}, time to maximum concentration; $t_{1/2}$, terminal elimination half-life; Day-7 concentrations, lumefantrine capillary blood concentrations 7 days after the first dose; $AUC_{0\text{-}28\ days}$, area under the concentration-time curve from time zero to 28 days.

[a] Median secondary parameter estimates (95% confidence intervals) were obtained from the Bayesian *post hoc* estimates of the final population pharmacokinetic model.

[b] p-values were calculated using the Mann-Whitney U test.

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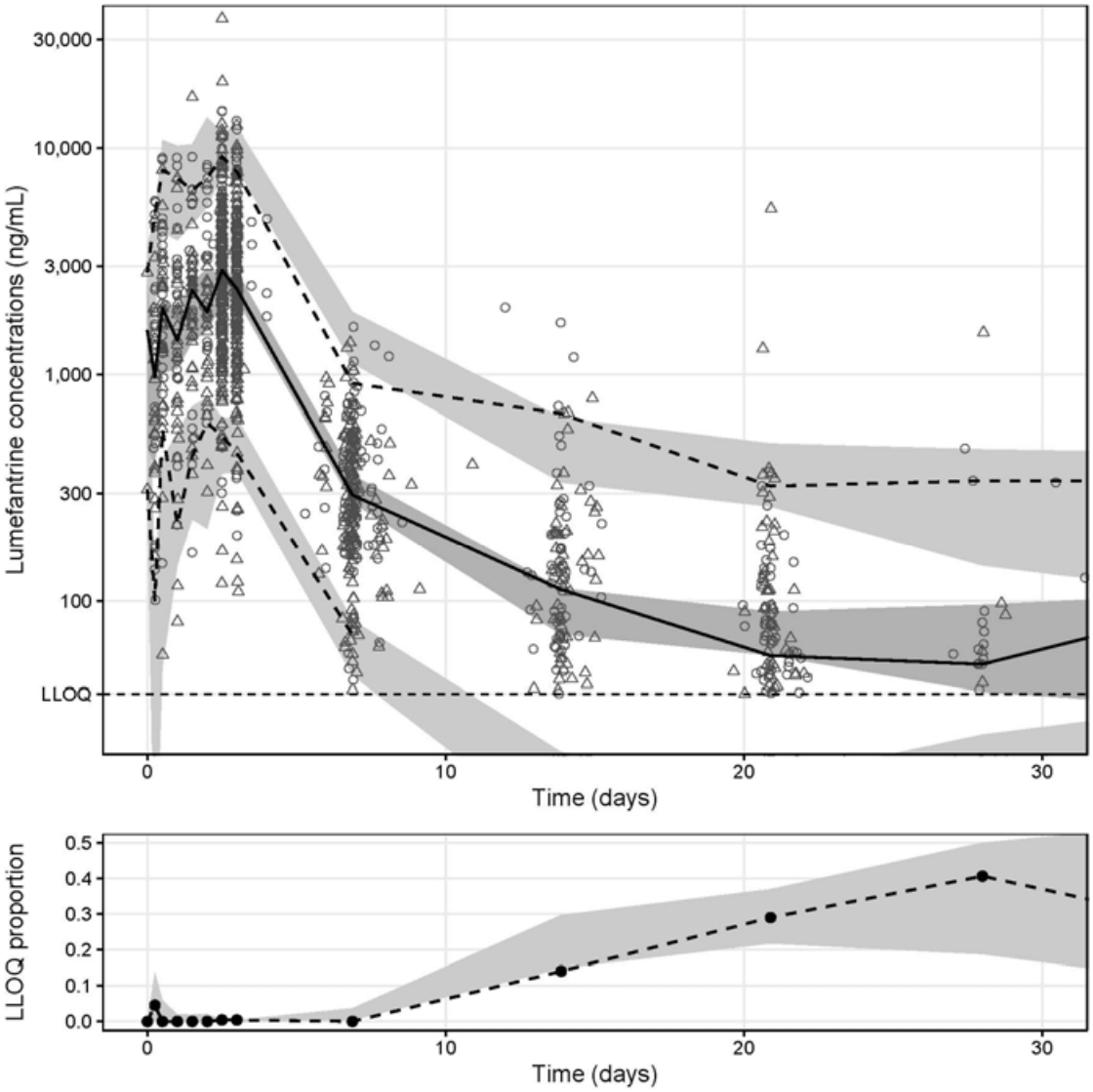

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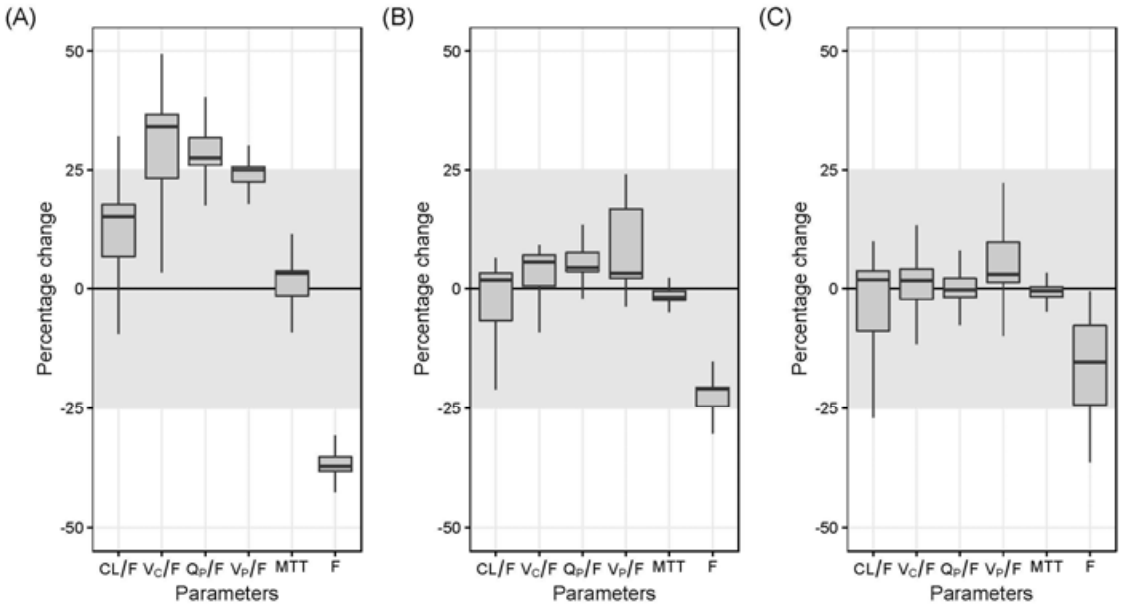

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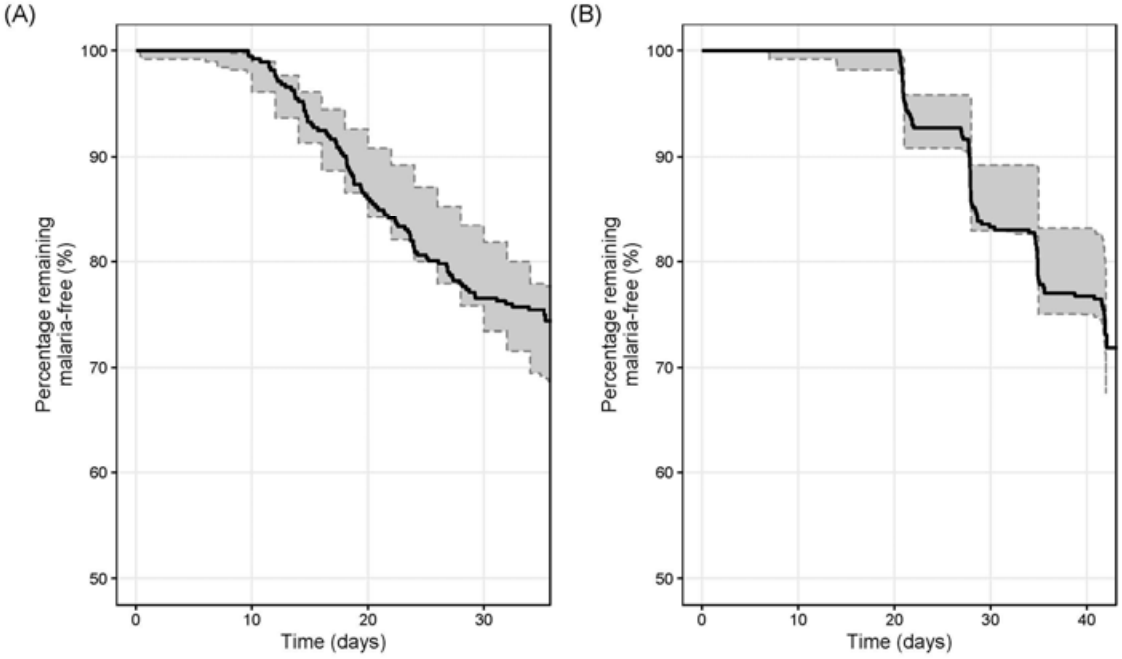

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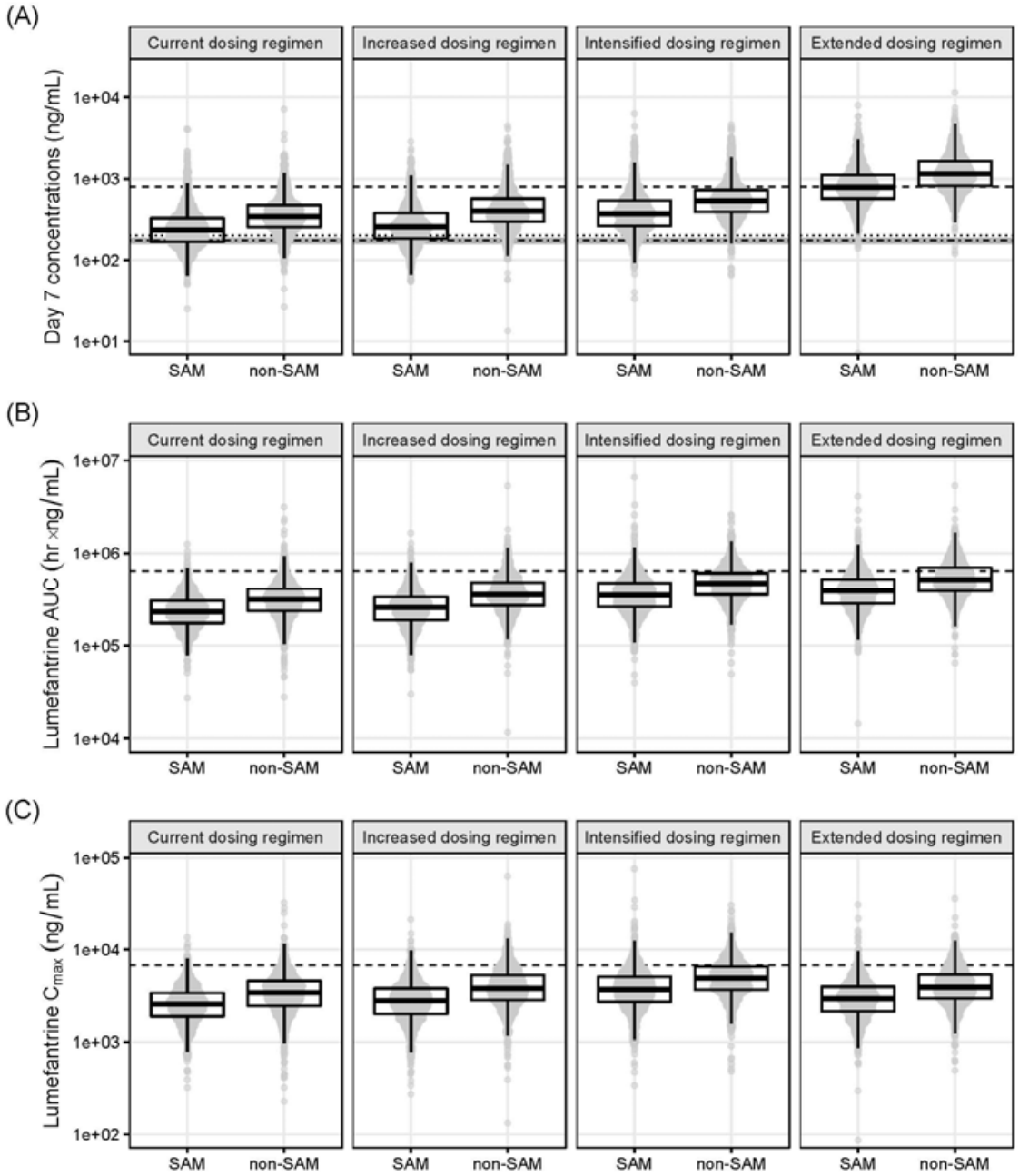

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