Pharmacokinetics of two paediatric artesunate–mefloquine drug formulations in the treatment of uncomplicated falciparum malaria in Gabon

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Objectives: Paediatric drug formulations of artemisinin combination therapies and pharmacokinetic data supporting their use in African children are urgently needed for the effective treatment of young children suffering from falciparum malaria in sub-Saharan Africa.

Patients and methods: In this study, the pharmacokinetic characteristics of a novel paediatric granule formulation of artesunate–mefloquine therapy were evaluated in comparison to the standard tablet formulation in the treatment of uncomplicated malaria in paediatric patients. Twenty-four patients were assigned to treatment according to body weight with either a fixed-dose paediatric granule co-formulation (10–20 kg body weight) or a free-dose co-blister tablet formulation of artesunate–mefloquine (>20–40 kg body weight).

Results: Median values for $C_{\text{max}}$ (861 and 930 ng/mL), $T_{\text{max}}$ (1.5 and 1.5 h) and AUC$_{0-\text{t}}$ (2050 and 2470 ng.h/mL) were comparable for dihydroartemisin in the two groups. Exploratory analysis of mefloquine plasma levels revealed a trend towards higher concentrations in the younger age group during the absorption phase (2550 and 1815 ng/mL, 54 h after initiation of treatment, respectively). Median mefloquine concentrations at day 28 were 197 and 343 ng/mL, respectively.

Conclusions: The pharmacokinetic characteristics of the two paediatric dosage forms, i.e. the novel fixed-dose co-formulation and the standard co-blister of artesunate–mefloquine show comparable results in the two treatment groups. The novel fixed-dose paediatric formulation is an interesting option for outpatient treatment of uncomplicated malaria in African children.

Keywords: malaria, Plasmodium falciparum, PK, Africa

Introduction

African children suffer the highest morbidity and mortality attributed to malaria worldwide. Current WHO guidelines for the treatment of uncomplicated falciparum malaria recommend the use of artemisinin-containing combination regimens.1 Artesunate–mefloquine was historically the first representative of novel artemisinin combinations and for more than one decade, it has remained a highly successful therapeutic regimen in regions harbouring the most resistant isolates worldwide.2,3 The use of artesunate–mefloquine as antimalarial therapy for African children was first precluded because of sparse data on

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safety and tolerability in this target population and the lack of paediatric drug formulations. Furthermore, no data on the pharmacokinetics of artesunate–mefloquine combination therapy supporting their use in African children were available.

Recently, an innovative galenic co-formulation of artesunate–mefloquine was developed for the treatment of paediatric patients. The drug combination is formulated as granules, which may be administered directly into the mouth of the patient. Taste-masking of active ingredients with mango flavour and a slippery consistency of the drug formulation are further characteristics for improved acceptability by paediatric patients. This novel drug formulation is a line extension of mefloquine–artesunate co blister tablet formulations developed by Mepha Ltd, with varying strengths of mefloquine. Following a recent change in recommendations of WHO for areas of high malaria transmission, the total mefloquine dosage in the co blister tablet formulation and the novel paediatric formulation was increased to 25 mg/kg body weight.

In this study, we evaluated two paediatric drug formulations—the co blister artesunate–mefloquine tablet formulation (Artequin 300/750) and the novel fixed-dose paediatric co-formulation (Artequin Paediatric)—in the treatment of uncomplicated falciparum malaria in African children. It was the first use in humans and the first clinical evaluation of the fixed-dose paediatric drug formulation. Here, we report on the pharmacokinetic characteristics of artesunate–mefloquine therapy in a subgroup of 24 patients participating in the extended pharmacokinetics protocol.

Materials and methods

The study was conducted at the Medical Research Unit of the Albert Schweitzer Hospital, Lambaréné and the Department of Paediatrics at the Centre Hospitalier de Libreville, from October 2005 to February 2006. Gabon is characterized by high perennial malaria transmission and local strains of Plasmodium falciparum are highly resistant to chloroquine in vitro and in vivo. Mefloquine is still active against P. falciparum isolates in vitro and in vivo despite the rare occurrence of borderline resistant isolates.

The study was designed as an open label, stratified clinical trial assessing the efficacy, tolerability, safety and pharmacokinetics of two paediatric formulations of artesunate–mefloquine. Treatment allocation of patients was based on body weight (group A 10–20 kg and group B >20–40 kg). Antimalarial treatment in group A was the novel fixed-dose paediatric formulation of artesunate–mefloquine, whereas patients in group B received the paediatric dose of standard co blister tablets. The first 12 patients of each cohort who were eligible for pharmacokinetic analysis were included in the pharmacokinetic protocol at the Medical Research Unit of the Albert Schweitzer Hospital. The study was approved by the Ethics Committee of the International Foundation for the Albert Schweitzer Hospital in Lambaréné and written informed consent was obtained from all study participants legal representatives. The study protocol was registered prior to recruitment at clinicaltrials.gov (NLM identifier NCT00243737).

Patients presenting with symptomatic P. falciparum infection were eligible for this study if the following inclusion criteria were met: peripheral asexual P. falciparum parasitaemia between 1000 and 250 000 per µL of blood, fever (≥37.5 °C) or history of fever in the last 48 h, haemoglobin ≥7 g/100 mL blood. Exclusion criteria were the presence of any of the following criteria: signs or symptoms of severe malaria; known hypersensitivity or allergy to artemisinin derivatives, mefloquine, or related compounds; adequate antimalarial treatment within 1 week prior to inclusion; administration of quinine or artemisinin derivatives at any dose within 12 h prior to inclusion; known history of psychiatric disorders, cardiac diseases, arrhythmia, sickle cell disease; clinical signs or laboratory evidence of any other severe underlying disease; pregnancy or lactation.

Study flow

Demographic characteristics, physical examination and medical history were obtained at admission. Investigations comprised electrocardiography, measurement of oral temperature, biochemistry, haematology, vital signs and thick blood smear. Follow-up assessments of parasitaemia and temperature were performed every 12 h until resolution. Weekly follow-up visits were scheduled until day 28.

Study drugs

Artesunate–mefloquine was administered orally once daily for 3 days at the nearest approximation of a daily dose of 4 and 8 mg/kg body weight for each group, respectively. The novel fixed-dose paediatric formulation (Artequin Paediatric, Mepha Ltd, Aesch, Switzerland) was used for group A (body weight from 10 to 20 kg). Each co blister package consists of one tablet artesunate and one tablet mefloquine, containing 100 and 250 mg of active substance, respectively. Patients in group B were treated with one co blister package once daily for 3 days. Study drugs were administered with a glass of water under the supervision of a study physician.

Blood sampling and pharmacokinetic analysis

The aim of the analysis was to evaluate standard pharmacokinetic parameters for dihydroartemisinin, the major metabolite of artesunate, and to evaluate the concentration of mefloquine at four predefined time points. These included the absorption phase in which time mefloquine supports artesunate in eliminating the parasites as well as the plasma concentration at the end of the follow up period, bridging the period of prophylactic efficacy. For each sample, 4 mL of blood was drawn from the cubital vein in lithium heparinized tubes. Owing to the young age of our study participants, the quantity and frequency of blood draws for pharmacokinetic analysis were reduced to the minimal acceptable amount. Blood sampling for dihydroartemisinin was scheduled for the following time points on the first day of treatment: before and 30, 60, 90, 120, 240 and 360 min after drug administration. Blood samples for mefloquine analysis were obtained prior to study drug administration and 6 h, 54 h and 28 days after drug intake. Plasma was stored at −80 °C immediately after centrifugation of blood samples.

Dihydroartemisinin was extracted prior to analysis by solid-phase extraction (Inertsil ODS 10 µm extract column; Knauer, Mainz, Germany). Plasma concentrations were obtained by HPLC and tandem mass spectroscopy (API 2000; Applied Biosystems/MD S Sciex, Foster City, CA, USA). Artemisinin was used as internal standard.
Pharmacokinetics of artesunate–mefloquine therapy

standard. Mefloquine was extracted from plasma samples (Perisorb RP-2 extraction column; Merck, Darmstadt, Germany) before measurement by HPLC with UV detection (UV-2075, Jasco; 222 nm). The lowest concentration quantified by the system was 10 ng/mL plasma for dihydroartemisinin and mefloquine (inter-assay repeatability coefficient 4.7% to 6.2% and 1.1% to 4.2%, respectively).

Assessment of classic pharmacokinetic parameters was sought for dihydroartemisinin. These were the observed maximum plasma concentration ($C_{\text{max}}$), time to $C_{\text{max}}$ ($T_{\text{max}}$), elimination constant $\lambda_z$, which was estimated for each individual from at least three concentration–time points, terminal elimination half-life ($t_{1/2}$) calculated as $\ln 2/\lambda_z$, the area under the plasma concentration–time curve to the last sample with quantifiable drug concentration (AUC$_{0-z}$) and AUC extrapolated to infinity (AUC$_{z,\infty}$). The elimination constant $\lambda_z$ was computed by log-linear regression employing the method of least squares. Mefloquine analysis was restricted to the assessment of plasma levels at respective time points due to the limited number of scheduled blood draws. Pharmacokinetic analysis of plasma samples was computed with standard non-compartmental methods.

Data management and statistical analysis

Data were captured on paper case record forms. Double data entry and additional manual review were performed prior to closure of the database. Descriptive statistics and linear regression analysis of mefloquine drug concentrations were performed. Comparisons of groups were performed using non-parametric tests (Wilcoxon Rank Sums Test; JMP 5.0, SAS Institute Inc., NC, USA). The association of potential confounding variables on peak plasma concentrations was evaluated by multivariate regression analysis. Correlation analysis of dihydroartemisinin and mefloquine plasma concentrations was analysed by non-parametric correlation analysis (Spearman’s rho).

Results

Study flow

Seventy-one patients were enrolled in this clinical trial: 41 in group A and 30 in group B, respectively. Twelve patients of each group participated in the pharmacokinetics protocol. One patient in group A was withdrawn from the study and treated with rescue medication due to repeated vomiting on the first day of treatment. He was excluded from pharmacokinetic analysis and replaced by an additional patient.

Baseline characteristics of the study population were similar in both treatment groups (Table 1) and not different from the total study population (data not shown). Patients in treatment group A were of younger age, less weight and therefore lower body mass index and body surface area following inclusion criteria. Biochemical markers for renal and hepatic function were within the expected range for paediatric patients suffering from uncomplicated *Plasmodium falciparum* malaria. The effective mean total dose of arsensate was 10.1 ($\pm$2.2; range: 7.9–13.4) and 11.0 ($\pm$2.2; range: 8.1–14.3) mg/kg body weight in treatment groups A and B, respectively. Mefloquine was administered at a mean total dose of 25.1 ($\pm$3.9; range: 19.7–33.5) and 27.6 ($\pm$5.4; range: 20.3–35.7) mg/kg body weight over a 3 day period. There was no clinical or parasitological treatment failure in this study population up to day 28.

<table>
<thead>
<tr>
<th>Package</th>
<th>No. of participants</th>
<th>No. of female participants</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Body surface (m²)</th>
<th>Body mass index (kg/m²)</th>
<th>Body temperature (°C)</th>
<th>Heart rate (beats/min)</th>
<th>Systolic pressure (mmHg)</th>
<th>Diastolic pressure (mmHg)</th>
<th>Haematology</th>
<th>Biochemistry</th>
<th>Pharmacokinetic analysis</th>
</tr>
</thead>
</table>
| Group A | 12                  | 7                           | 5.0 (2.3–6.0) | 15.5 (11.4–18.7) | 104 (92–113) | 0.66 (0.55–0.77) | 14.5 (11.6–16.2) | 37.6 (36.8–39.7) | 130 (83–148) | 93.5 (76.4–106.9) | 65.0 (40.4–74.7) | 27.3 (22.3–33.4) | 9.0 (3.9–31.3) | Dihydroartemisinin. Median peak plasma concentrations for dihydroartemisinin were 861 and 930 ng/mL in treatment groups A and B, respectively (Table 2 and Figure 1). A higher variation of $C_{\text{max}}$ was observed in the lower body-weight group A compared with group B (range: 130–3390 and 286–2190 ng/mL, respectively). Median $T_{\text{max}}$ values were very similar for both drug formulations (1.5 and 1.5 h, respectively). Median AUC$_{0-t}$ of dihydroartemisinin was 2050 and 2470 ng.h/mL, respectively. Four patients showed a delayed pattern of peak plasma concentrations reaching maximum—but still considerably lower—drug concentrations only at the last sampling time point for dihydroartemisinin (6 h: 158, 420, 130 ng/mL in group A and 286 ng/mL in group B, respectively). Observed peak plasma concentrations were considerably lower in these participants and cumulative results for $C_{\text{max}}$, $T_{\text{max}}$ and AUC$_{0-t}$ were therefore distorted. Similarly, elimination constant $\lambda_z$, $T_{1/2}$ and AUC$_{0-\infty}$ could not be computed in these patients. For the remaining participants, AUC$_{0-\infty}$ was comparable in treatment groups A (3024 ng·h/mL) and B (2815 ng·h/mL). The terminal half-life of
Dihydroartemisinin was 0.9 and 1.0 h for the two drug formulations, respectively. The influence of potentially confounding co-variables (treatment group, age, gender, weight, body mass index, packed cell volume, parasitaemia and temperature) on pharmacokinetic parameters ($C_{\text{max}}$, $T_{\text{max}}$ and AUC$_{0–t}$) was assessed in post hoc analysis by multivariate regression analysis using stepwise forward selection. Among those, gender showed a considerable effect on peak plasma concentrations of dihydroartemisinin. Male participants had median peak plasma concentrations of 737 ng/mL (10% and 90% quantiles: 130–1700 ng/mL) in group A and 543 ng/mL (10% and 90% quantiles: 286–1710 ng/mL) in group B. Median $C_{\text{max}}$ levels of females were higher in group A (922 ng/mL; 10% and 90% quantiles: 420–3390 ng/mL; $P = 0.12$) and group B (1730 ng/mL; 10% and 90% quantiles: 927–2190 ng/mL; $P = 0.04$), respectively. Plasma concentrations of dihydroartemisinin were positively correlated with mefloquine concentrations 6 h after drug administration but not later on ($r = 0.53$, $P = 0.007$). These findings might be explained by varying rates of drug absorption or biotransformation in a subgroup of patients.

Mefloquine. Mefloquine plasma samples were obtained 6 h, 54 h and 28 days after initiation of antimalarial treatment. All drug concentrations were comparable in the two treatment groups, although mefloquine concentrations in the younger age group receiving the fixed-dose paediatric drug formulation showed a statistically non-significant trend towards higher concentrations 54 h after initiation of treatment ($n = 24$; $P = 0.10$) and lower plasma levels on day 28 ($n = 24$; $P = 0.06$). Median mefloquine plasma levels for treatment groups A and B were 724 and 588 ng/mL, 2550 and 1815 ng/mL and 197 and 343 ng/mL for the respective time points (Table 2 and Figure 2). The limited number of sample time points precluded the computation of classical pharmacokinetic parameters.

**Table 2.** Pharmacokinetic characteristics of artesunate–mefloquine in the fixed-dose drug formulation and as co-blister tablets ($n = 12$ per group)

<table>
<thead>
<tr>
<th></th>
<th>Group A (paediatric formulation)</th>
<th>Group B (co-blister tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean 90% CI median range</td>
<td>mean 90% CI median range</td>
</tr>
<tr>
<td>DHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)$^a$</td>
<td>812 673–1689 861 130–3390</td>
<td>878 736–1425 930 286–2190</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>— — 1.5 1.0–6.1</td>
<td>— — 1.5 0.5–4.1</td>
</tr>
<tr>
<td>AUC$_{0–t}$ (ng·h/mL)$^a$</td>
<td>1763 1539–3305 2050 130–6641</td>
<td>2151 1810–3045 2470 965–4781</td>
</tr>
<tr>
<td>AUC$_{0–\infty}$ (ng·h/mL)$^b$</td>
<td>2867 2186–4129 3024 1399–6679</td>
<td>2679 2086–4200 2815 1049–7791</td>
</tr>
<tr>
<td>%AUC$_{0–\infty}$</td>
<td>0.8 0.60–0.90 0.8 0.3–1.1</td>
<td>0.67 0.52–0.82 0.7 0.1–0.7</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)$^b$</td>
<td>0.8 0.60–0.90 0.8 0.3–1.1</td>
<td>0.67 0.52–0.82 0.7 0.1–0.7</td>
</tr>
<tr>
<td>Mef</td>
<td></td>
<td></td>
</tr>
<tr>
<td>conc. 6 h (ng/mL)$^a$</td>
<td>706 522–891 724 85–1330</td>
<td>620 461–778 588 287–1380</td>
</tr>
<tr>
<td>conc. 54 h (ng/mL)$^a$</td>
<td>2578 2021–3134 2550 810–4460</td>
<td>1907 1585–2230 1815 859–2950</td>
</tr>
<tr>
<td>conc. 28 days (ng/mL)$^a$</td>
<td>239 170–308 197 100–518</td>
<td>337 276–398 343 156–544</td>
</tr>
</tbody>
</table>

DHA, dihydroartemisinin; Meff, mefloquine.

$^a$Means and 90% confidence intervals are depicted as antilog of arithmetic mean of transformed data using the natural logarithm.

$^b_n = 9$ in group A and $n = 11$ in group B.

Dihydroartemisinin was 0.9 and 1.0 h for the two drug formulations, respectively.

The influence of potentially confounding co-variables (treatment group, age, gender, weight, body mass index, packed cell volume, parasitaemia and temperature) on pharmacokinetic parameters ($C_{\text{max}}$, $T_{\text{max}}$ and AUC$_{0–t}$) was assessed in post hoc analysis by multivariate regression analysis using stepwise forward selection. Among those, gender showed a considerable effect on peak plasma concentrations of dihydroartemisinin. Male participants had median peak plasma concentrations of 737 ng/mL (10% and 90% quantiles: 130–1700 ng/mL) in group A and 543 ng/mL (10% and 90% quantiles: 286–1710 ng/mL) in group B. Median $C_{\text{max}}$ levels of females were higher in group A (922 ng/mL; 10% and 90% quantiles: 420–3390 ng/mL; $P = 0.12$) and group B (1730 ng/mL; 10% and 90% quantiles: 927–2190 ng/mL; $P = 0.04$), respectively. Plasma concentrations of dihydroartemisinin were positively correlated with mefloquine concentrations 6 h after drug administration but not later on ($r = 0.53$, $P = 0.007$). These findings might be explained by varying rates of drug absorption or biotransformation in a subgroup of patients.

**Figure 1.** Mean plasma concentration–time profile of dihydroartemisinin for treatment groups A (paediatric formulation) and B (co-blister tablets). Time points for plasma sampling are depicted on x-axis. Log transformed mean plasma concentrations (and standard error of the mean) are depicted on y-axis.

**Figure 2.** Mean plasma concentration–time profile curve of mefloquine for treatment groups A (paediatric formulation) and B (co-blister tablets). Time points for plasma sampling are depicted on x-axis. Log transformed mean plasma concentrations (and standard error of the mean) are depicted on y-axis.

**Discussion**

African children are the main target population for artemisinin combination therapy. Therefore, there is an urgent need for adequate paediatric drug formulations for most current artemisinin combinations. Data on pharmacokinetics of current artemisinin combination therapies are limited for paediatric patients in Africa.
Pharmacokinetics of artesunate–mefloquine therapy

Artesunate–mefloquine is one therapeutic option recommended by WHO for the treatment of uncomplicated malaria.\(^1\) Recently, an innovative paediatric granule formulation of artesunate and mefloquine has become available for use in young children. In this study, we assessed the pharmacokinetics of this novel drug formulation in comparison with a standard co-blistered tablet when administered to paediatric patients of two body-weight groups (10–20 and 20–40 kg body weight, respectively).

Dihydroartemisinin—the major active metabolite of artesunate—is responsible for most of the antimalarial activity of artesunate and was used for pharmacokinetic analysis in this study. Median \(C_{\text{max}}\) for dihydroartemisinin was similar in both groups but marked inter-participant variations were observed. Three patients in group A did not reach maximum plasma levels within the 6 h sampling schedule. This variation was similarly reflected by a wide variation of AUC\(_{0–t}\). Despite these marked inter-participant variations of dihydroartemisinin plasma levels, efficacy of the study treatment was 100% at 14 and 28 days in both study groups (manuscript in preparation).

Our data on dihydroartemisinin pharmacokinetics are comparable to a previous report on Vietnamese children suffering from moderately severe malaria.\(^15\) In that study, dose normalized \(C_{\text{max}}\) and AUC\(_{0–t}\) levels—analysed by using a radioisotopic bioassay—were similar (885 ng/mL and 1714 h-ng/mL if extrapolated to 4 mg/kg body-weight dosing of artesunate) and distinct inter-personal differences were described. Bioavailability of artemisinin derivatives showed similar high variation after intramuscular or rectal route of administration.\(^15–18\)

A considerable difference of dihydroartemisinin peak plasma concentrations was observed between male and female participants confirming findings of a recent report on pharmacokinetic characteristics of artesunate suppositories.\(^18\)

To date the clinical importance of reduced plasma levels of dihydroartemisinin is not understood. In general, 99% in vitro growth inhibition by an antimalarial is considered as threshold for MICs in non-immune patients. Even the lowest observed \(C_{\text{max}}\) level in our study population (130 ng/mL) was more than 13 times higher than previous results for the MIC in various in vitro drug sensitivity studies in Gabon (34 nmol/L equivalent to 9.7 ng/mL).\(^19\) Despite advances in the understanding of the mechanism of action of artemisinin derivatives, there is a lack of appropriate pharmacokinetic–pharmacodynamic models for this class of antimalarials.\(^20\)

Mefloquine plasma concentrations were predictive for treatment outcome in previous studies.\(^21\) In our trial, pharmacokinetic analysis of mefloquine was essentially restricted to descriptive statistics of plasma levels at the respective sampling time points. Mefloquine concentrations at 6 and 54 h after initiation of treatment were used for evaluation of absorption. True \(C_{\text{max}}\)—and therefore also \(T_{\text{max}}\)—were most likely missed due to the restricted sampling schedule. The mean mefloquine plasma concentrations 6 h after the administration of the first dose of each formulation are similar in the two groups. The mean observed plasma concentration 6 h after dosing on day 3 appears lower in group B. However, maximum observed plasma levels of mefloquine were within the range of previous reports.\(^22,23\)

Values at the end of the observation period, on the other hand, are slightly higher in treatment group B as compared with group A.

Median mefloquine plasma concentrations at the end of the study were 197 and 343 ng/mL, respectively. This finding may be interpreted as a trend towards a higher rate of mefloquine elimination in smaller children although the difference between groups was not statistically significant in our study population. In previous studies, 500 ng/mL has been determined as threshold level for therapeutic and prophylactic efficacy.\(^21,23\) This would translate into a median effective prophylactic period of 21.6 and 22.2 days post-treatment for groups A and B, respectively. The advantage of such a prolonged period of protection against new \(P.\) falciparum infections has to be weighed against the suspected increase in the risk for the selection of drug-resistant isolates in areas of high malaria transmission. More recently however, the benefit of reduced rates of re-infection and relapse due to long acting antimalarial drugs has been emphasized.\(^24,25\) The debate on this risk/ benefit analysis is still ongoing and needs further epidemiological evidence for areas of both low and high malaria endemicity.\(^4,26,27\)

In summary, we report on the pharmacokinetic characteristics of two paediatric artesunate–mefloquine combinations for the treatment of uncomplicated falciparum malaria in paediatric patients. In our study, plasma concentrations of dihydroartemisinin and mefloquine were satisfying and in concordance with previous reports from differing patient populations and drug formulations, there was no treatment failure observed in this study protocol. The development of adequate paediatric drug formulations is of high importance for the effective treatment of paediatric patients on an outpatient basis.\(^27\) By this means, paediatric formulations also contribute to an improved allocation of resources in health services of malaria endemic regions. Further careful monitoring of safety, tolerability and efficacy of this new fixed-dose, artesunate–mefloquine combination is needed for continuous confirmation of its qualification for wide scale use also in African children.

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Transparency declarations

N. C. and J. L. H. are employees of Mepha Ltd. The sponsor had no influence on study conduct, data analysis and interpretation of data. All other co-authors report no conflict of interest.

References


