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Pharmacokinetics of ganaplacide and lumefantrine in a pediatric population with Plasmodium falciparum uncomplicated malaria, treated with ganaplacide plus lumefantrine solid dispersion formulation: analysis of data from KALUMI, a multinational Phase 2 study

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Abstract

Background

The new antimalarial combination ganaplacide plus lumefantrine-SDF was shown in a previous phase 2 study to be effective and well-tolerated in the treatment of uncomplicated falciparum malaria in adults, adolescents and children ≥ 2 years old. Here we report pharmacokinetic data from a second phase 2 study, which aimed to optimize the dose regimen and food intake with dosing, and to assess efficacy, safety and pharmacokinetics in children aged 6 months to 2 years with acute uncomplicated falciparum malaria.

Methods

In this randomized, open-label phase 2 study in uncomplicated falciparum malaria, sequential cohorts of patients aged 2 to < 12 years, body weight ≥ 10 kg (Cohort 1, N = 140), and 6 months to < 2 years, body weight ≥ 5 kg (Cohort 2, N = 80) were randomized to a loose combination of ganaplacide 400 mg plus lumefantrine solid dispersion formulation (SDF) 480 mg, administered with a light meal (100–300 calories, 5-10g fat) q.d. for 3 days, or artemether-lumefantrine (b.i.d. 3 days, per prescribing information). Doses were adjusted by body weight range. The ganaplacide plus lumefantrine-SDF treatment regimen was selected based on data from run-in cohorts of patients aged 12 to < 18 years (reported separately). We report pharmacokinetic data from the study. Sparse sampling was used. Drug concentrations were determined by liquid chromatography-mass spectrometry. Pharmacokinetic parameters including AUC_{0-24}, C_{max}, and C_{168h} were determined using non-compartmental analysis.

Results

Ganaplacide and lumefantrine exposures were within targeted ranges in both cohorts as confirmed by good efficacy and safety. Lumefantrine C_{168h} was higher in the ganaplacide plus lumefantrine-SDF group than the artemether-lumefantrine group in both cohorts. Drug exposures were comparable to those in patients treated with ganaplacide 400 mg plus lumefantrine-SDF 960 mg (doses adjusted by body weight range) given under fasted conditions in a previous study.

Conclusions

Ganaplacide 400 mg plus lumefantrine-SDF 480 mg given with a light meal q.d. for 3 days achieved effective drug exposures in patients with uncomplicated falciparum malaria.

Trial registration

The study is registered with EudraCT (2021-003583-27) and ClinicalTrials.gov (NCT04546633).

Background

Malaria caused by *Plasmodium falciparum* is one of the leading causes of death in low- and lower middle-income countries. In 2024, an estimated 282 million cases of malaria and 610,000 deaths occurred worldwide, with an estimated 94% of cases and 95% of deaths in the WHO African region. Children aged under 5 years bear the highest burden from malaria and accounted for 75% of all malaria deaths in the African region [1].

Antimalarial drugs have played an important role in malaria control, and artemisinin-based combination therapies (ACTs) have been the mainstay of treatment for several years. However, the recent emergence of partial resistance to artemisinins in *Plasmodium* species threatens the effectiveness of ACTs [2]. As a result, there is an urgent need for new antimalarials with novel mechanisms of action distinct from that of artemisinin derivatives. In addition, treatments that are effective when given once daily could improve adherence to therapy, and consequently increase treatment success rates and reduce the probability of developing resistance.

Ganaplacide (KAF156) is an imidazolopiperazine with a novel mechanism of action involving inhibition of parasite protein trafficking, blocking the establishment of new permeation pathways, and causing endoplasmic reticulum expansion that leads to parasite death [3]. Ganaplacide is equally potent against drug-sensitive malaria strains and a broad panel of drug resistant strains [4,5].

The use of combination antimalarial therapies is recommended to help prevent the development of drug resistance [2]. Artemether-lumefantrine, a WHO-approved first-line treatment for uncomplicated *Plasmodium falciparum* malaria in both adults and children (including infants), contains a conventional formulation of lumefantrine that requires twice-daily dosing. A new solid dispersion form of lumefantrine (lumefantrine-SDF) with increased bioavailability has been developed that permits once daily dosing [6]. Ganaplacide in combination with lumefantrine-SDF administered once daily was shown in a Phase 2 trial [7] to be effective in the treatment of uncomplicated falciparum malaria in adults, adolescents, and children (≥2 years) and has gametocytocidal activity that suggests potential for transmission blocking [4].

Here we report pharmacokinetic data from a recent Phase 2 interventional, multicenter, randomized, open- label study (EudraCT 2021-003583-27, Clinicaltrials.gov NCT04546633) that evaluated the efficacy, safety and tolerability of ganaplacide plus lumefantrine-SDF, given as a loose combination, in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in pediatric patients. This study showed that ganaplacide plus lumefantrine-SDF was effective and well-tolerated in the treatment of uncomplicated *P. falciparum* malaria in pediatric patients (≥6 months to <12 years); efficacy was non-inferior to artemether-lumefantrine, with PCR-corrected adequate clinical and parasitological cure rates of 99% in both treatment groups [8].

Methods

The study protocol and amendment were reviewed and approved by ethics committees and health authorities at each participating center (Additional file 1), and written informed consent was obtained from all patients and their parents or guardians. The study design and patient population have been described elsewhere [8]; an overview is provided in Figure 1. The study had two run-in cohorts (both in patients 12 to < 18 years of age) and a main part with two sequential age-descending cohorts.

The primary objective of the run-in part of the study was to assess potential food effects on ganaplacide and lumefantrine exposure in patients with uncomplicated *P. falciparum* malaria, 12 to < 18 years of age with body weight ≥ 35 kg; the food intake and dose regimen to be used with dosing for the main part of the study were determined by the results of the run-in part. Analysis of lumefantrine and ganaplacide exposure in the run-in cohorts, reported previously , led to the selection of ganaplacide 400 mg plus lumefantrine-SDF 480 mg, once daily for 3 days administered, with a light meal (100-300 kcal, 5-10 g fat) for the main part of the study [8].

In the main part of the study, both Cohort 1 (patients 2 to < 12 years of age with body weight ≥ 10 kg), and Cohort 2, (6 months to < 2 years, with body weight ≥ 5 kg) were randomized to treatment with ganaplacide plus lumefantrine-SDF or artemether–lumefantrine in a 1:1 ratio. Ganaplacide plus lumefantrine-SDF was given once daily (q.d.) in a 3-day dose regimen with a light meal. Patients of ≥35 kg received the full dose (ganaplacide 400 mg plus lumefantrine-SDF 480 mg), those 25 - <35 kg received 75% of the full dose (300 mg plus 360 mg, respectively), those 15 - <25 kg received 50% of the full dose (200 mg and 240 mg, respectively), and patients of 5 - <15 kg received 25% of the full dose (100 mg and 120 mg, respectively). Artemether-lumefantrine was given twice daily (b.i.d.) for 3 days (administered with food, with dose adjustments for body weight ranges according to prescribing information). Patients were followed up for 42 days after the initiation of treatment.

The PK objective of the main part of the study was to assess the PK of ganaplacide and lumefantrine in pediatric patients, 6 months to <12 years of age. Both Cohort 1 and 2 provided sparse PK samples. Sampling times were as follows; 6 to <12 years: 3, 6, 24, 48, 51, 54, 72 & 168 h post Day 1 dose (ganaplacide in combination with lumefantrine-SDF), 6 months to <6 years: 24, 48, 51, 54, 72 & 168 h post Day 1 dose (ganaplacide in combination with lumefantrine-SDF). For artemether-lumefantrine, samples for analysis of lumefantrine PK were taken at 24, 48, 68 and 168 h after the first dose.

Ganaplacide and lumefantrine concentrations in plasma samples were determined by validated methods, using protein precipitation followed by reverse phase liquid chromatography with tandem mass spectrometry detection. The lower limit of quantification (LLOQ) was 5.00 ng/mL and the upper limit of quantification (ULOQ) was 5000 ng/mL, using 20 µL of plasma for ganaplacide. For lumefantrine the LLOQ was 50.0 ng/mL, and ULOQ was 20000 ng/mL, also based on 20 µL of plasma.

Analyses were based on the PK set: this was a subset of the safety analysis set (all patients who received at least one dose of study treatment, were analyzed according to the study treatment received)

who had at least one evaluable PK concentration, took at least 80% of randomized study medication, and had no protocol deviations that impacted PK data. Patients who vomited medication within 1 hour were included provided that they did not vomit the replacement dose. The PK set was further classified into 2 subsets, based on meal compliance: the PK analysis set - partial food compliance where patients were compliant to meal criteria (within 30 minutes of drug administration and took at least 70% of the meal) on Day 2 and Day 3, and the PK analysis set - full food compliance where patients were compliant to meal criteria (within 30 minutes of drug administration and took at least 70% of the meal) on all three dosing days. Pharmacokinetic parameters were determined using non-compartmental analysis methods. The following PK parameters were assessed for ganaplacide and lumefantrine from the ganaplacide plus lumefantrine-SDF group in Cohort 1 (Day 1 and 3) and Cohort 2 (Day 3) where available: peak plasma concentration (C_{max}), time to peak concentration (t_{max}), area under the concentration-time curve from zero to 24 hours (AUC_{0-24h}), to infinity (AUC_{inf}), and to time of last quantifiable concentration (AUC_{last}), plasma half-life ($t_{1/2}$), and concentration at Day 7 (168 hours: C_{168h}). For the artemether-lumefantrine group, lumefantrine C_{max} and C_{168h} were assessed. Geometric means and coefficients of variation (CV%) were calculated for C_{max}, AUC_{0-24h}, AUC_{inf}, AUC_{last}, $t_{1/2}$ and $C_{168h,}$ and arithmetic mean and standard deviation (SD) were also calculated for C_{168h}. For t_{max}, median and range were calculated. Pharmacokinetic parameters were also summarized by body weight group (5 to <10 kg, 10 to <15 kg, 15 to <25 kg, 25 to <35 kg, and 35 to <55 kg) and age group (6 months to <2 years, 2 to <6 years, and 6 to <12 years).

Results

The study was conducted from 16 February 2021 (first patient first visit) to 28 August 2024 (last patient last visit). Patients were recruited at 10 study sites in 5 countries: Burkina Faso (4 sites), Congo Democratic Republic (1 site), Cote d'Ivoire (1 site), Gabon (1 site), Mali (3 sites).

In Cohorts 1 and 2 combined, 207 of the 220 randomized patients (94.1%) completed the study treatment. In Cohort 1, 68 of 70 randomized patients who received ganaplacide plus lumefantrine-SDF and 69 of 70 randomized patients from the artemether-lumefantrine group were included in the PK analysis set; in Cohort 2, 31 of 40 randomized patients from the ganaplacide plus lumefantrine-SDF group and 39 of 40 randomized patients from the artemether-lumefantrine group were included in the PK analysis set. Eleven patients (10.0%) from the ganaplacide plus lumefantrine-SDF group (two from Cohort 1 and nine from Cohort 2) and two patients (1.8%) from the artemether-lumefantrine group (one from each cohort) were excluded from the PK analysis set due to lack of evaluable PK data or low compliance (<80%) with study medication intake. Demographic and baseline characteristics of the study population have been reported previously [8].

Summary statistics of plasma PK parameters for ganaplacide and lumefantrine in Cohort 1 and Cohort 2 are provided in Table 1 and Table 2, respectively.

In Cohort 1, comparing the PK parameters between Day 1 and Day 3, we observed 1.8- and 1.9-fold accumulation of ganaplacide in C_{max} and $AUC_{0\text{-}24h}$, respectively, after q.d. dosing for 3 days. Similarly, lumefantrine showed 2.7 and 3.2-fold accumulation in C_{max} and $AUC_{0\text{-}24h}$, respectively, after q.d. dosing for 3 days (Table 1). Of note, ganaplacide and lumefantrine (the latter in both treatment groups) exposures in Cohort 2 were approximately 2-fold lower compared to Cohort 1 (Table 1, Table 2). Despite the lower exposures observed in Cohort 2, lumefantrine exposures in the ganaplacide plus lumefantrine-SDF treatment group were consistently higher than those in the artemether-lumefantrine treatment group. Comparable results were observed when the PK analyses were repeated for the subset of patients in the PK analysis set with partial and full food compliance (see Additional files 1-4).

In the ganaplacide 400 mg plus lumefantrine-SDF 480 mg treatment group (combined Cohorts), the exposures were comparable for both ganaplacide and lumefantrine between 35 to <55kg, 25 to <35kg and 15 to <25 kg body weight groups (Table 3). The exposures were approximately 2-fold lower in the 5 to <10kg and 10 to <15 kg body weight groups compared to higher body weight groups. A similar trend was observed for lumefantrine exposures from the artemether-lumefantrine treatment group. Consistent with the observations made for body weight, analyzing PK parameters by age-group revealed that in the ganaplacide 400 mg plus lumefantrine-SDF 480 mg group, a decreasing trend in exposures (C_{max}, AUCs and C_{168h}) with lower age groups (particularly patients 6 months to <2 years of age) was observed for both ganaplacide and lumefantrine (Table 4).

Discussion

The novel imidazolopiperazine ganaplacide has activity against *Plasmodium* species, including strains that show resistance to current antimalarials, including artemisinin derivatives [4, 5]. As the use of combination antimalarial therapies is recommended by WHO to help prevent the development of drug resistance [2], ganaplacide is being developed as a combination with a solid dispersion formulation of lumefantrine (lumefantrine-SDF). In contrast to the conventional lumefantrine formulation, lumefantrine-SDF has an improved bioavailability [6].

The combination of ganaplacide and lumefantrine-SDF was previously assessed in a Phase 2b dose finding study (EudraCT 2020-003284-25, Clinicaltrials.gov NCT03167242) [7]. That study showed that a dose regimen of ganaplacide 400 mg plus lumefantrine-SDF 960 mg, once daily for 3 days given under fasted conditions was efficacious, safe and well tolerated in adults, adolescents and children up to 2 years of age with acute uncomplicated falciparum malaria. The pharmacokinetics of ganaplacide and lumefantrine in malaria patients treated with the combination were also characterized in that study [9].

In a previous study in healthy volunteers, food intake did not affect the bioavailability of ganaplacide in healthy volunteers [10]. Lumefantrine is a highly lipophilic compound, with limited absorption when dose orally under fasting conditions [6, 11, 12], and for this reason artemether-lumefantrine is recommended to be administered with fat-containing food [2]. Food administration with lumefantrine-SDF in healthy volunteers also leads to improved bioavailability [6].

In the current study, the effects of food on lumefantrine and ganaplacide PK in patients with *P. falciparum* malaria who were 12 to < 18 years of age were explored in the run-in cohorts [8]. The food effect with a standard meal (400–500 calories, 20-30g fat) on ganaplacide exposure was minimal, as previously observed in healthy adult volunteers [10], and a significant food effect on lumefantrine exposure was observed, consistent with that previously seen in healthy volunteers [6]. For the main part of the study, the dose regimen of ganaplacide 400 mg plus lumefantrine-SDF 480 mg, once daily for 3 days given with a light meal (100–300 kcal, 5–10 g fat) was selected to minimize drug load [8]; dose adjustments were made by patient body weight range.

In the main part of the study, two age-descending cohorts (Cohort 1: 2 to < 12 years, Cohort 2: 6 months to < 2 years) of pediatric patients with acute, uncomplicated *P. falciparum* were enrolled. Lumefantrine exposures including C_{168h} were consistently higher in the ganaplacide plus lumefantrine-SDF treatment group compared to the artemether-lumefantrine group in both cohorts. The difference in C_{168h} is noteworthy, as this parameter is recognized as a surrogate marker of efficacy of particular relevance to the longer-acting partner drug in a combination, which in both combination treatments in this study is lumefantrine [13, 14].

Comparing the ganaplacide and lumefantrine exposures between the cohorts in the main study part, the exposures for both analytes were approximately 2-fold lower in Cohort 2 compared to Cohort 1. A similar decrease was observed with lumefantrine exposures in patients receiving artemether-lumefantrine. The trend of lower bioavailability of lumefantrine in younger children was reported previously where after accounting for allometric scaling of clearances and volumes, older children had significantly higher exposures compared to younger children [15]. While the exact mechanistic reason for the lower exposures in younger children is not known [16], one possible reason could be the higher expression of cytochrome P450 3A4 (CYP3A4) in younger children compared to adults [17]. Both ganaplacide and lumefantrine are metabolized by CYP3A4 [18–20] and the increased expression in younger children could possibly lead to higher metabolism resulting in lower exposures. Despite lower exposures, the efficacy was consistent between the cohorts indicating a broad therapeutic range of exposures for the ganaplacide plus lumefantrine-SDF combination [8].

The pharmacokinetics of ganaplacide plus lumefantrine-SDF in malaria patients have previously been assessed across a range of dose regimens given under a fasting conditions in the previous Phase 2 study [9]. Comparing PK parameters for 3-day dosing regimens (ganaplacide 400 mg plus lumefantrine-SDF 960 mg under fasted conditions described in the previous study [9] versus ganaplacide 400 mg plus lumefantrine-SDF 480 mg with a light meal in this study), the exposures of both ganaplacide and lumefantrine are comparable in the 2 to < 12 year age group. Key parameters (geometric means) for ganaplacide were: Day 3 C_{max}: 1380 vs 1240 ng/mL and Day 3 AUC_{0-24h}: 23700 vs 20300 ng h/mL, in the previous study [9] and the current study, respectively. While of less clinical relevance, given that ganaplacide is the fast-acting partner in the combination, used to achieve rapid initial parasite clearance, mean C_{168h} values were also similar between studies (geometric mean 24.8 ng/mL in the current study and 25.8 ng/mL reported previously). For lumefantrine, the geometric mean C_{168h} was 1320 ng/mL in

both studies [9]. Lumefantrine Day 3 C_{max} and AUC_{0-24h} were also very similar between the two studies. In the previous study, the ganaplacide and lumefantrine exposures needed for efficacy were achieved with a regimen of 400 mg ganaplacide plus lumefantrine-SDF 960 mg once daily for 3-days given under fasted conditions [7, 9]. While exposure-response relationships were not evaluated in the current study, the similar PK data obtained with ganaplacide 400 mg plus lumefantrine-SDF 480 mg given with a light meal, together with the efficacy data [8], indicate that the regimen studied here achieved efficacious drug exposures.

Conclusions

Key pharmacokinetic parameters of both ganaplacide and lumefantrine indicate that a dose regimen of ganaplacide 400 mg plus lumefantrine-SDF 480 mg q.d. for 3 days with a light meal resulted in drug exposures sufficient for efficacy that was non-inferior to artemether-lumefantrine [8], the current standard of care, and met WHO thresholds for efficacy, with an adequate safety profile. This regimen will be assessed further in a Phase 3 study in adults and children (≥ 5 kg body weight) with uncomplicated *P. falciparum* malaria (NCT05842954, EudraCT 2022-002675-10).

Abbreviations

ACT
artemisinin-based combination therapy
AUC_{0-24h}
area under the concentration-time curve from zero to 24 hours
AUC_{inf}
area under the concentration-time curve from zero to infinity
AUC_{last}
area under the concentration-time curve from zero to to time of last quantifiable concentration
b.i.d.
twice daily
C_{max}
peak plasma concentration
CV%
coefficients of variation
LLOQ
lower limit of quantification
PK
pharmacokinetic(s)
q.d.
once daily
SDF

solid dispersion form
$t_{1/2}$
half-life
t_{max}
time to peak concentration
ULOQ
upper limit of quantification

Declarations

Ethics approval and consent to participate

The study protocol and amendment were reviewed and approved by ethics committees and health authorities at each participating center; Additional file 1 provides details of ethics committee approvals. Written informed consent was obtained from all patients or their parents or guardians.

Consent for publication

Not applicable.

Availability of data and materials

Individual participant data will be shared with qualified external researchers under a signed data sharing agreement. All data are anonymized in line with applicable laws and regulations and available from the time of publication. The study protocol and statistical analysis plan are available on ClinicalTrials.gov (NCT04546633). Requests for data are reviewed and approved by an independent review panel on the basis of scientific merit. Data are available on https://www.clinicalstudydatarequest.com/

Competing Interests

RS, CW, CR, GS, GZ, JT, JS, HC, and ZQ are employees and/or stockholders of Novartis. MEG is an employee of Medicines for Malaria Venture. ACM is an employee of Medicines for Malaria Venture and a stockholder of Novartis, Alcon, and Idorsia. The other authors declare no conflicts of interest.

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conceptualization, design, data collection, analysis, decision to publish, and preparation of the manuscript.

Authors' contributions

RS contributed to study design, data analysis, data interpretation, data review and manuscript writing. BF treated patients and contributed to data acquisition. RZM contributed to supervision. SBS contributed to data collection, data analysis and data interpretation. ATO recruited patients and contributed to methodology, project administration, data collection and validation and visualization. JBO contributed to investigation, project administration, data collection and data analysis. MK contributed to investigation, data collection, data analysis and data interpretation. ACM and ME-G contributed to study design and data review. CW and CR contributed to study design, data collection, data analysis, data interpretation and manuscript writing. GS contributed to study design, data analysis supervision and data interpretation. GZ contributed to formal analysis, methodology, software and validation. JT contributed to supervision and project administration. HC contributed to sample analysis, data curation and manuscript writing. JS contributed to methodology, data analysis, data interpretation, data curation, formal analysis and manuscript writing. IS contributed to investigation, funding acquisition, methodology, data analysis and data interpretation. ZQ contributed to data collection, data review, data analysis, data interpretation, investigation, project administration, supervision and manuscript writing.

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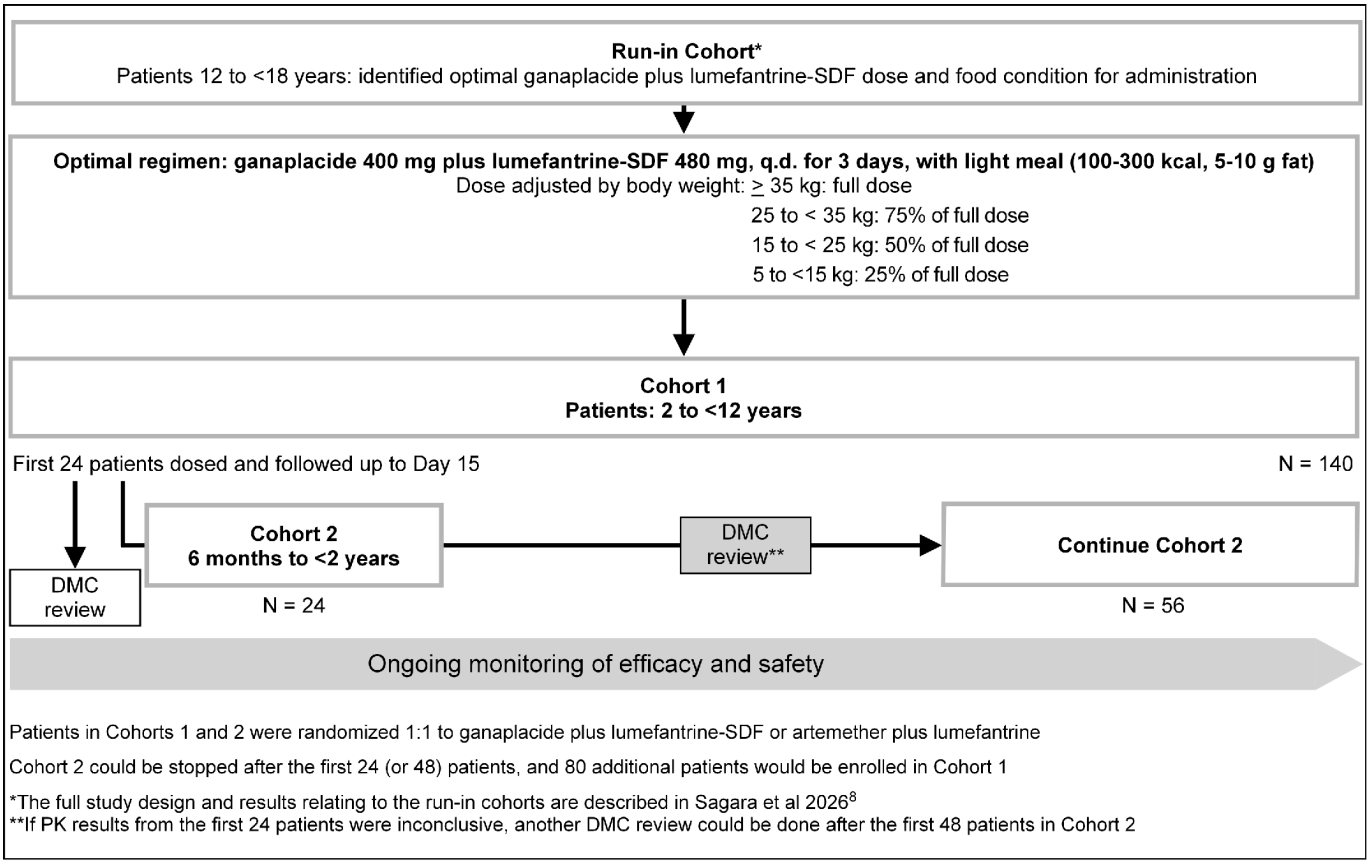
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Tables

Tables 1 to 4 are available in the supplementary files section

Figures



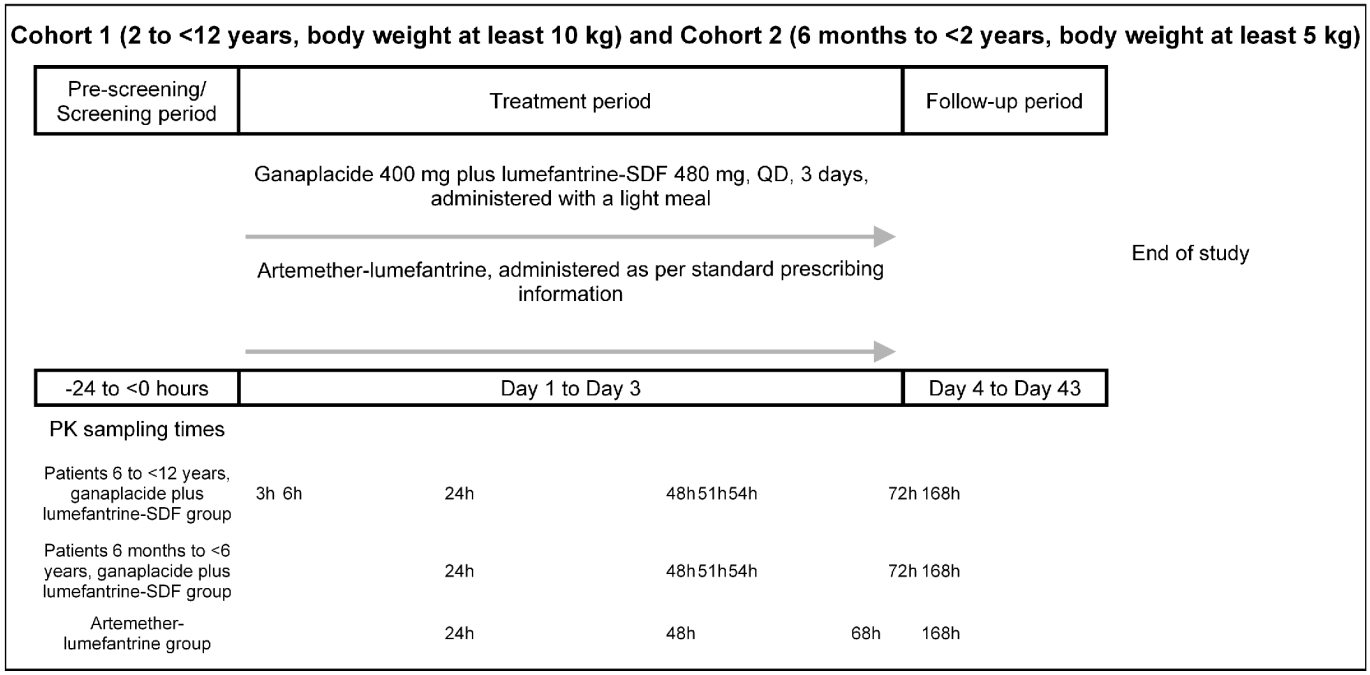


Figure 1

Study design

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SanganaetalKALUMIPKtable1.docx
- SanganaetalKALUMIPKtable2.docx
- SanganaetalKALUMIPKtable3.docx
- SanganaetalKALUMIPKtable4.docx
- Additionalfile1.pdf
- Additionalfile3.pdf
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- Additionaldata.docx