OBJECTIVE

Develop a population pharmacokinetic (PK) model for DHA by pooling data from 5 studies and apply it to predict the PK of DHA in pediatric patients (6-12 months) infected with Plasmodium falciparum malaria following a new dispersion of a disposable formulation.

DATA

Study 1: Phase II, open-label, PK, safety and efficacy study on Eurartesim tablets (40 mg DHA/320 mg PQP) in pediatric patients with P. falciparum malaria in Africa (Burkina Faso). A total of 32 patients (16 males and 16 females) were enrolled. The tablet was crushed, mixed with water, and administered as a 120 mL slurry. Three doses were administered over 3 consecutive days at 24-hour intervals (once a day on Days 1, 2, and 3). The number of tablets administered was based on patient body weight: 1 pediatric tablet for patients with body weight less than or equal to 13 kg and 2 pediatric tablets for patients with body weight greater than 13 kg. On the first day of treatment the dose was administered between 1 and 2 hours following last food intake (mean 4.5 hours). PK blood samples for DHA were sparse with 1 or 2 samples per patient collected at the following times: pre-dose, 1.5, 3, 6, and 12 hours following the first dose.

Study 2: Phase II, open-label, PK, safety, and efficacy study on Artekin tablets (40 mg DHA/320 mg PQP) in adult patients with P. falciparum malaria in Thailand. Data from 25 male patients were used in the PK analysis. Three doses were administered 24 hours apart over 3 days. Blood samples were collected once a day, based on patient body weight, all patients were < 75 kg. On the 3 days of treatment the dose was administered 3 - 6 hours following the last intake of food (mean 4.5 hours). Blood sampling for PK analysis of DHA in plasma were collected at each dose (within 1 hour prior to the first dose administration) and at the following times: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post dose.

Study 3: Phase I, PK study in healthy male and female adult Asian and Caucasian participants to investigate the PK profiles of Eurartesim tablets 40 mg DHA/320 mg PQP. Eurartesim tablets were administered orally under fasting conditions, following a light continental breakfast (approximately 350 kcal) for 3 consecutive days (Days 0, 1, and 2). The dose administered was based on body weight (5 tablets/day for body weight < 75 kg and 4 tablets/day for body weight > 75 kg). Seventy-eight (78) participants were included in the PK analysis for DHA. Blood samples for determination of plasma DHA were collected at the following times: pre-dose on Day 0 and Day 2 and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post dose administration on Day 1 and Day 2.

Study 4: Phase I, randomized, open-label, balanced, single-dose, 2-treatment (fed and fasting conditions) parallel design study conducted in healthy male participants. The study population consisted of healthy Caucasian males, age ranging between 18 - 50 years, BMI ranging between 19 - 27 kg/m2 and body weight ≥ 75 kg. A total of 36 healthy adult male participants with body weight < 75 kg (2 groups of 18 participants) were enrolled. On the 3 days of treatment the dose was administered 3 - 6 hours following the first dose. A total of 32 patients (16 males and 16 females) were dosed. The tablet was crushed, mixed with water, and administered as a 120 mL slurry. Three doses were administrated over 3 consecutive days at 24 hour intervals (3 tablets once a day following the administration of a new dispersible formulation. Three doses were administrated over 3 consecutive days at 24 hour intervals (3 tablets once a day following the administration of a new dispersible formulation. A total of 36 to drug administration (fed group). During the study, blood samples were collected from each participant for standardized high fat and high caloric breakfast (50% fat and 800 - 1000 kcal), which started 30 minutes prior to the administration of Eurartesim dispersible formulation (New) dispersed in 60 mL of non-carbonated water. After ingestion, a single oral dose was administrated with 250 mL of water on the morning of Day 0, following an overnight fast of at least 10 hours (fasted group) or following a standardized high fat and high caloric breakfast (50% fat and 800 - 1000 kcal), which started 30 minutes prior to the administration of Eurartesim dispersible formulation (New) dispersed in 60 mL of non-carbonated water. On the 3 days of treatment the dose was administered 3 - 6 hours following the first dose.

Study 5: Phase I, open-label, randomized, balanced, single-dose, 2-treatment, parallel groups study. This relative bioavailability study was to assess the PK of DHA of a new Eurartesim dispersible formulation versus the currently approved Eurartesim film coated formulation following a single oral administration in healthy male participants. A total of 36 healthy adult male participants with body weight < 75 kg (2 groups of 18 participants) were enrolled. Each patient in this study received one formulation (dispersible tablet or film coated tablet) to be crushed and to be administrated 201 DHA profiles, 3407 samples (2319 were measurable). The MLEM algorithm in ADAPT5 was used to determine the goodness of fit plots for the final DHA model.