

Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial



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Summary

Background Combination treatments, preferably containing an artemisinin derivative, are recommended to improve efficacy and prevent *Plasmodium falciparum* drug resistance. Our aim was to show non-inferiority of a new dispersible formulation of artemether-lumefantrine to the conventional crushed tablet in the treatment of young children with uncomplicated malaria.

Methods We did a randomised non-inferiority study on children weighing 5–35 kg with uncomplicated *P falciparum* malaria in Benin, Kenya, Mali, Mozambique, and Tanzania. The primary outcome measure was PCR-corrected 28-day parasitological cure rate. We aimed to show non-inferiority (with a margin of –5%) of dispersible versus crushed tablet. We constructed an asymptotic one-sided 97·5% CI on the difference in cure rates. A computer-generated randomisation list was kept centrally and investigators were unaware of the study medication administered. We used a modified intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT00386763.

Findings 899 children aged 12 years or younger were randomly assigned to either dispersible (n=447) or crushed tablets (n=452). More than 85% of patients in each treatment group completed the study. 812 children qualified for the modified intention-to-treat analysis (n=403 vs n=409). The PCR-corrected day-28 cure rate was 97·8% (95% CI 96·3–99·2) in the group on dispersible formulation and 98·5% (97·4–99·7) in the group on crushed formulation. The lower bound of the one-sided 97·5% CI was –2·7%. The most common drug-related adverse event was vomiting (n=33 [7%] and n=42 [9%], respectively). No signs of ototoxicity or relevant cardiotoxicity were seen.

Interpretation A six-dose regimen of artemether-lumefantrine with the new dispersible formulation is as efficacious as the currently used crushed tablet in infants and children, and has a similar safety profile.

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Introduction

Plasmodium falciparum malaria is one of the commonest causes of morbidity and mortality in large areas of the world. Most deaths happen in children in sub-Saharan Africa.^{1–3} Efforts to fight this disease are based on the combined use of preventive and therapeutic measures, including the adequate use of available antimalarial drugs, which are under constant threat from the emergence and spread of drug resistance of *P falciparum*. WHO now recommends combination treatments, preferably including an artemisinin derivative, to improve efficacy and prevent the emergence of parasite drug resistance.⁴ Artemisinin-based combination therapy is highly effective against multidrug-resistant *P falciparum* malaria in Asia and Africa,^{3,5} and has been used in southeast Asia for more than 10 years. Sub-Saharan African countries are currently implementing artemisinin-based combination therapies as first-line or second-line treatments.^{5,6}

Artemether-lumefantrine (Coartem, Novartis Pharma AG, Basel, Switzerland) became the first fixed-dose

combination therapy that was prequalified by WHO in April, 2004. A tablet consists of 20 mg artemether and 120 mg lumefantrine. A 3-day, six-dose regimen of artemether-lumefantrine is efficacious and safe in both adults and children,^{7,8} and is recommended for infants and children weighing 5–35 kg, and adults weighing more than 35 kg. Many countries in sub-Saharan Africa have already adopted artemether-lumefantrine as first-line treatment for uncomplicated malaria, or have initiated the implementation process.⁶ Studies in animals⁵ suggested that artemisinin derivatives might have neurotoxic effects, although these findings have never been reproduced in people. Artemether-lumefantrine was reported to cause audiometric changes; however, that study has been much criticised.⁹ Furthermore, the chemical similarity of lumefantrine and halofantrine, which prolongs corrected QT interval (QTc), has generated concern that artemether-lumefantrine might have cardiac adverse effects. To date, no clinically significant cardiovascular toxic effects have been seen with the combination.¹⁰

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In African children, efficacy of artemether-lumefantrine at day 28 after treatment is consistently more than 90%,^{11–16} even with unsupervised administration.^{17,18} However, many young children cannot swallow whole tablets, and the bitter taste of the crushed commercial tablet added to water could compromise tolerability. Also, crushing tablets is an inefficient procedure, which could result in loss of drug and reduced dose ingested. To overcome these problems, a sweetened cherry-flavoured dispersible formulation has been developed for young children. Dispersible tablets contain the same amounts of artemether and lumefantrine as crushed tablets. We compared the efficacy and safety of the new dispersible formulation of artemether-lumefantrine with the crushed one in children with uncomplicated *P falciparum* malaria. Our primary aim was to show non-inferiority of the new formulation compared with the conventional one on day-28 PCR-corrected cure rates. Major secondary and exploratory outcomes included time to fever clearance and the day-42 PCR-corrected cure rate. Additionally, safety and tolerability profiles (including QTc changes) were compared between the two groups.

Methods

Patients

We recruited infants and children with microscopically confirmed acute uncomplicated *P falciparum* malaria from eight health-care facilities in five malaria-endemic countries: one centre each in Benin, Mali, Mozambique, Tanzania mainland, and Zanzibar, and three in Kenya. Except one site in Kenya, study centres were located in rural and periurban areas. At these locations, malaria transmission is intense and perennial, with the exception of the two study sites in Mozambique and Zanzibar, where malaria is mesoendemic with transmission peaks during the rainy season. Patients were not systematically provided with insecticide-treated bednets.

Male or female infants or children presenting with symptoms of malaria were screened for study eligibility. Inclusion criteria were age 12 years or younger, bodyweight between 5 kg and less than 35 kg, fever (temperature $\geq 37.5^{\circ}\text{C}$ axillary or $\geq 38^{\circ}\text{C}$ rectally) or history of fever in the preceding 24 h, *P falciparum* malaria (single or mixed infection) with a density between 2000/ μL and 200 000/ μL blood, negative pregnancy test for patients of childbearing potential, ability to take drugs by mouth and to attend the study centre on stipulated days for follow-up, provision of written informed consent by parent or guardian, and no severe and complicated malaria as defined by WHO.¹⁹ Exclusion criteria were haemoglobin less than 50 g/L, history of serious side-effects related to artemether-lumefantrine or similar drugs, use of antimalarial drugs other than chloroquine within the previous 2 weeks, ingestion of co-trimoxazole or any other agent with antimalarial activity within the previous 2 weeks, use of any drug known to affect cardiac function in the preceding 4 weeks, presence of QTc

prolongation (>450 and >470 ms for male and female patients, respectively) or any condition known to prolong QTc, serious underlying disease, and artemether-lumefantrine treatment within the previous 30 days.

The trial protocol was approved by local institutional review boards and those of the University of Heidelberg School of Medicine (Germany); Centers for Disease Control and Prevention (Atlanta, GA, USA); Walter Reed Army Institute of Research (Silver Spring, MD, USA); Hospital Clínic i Provincial de Barcelona (Spain); Regional Ethics Committee, Stockholm (Sweden); and the Universitair Ziekenhuis Antwerp (Belgium). Before enrolment, written informed consent was obtained from the parents or legal guardians of the children. Children capable of writing were also asked to give assent.

Study design, treatment, and procedures

We did a randomised, investigator-masked, multicentre, parallel-group study in sub-Saharan Africa between August, 2006, and March, 2007, according to WHO guidelines that were applicable at the time the study was set up. Patients were admitted to hospital during the 3-day treatment phase and then followed up until day 42 after treatment. A follow-up period of 42 days complied with a WHO guideline from 2003, which recommended this observation period for patients treated with artemether-lumefantrine to avoid underestimation of recrudescence rates.²⁰ Between August, 2006 and September, 2006, about 20% of patients were recruited at four sites for a protocol-mandated interim analysis. From these patients, data up to day 7 after treatment were reviewed by an independent data monitoring board to stop the study if there was insufficient efficacy (based on prespecified futility criteria) or potential early safety signals.

Eligible patients were randomly assigned to artemether-lumefantrine either in dispersible (intervention group) or in crushed form (control group) on a one to one basis. Children were stratified into three dosing groups, and treatment was administered twice daily over 3 days. The treatment was given according to bodyweight: one tablet per dose for patients weighing 5–14 kg, two per dose for those weighing 15–24 kg, and three per dose for those weighing 25–34 kg. For each weight group, an independent computer-generated randomisation list was used. Randomisation lists were kept centrally and were not communicated to the sites. Both dispersible and crushed tablets were administered under supervised conditions with a cup, beaker, or syringe in suspension in 10 mL water. Immediately afterwards, another 10 mL water was given with the same device. The consumption of some food or drink (eg, breastmilk, broth, or sweetened condensed milk) was recommended after the intake of medication to increase absorption. Patients who vomited a dose within 1 h of treatment received a full replacement dose. During the entire treatment phase, no more than two doses were to be replaced. Antipyretic drugs were used to control high fever. Investigators were unaware of

the study medication administered. Both treatments were identically packaged, prepared, and administered by a member of the staff not directly involved in clinical assessments.

After discharge, parents or guardians were asked to bring their children back to the clinic on days 3, 7, 14, 28, and 42 of follow-up or on any other day if the child was ill. Patients who developed severe malaria or danger signs of malaria were admitted and received rescue therapy (intravenous quinine), which, according to local treatment guidelines, was also given to children with early or late treatment failures,²⁰ and in case of vomiting the study replacement dose within 2 h of intake. Patients who discontinued study treatment before completing the study and those who prematurely withdrew from the study for any reason were scheduled for a final visit before or on day 42. We contacted those who did not return to the study site to find out the final outcome of the malaria episode.

Assessments of vital signs, body temperature, and neurological status were done twice daily during the first 3 days and at every follow-up visit. Neurological examination included tests for coordination (ie, heel-toe ataxia), fine finger dexterity (ie, ability to pick up a tablet), hearing (with a tuning fork), and an assessment for nystagmus, balance, and behaviour abnormality according to age groups. A 12-lead electrocardiogram was recorded at baseline and on day 3 (6–10 h after last dose). Two formulae (Bazett's and Fridericia's) were used to calculate QTc. Haematological and biochemical measurements were done at baseline and on days 3, 7, 28, and 42. During the hospital stay and at every follow-up visit, adverse events were assessed for severity and association with study medication.

Giemsa-stained thick and thin blood films were examined before every dose of study medication during the hospital stay and at every follow-up visit. Readings were done locally; two qualified microscopists independently read all the slides. Parasite densities were calculated by averaging the two counts. Blood smears with non-concordant results were re-examined independently by a third microscopist. Quality control was done on a percentage of randomly selected slides. Parasite density was calculated by counting the number of parasites per 200 leucocytes (or per 1000 leucocytes for gametocytes). Parasite density per μL was computed according to the actual leucocyte count or assuming an average of 8000 leucocytes per μL blood. Blood films were judged as negative if no parasites were seen in 200 oil-immersion fields in a thick blood film. The thin film was used for species identification.

To distinguish between recrudescence and new infection, blood samples were taken from every patient at baseline and from those with recurrent parasitaemia for PCR analysis. PCR experiments were processed centrally on all recurrent parasitaemias after day 7. Paired samples were genotyped by use of a standard protocol in a stepwise way on the basis of the *P falciparum* genes merozoite

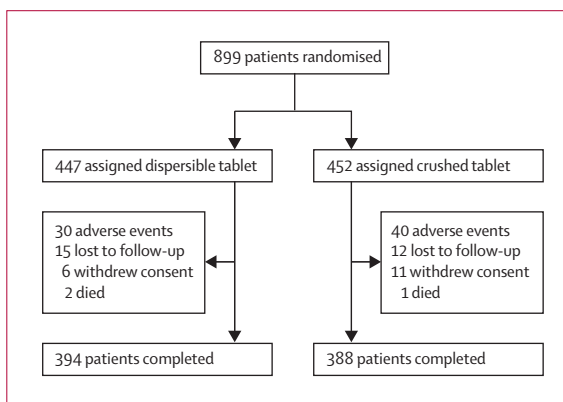


Figure 1: Trial profile

surface protein 2 (*msp2*), merozoite surface protein 1 (*msp1*), and genetic variation of the glutamate-rich protein (*glurp*).^{21,22} A new infection was defined as the absence of any matching allelic band at baseline and on the day of parasitaemia recurrence in at least one of the markers. Recrudescence was defined as at least one matching allelic band in all markers.

In all patients enrolled before the interim analysis, two blood samples were taken at 1 h and 2 h after the first dose of dispersible or crushed tablet for measurement of artemether and its active metabolite dihydroartemisinin in the plasma. To reconstitute a full lumefantrine pharmacokinetic profile for the population studied, a blood sample was taken from every patient enrolled after the interim analysis at six different timepoints across individuals. Pooled samples allowed an estimate of the area under the curve from time 0 to the last quantifiable lumefantrine plasma concentration, and samples collected at 6 h after the sixth (last) dose of study medication, an estimate of the highest plasma concentration.

	Dispersible tablet (N=447)	Crushed tablet (N=452)
Female patients	215 (48%)	205 (45%)
Median age (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)
0–<6 months	7 (2%)	8 (2%)
6–<12 months	23 (5%)	28 (6%)
1–<6 years	318 (71%)	311 (69%)
6–12 years	99 (22%)	105 (23%)
Bodyweight (kg)	14.4 (6%)	14.5 (6%)
5–<15	274 (61%)	273 (60%)
15–<25	144 (32%)	145 (32%)
25–<35	29 (7%)	34 (8%)
Temperature (°C)	38.0 (1.1)	38.0 (1.1)
Median parasite density per μL (IQR)	26 364 (11 040–59 532)	32 288 (10 050–71 274)
Haemoglobin (g/L)	93 (17)	94 (17)
Chloroquine use before the study	27 (6%)	22 (5%)

Data are mean (SD) or number (%), unless otherwise indicated. IQR=interquartile range. *For the safety population.

Table 1: Baseline characteristics of patients*

	Dispersible tablet	Crushed tablet
Modified ITT (primary analysis)		
N	403	409
Cured	394	403
Cure rate (95% CI)	97.8% (96.3–99.2)	98.5% (97.4–99.7)
Treatment group difference*	-0.8%	..
Lower limit of one-sided 97.5% CI	-2.7	..
ITT		
N	418	423
Cured†	397	407
Cure rate (95% CI)	95.0% (92.9–97.1)	96.2% (94.4–98.0)
Treatment group difference*	-1.2%	..
Lower limit of one-sided 97.5% CI	-4.0	..
PP		
N	398	406
Cured	391	400
Cure rate (95% CI)	98.2% (96.9–99.5)	98.5% (97.3–99.7)
Treatment group difference*	-0.3%	..
Lower limit of one-sided 97.5% CI	-2.2	..

Data are n (%), unless otherwise indicated. ITT=intention-to-treat. PP=per protocol. *Dispersible minus crushed tablet group. †Patients with unclear or missing PCR results were considered not cured.

Table 2: PCR-corrected day-28 cure rate by analysis population

Outcome measures

The day-28 PCR-corrected parasitological cure rate was the primary efficacy outcome—ie, proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of treatment, without recrudescence within 28 days after initiation of treatment, and without use of rescue medication for clinical signs of malaria. Secondary efficacy outcomes included day-7 parasitological cure rate, day-14 PCR-corrected parasitological cure rate, time to fever clearance, parasite-clearance time, and gametocyte clearance. Exploratory efficacy variables included day-42 PCR-corrected cure rate, early treatment failure, late clinical failure, late parasitological failure, adequate clinical and parasitological response, and development of danger signs of malaria or severe malaria.²³ Parasitaemia in these definitions was PCR-corrected. Adequate clinical and parasitological response was defined as absence of parasitaemia from day 28 to day 42 irrespective of axillary temperature, without any previous occurrence of early treatment failure, late clinical failure, or late parasitological failure. Safety endpoints included adverse-event rates, laboratory assessments, and electrocardiographic data.

Statistical analysis

The non-inferiority hypothesis of the dispersible form of artemether-lumefantrine to the crushed form on the day-28 PCR-corrected cure rates was assessed by construction of a one-sided, lower limit, asymptotic 97.5% CI on the difference in cure rates between the two formulations.

	Dispersible tablet	Crushed tablet
5–<15 kg		
N	236	241
Cured	230	239
Cure rate (95% CI)	97.5% (95.4–99.5)	99.2% (98.0–100.0)
15–<25 kg		
N	139	138
Cured	137	134
Cure rate (95% CI)	98.6% (96.6–100.0)	97.1% (94.3–99.9)
25–<35 kg		
N	28	30
Cured	27	30
Cure rate (95% CI)	96.4% (89.6–100.0)	100.0% (100.0–100.0)

Data are n (%), unless otherwise indicated. ITT=intention-to-treat.

Table 3: PCR-corrected day-28 cure rate by bodyweight group in the modified ITT population

Non-inferiority was proven if the lower limit of CI was greater than -5% (for dispersible minus crushed). We used standard asymptotic methods to construct two-sample, one-sided 95% CI for cure rate proportions. We assessed parasite-clearance time and time to fever clearance by survival analysis (Kaplan-Meier estimation, log-rank test). We chose the non-inferiority margin of 5% on the basis of WHO guidelines²⁴ applicable at the time the study protocol was written, suggesting that a failure rate exceeding 15% is a threshold for a change in policy on the treatment of acute uncomplicated malaria. Furthermore, WHO guidelines recommended that any artemisinin-based combination therapy has cure rates of at least 90%. On the basis of expected day-28 PCR-corrected cure rates of at least 95%, the margin of 5% was chosen to meet the recommended 90% threshold. With an estimated cure rate of 95% for both treatments, we calculated that 800 patients (400 per group) would be needed to show non-inferiority of the dispersible formulation to the crushed one with about 90% power. Assuming a 10% non-evaluability rate (eg, loss of follow-up), we planned to enroll 445 patients per group. We did not do any adjustment for type I error (ie, the result is claimed positive when that is not the case) because the planned interim analysis meant that the study was not going to be stopped for positive efficacy. The study would not be stopped early unless the study drug was shown to lack efficacy (ie, futility with respect to efficacy).

Data from all sites were pooled and analysed on the basis of different populations. The intention-to-treat population included all randomised patients with confirmed *P. falciparum* malaria who took at least one full dose of study medication and had at least one post-baseline efficacy assessment. Missing cure-rate data were imputed^{25,26} to assess the robustness of results based on patients who provided observable data. The modified intention-to-treat population consisted of all patients in the intention-to-treat population who completed 28 days with a valid parasitological assessment (PCR if para-

sitaemia was present at day 28). All patients who were classified as treatment failures before day 28 (ie, discontinuation of study drug and administration of rescue treatment) were also included. This analysis excluded patients if they: used other antimalarial drugs or antibiotics with antimalarial activity before day 28 for reasons other than rescue medication; had two replacement doses and vomited a subsequent dose within 1 h; vomited the replacement dose within 2 h; switched to rescue medication during the 3-day treatment period with study medication for withdrawal of consent or for other reasons (eg, overdose); experienced a new infection (confirmed by PCR) before day 28; or had unclear or missing PCR results at day 28. The per-protocol population included all patients of the modified intention-to-treat population who took at least 80% of study drug, had parasite counts between 2000 per μL and 200000 per μL at baseline, and had a bodyweight between 5 kg and 35 kg. The safety population included all patients who received at least one dose of study drug and had at least one relevant post-baseline safety assessment. The primary analysis was based on the modified intention-to-treat population as specified in the study protocol. Analyses of all secondary and exploratory efficacy objectives were based mainly on the intention-to-treat population. The safety population was used for safety data analyses. This study is registered with ClinicalTrials.gov as NCT00386763.

Role of the funding source

The sponsors were responsible for collection and analysis of data. The authors and the sponsors were involved in study design, interpretation of data, and writing of the report. All authors had full access to all data in the study and they held final responsibility for the decision to submit for publication.

Results

Overall, 899 patients were randomly assigned to the two treatment groups (figure 1; 447 to dispersible tablets and 452 to crushed tablets; 110 in Benin, 193 in Kenya, 225 in Mali, 102 in Mozambique, 240 in Tanzania mainland, and 29 in Zanzibar). More than 85% of patients in each treatment group completed the study. 4% of patients withdrew during the 3-day treatment period (16 of 447 in the dispersible formulation group and 17 of 452 in the crushed formulation group). 886 (99%) and 804 (89%) of patients were included in the intention-to-treat and per-protocol populations, respectively. 812 (90%) participants qualified for the modified intention-to-treat analysis. The main reason for exclusion from the modified intention-to-treat population was a missing day-28 parasite count, without having treatment failure before that day (7.6% and 7.5% for the dispersible and the crushed formulation groups, respectively). Table 1 shows the baseline characteristics of all participants. The data monitoring board

	Dispersible tablet	Crushed tablet
Modified ITT		
Day 14		
N	403	409
Cured	401	408
Cure rate (95% CI)	99.5% (98.8–100.0)	99.8% (99.3–100.0)
Day 42		
N	354	355
Cured	340	344
Cure rate (95% CI)	96.0% (94.0–98.1)	96.9% (95.1–98.7)
ITT*		
Day 14		
N	429	433
Cured	417	424
Cure rate (95% CI)	97.2% (95.6–98.8)	97.9% (96.6–99.3)
Day 42		
N	377	372
Cured	343	347
Cure rate (95% CI)	91.0% (88.1–93.9)	93.3% (90.7–95.8)
PP		
Day 14		
N	398	406
Cured	398	405
Cure rate (95% CI)	100.0% (100.0–100.0)	99.8% (99.3–100.0)
Day 42		
N	349	352
Cured	337	341
Cure rate (95% CI)	96.6% (94.6–98.5)	96.9% (95.1–98.7)

Data are n (%), unless otherwise indicated. ITT=intent-to-treat. PP=per protocol.
*Patients with unclear or missing PCR results were considered not cured.

Table 4: PCR-corrected day-14 and day-42 cure rates by analysis population

recommended continuing the study after an interim analysis on 166 patients showing 100% cure rates by day 7.

Cure rates were high in both treatment groups in the modified intention-to-treat population (table 2). The lower bound of the one-sided 97.5% CI calculated around the difference between the day-28 cure-rate point estimates in both groups was -2.7% , and thus within the prespecified -5% non-inferiority limit. The uncorrected day-28 cure rates were 92.1% for the dispersible formulation and 90.5% for the crushed formulation for the modified intention-to-treat population, and 87.6% and 87.0% in the intention-to-treat population. Cure rates were generally similar across bodyweight groups for both treatments (table 3). Overall, no difference between study centres for the primary efficacy variable was discernable (data not shown).

PCR-corrected cure rates at days 14 and 42 were also similar for the two formulations, irrespective of the study population analysed (table 4). Day-7 cure rate was 97.2% in the dispersible formulation group and 98.4% in the crushed formulation group. Similarly, uncorrected

day-14 cure rates were similar for both formulations (data not shown). Non-PCR-adjusted day-42 cure rates were 77.7% for dispersible tablets and 74.5% crushed tablets in the intention-to-treat population. Moreover, median time to fever clearance (7.9 vs 7.8 h) and median parasite-clearance time (34.3 h vs 34.9 h) did not differ significantly between groups (95% CIs overlapped). Similar proportions of patients in the dispersible and crushed tablet groups achieved parasite clearance within 24 h (170 of 442 [38.5%] vs 166 of 444 [37.4%]) and within 48 h (391 of 442 [88.5%] vs 397 of 444 [89.4%]). Only three patients in each treatment group had parasite presence after 72 h. Gametocyte clearance could not be assessed because too few patients had gametocytes at baseline (less than 5%). Only a small proportion of patients had gametocytes after day 8 ($\leq 1\%$ in both groups). The comparison of time to fever clearance between the two groups was not confounded by the use of paracetamol because intake was almost identical in both groups (263 of 447 [58.8%] vs 243 of 452 [53.8%]). Two patients in the dispersible formulation group had early treatment failure: one had low haemoglobin concentration (48 g/L) at baseline and was erroneously included in the study. He needed immediate treatment for severe malaria anaemia. The other patient developed severe malaria during the first 3 days of the study. Late clinical failure occurred in a patient in the dispersible formulation group and in four patients in the crushed formulation group. The proportion of patients with late parasitological failure was similar between treatments (44 of 387 [11.4%] vs 52 of 389 [13.4%]). Furthermore, the proportion of patients with adequate clinical and parasitological

response was also similar between the two groups (328 of 415 [79.0%] vs 318 of 420 [75.7%]). Few patients developed danger signs of malaria or severe malaria (three patients on dispersible tablets and four on crushed tablets).

Tolerability was adequate in both treatment groups, with no difference in pattern and overall frequency of adverse events (dispersible tablets 307 of 447 [68.7%] vs crushed tablets 318 of 452 [70.4%]). No new or unexpected adverse event was seen. Most commonly reported adverse events were also symptoms or signs of malaria (eg, pyrexia). The most frequent drug-related adverse event was vomiting (33 of 447 [7.4%] patients receiving the intervention treatment and 42 of 452 [9.3%] receiving the control treatment), but very few patients needed rescue medication because of vomiting the study drug (six vs 11). Vomiting was more frequently reported in the lowest bodyweight category. Other drug-related adverse events occurred in less than 1% of patients in either group. No clinically relevant neurotoxic effects were seen during the study. In particular, no adverse event related to the auditory system was reported. On systematic neurological examination, only five individuals in the dispersible tablet group and two in the crushed tablet group had baseline abnormalities that persisted on day 1 (mainly abnormal gait and tandem walk). Isolated cases of somnolence (three), convulsion (three), dyskinesia (one), epilepsy (one), dizziness (one), and tremor (one) were reported as unrelated adverse events. No patient in either group had hearing loss. Three individuals died during the study. In the group receiving the dispersible tablet, one patient died of haemorrhage after scarification by a witch doctor, and one from an unspecified infection accompanied by severe dehydration. One patient in the crushed tablet group died of severe *P falciparum* malaria (new infection). The proportion of patients with serious adverse events was low (between 1% and 2% in both groups), most being infections.

No clinically relevant findings or differences between study groups were found in vital signs or laboratory and electrocardiographic assessments. Haemoglobin concentration decreased from baseline to days 3 and 7, and thereafter recovered in both treatment groups. At day 42, haemoglobin concentration increased from baseline by a mean of 11 g/L (SD 17) in both groups. No cases of adverse events or serious adverse events were reported as haemolysis. Neither of the formulations had an effect on renal function, as assessed by serum creatinine measurements. Aspartate and alanine aminotransferase concentrations, as markers of hepatocyte damage, decreased or returned to normal during the course of the study with no difference between treatments. About 36% of patients had high aspartate aminotransferase concentrations (>62 U/L) and 47% had high alanine aminotransferase concentrations (>45 U/L) at baseline. Almost all returned to normal by day 3.

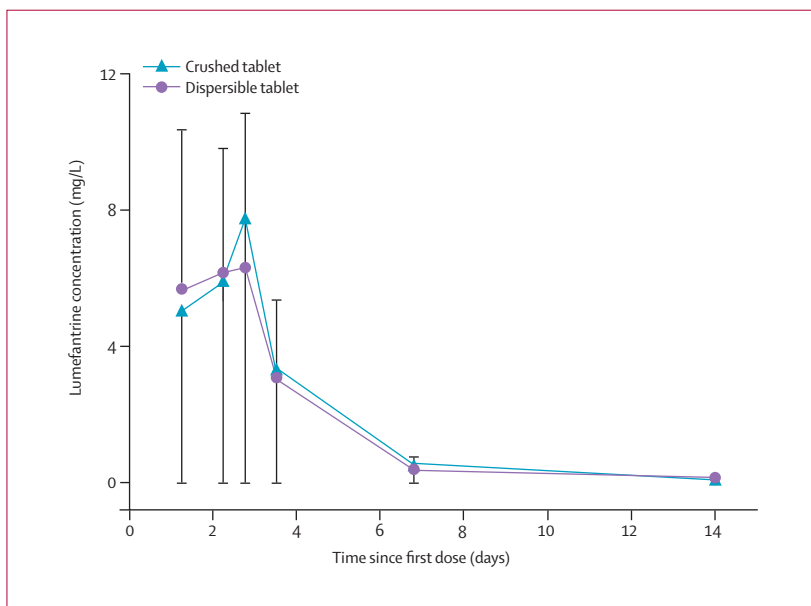


Figure 2: Lumefantrine plasma concentration during treatment with dispersible and crushed artemether-lumefantrine tablets

The QTc interval (by Bazett's formula) increased by a mean of 7.6 ms (SD 24.9) in the dispersible tablet group and 7.1 ms (24.3) in the crushed tablet group from baseline to day 3. 161 of 429 (37.5%) and 168 of 436 (38.5%) patients, respectively, did not have any QTc prolongation. The most frequent QTc change was an increase from baseline of less than 30 ms (183 of 429 [42.7%] and 196 of 436 [45.0%], respectively). The proportion with increases of more than 60 ms in QTc was low in both treatment groups (three of 429 vs ten of 436). No patient had a QTc interval of more than 500 ms after treatment, by either Bazett's or Fridericia's formula, and no clinical symptoms attributable to QTc prolongation (eg, syncope and sudden death) were reported. Overall, seven cases of arrhythmia (mostly tachycardia) were described as adverse events (four in the intervention group and three in the control group). All were mild, resolved without intervention, and did not lead to study drug discontinuation. In one patient of each group, this adverse event happened after day 25 of follow-up.

The maximum concentration of artemether plus dihydroartemisinin did not differ substantially across bodyweight subgroups, and the overall mean for artemether was 175 µg/L (SD 168; n=91) in the dispersible tablet group and 211 µg/L (262; n=93) in the crushed tablet group. The maximum concentrations for dihydroartemisinin were 68.0 µg/L (64.4) and 63.7 µg/L (64.9), respectively. Lumefantrine plasma concentrations were available from 310 patients assigned dispersible tablets and 315 assigned crushed tablets. No difference in lumefantrine pharmacokinetics between treatment groups was apparent (figure 2). The mean maximum lumefantrine concentrations were 6.3 mg/L (4.6) and 7.7 mg/L (5.9) after treatment with dispersed or crushed tablets, respectively. The areas under the concentration-time curve were 574 and 636 mg·h/L, respectively.

Discussion

The dispersible formulation of artemether-lumefantrine was not inferior in efficacy to crushed tablets in children with acute uncomplicated *P falciparum* malaria, and had a similar safety profile. PCR-corrected day-28 cure rates were high for both formulations in children. No differences were seen in the response to treatment across the various bodyweight groups, or between the two formulations in terms of clearance of asexual parasites and fever, which was rapid for both treatments.

Multiple imputation methods accounting for the patients excluded from primary intention-to-treat analysis showed that the day-28 cure rates for the modified intention-to-treat population (primary analysis population) were robust. The percentage of excluded patients (8%) was below the prespecified value of 10%. Results from intention-to-treat and per-protocol analyses were in agreement with those from the modified intention-to-treat analysis.

The PCR-corrected day-14 and day-28 cure rates in the control group were higher than or similar to those in previously published investigations on the efficacy of artemether-lumefantrine in African children, when administered as crushed or uncrushed tablets in a six-dose regimen.¹¹⁻¹⁶ For uncorrected day-7 cure rates, our findings confirm the results from Falade and co-workers¹¹ who used a non-comparative study design.

Follow-up periods longer than 28 days have been recommended for antimalarial drugs with a long half-life (eg, lumefantrine or mefloquine) to allow drug concentrations in the blood to fall below the minimum therapeutic threshold.²⁰ Short observation periods can yield an underestimation of recrudescence rates. Hence, the long follow-up and the large sample size reinforce the findings in this study. Because few day-42 cure-rate data with artemether-lumefantrine have been published, this efficacy variable deserves special attention. Conservative analysis of corrected day-42 cure rates that counted patients with unclear or missing PCR results as having recrudescence (91% and 93% for the two groups, respectively) showed they were high and suggested a sustained efficacy with both formulations. These results were in accordance with those of a smaller study by Martensson and colleagues,¹³ who reported a day-42 PCR-adjusted success rate of 92% in children from Zanzibar receiving the combined treatment, with a similarly conservative approach for analysis. Furthermore, in our study we did not see any substantial difference between the two formulations in non-PCR-adjusted day-42 cure rates. Because uncorrected cure rates are mainly affected by new infections in high-transmission areas, this finding suggests a similar prophylactic effect by the two formulations.

The dispersible formulation was well tolerated, and comparable with the crushed tablets. No new safety issues arose and our findings are in line with former ones.^{8,27} Most commonly reported adverse events were symptoms of malaria. Similarly, the pattern of changes in clinical laboratory variables was consistent with acute malaria and its resolution, with no difference between the treatment groups. The commonest drug-related adverse event was vomiting, and the frequency was similar to that previously reported in African children receiving crushed or uncrushed artemether-lumefantrine tablets.¹¹ Neurotoxic effects caused by artemisinin derivatives in animals and hearing loss by artemether-lumefantrine in people have raised concerns.^{9,28}

In our study, no adverse event indicating a possible neurotoxic effect of this drug combination (based on specific neurological examinations) and no adverse events related to the auditory system were reported, thereby confirming, in a large group of patients, previous findings.^{29,30} The chemical similarity between lumefantrine and halofantrine, which causes QTc prolongation, led to scrutiny of electrocardiographic findings in our study, which is thus the largest study

addressing this issue prospectively. We noticed a slight increase in QTc interval, which was similar for both treatments and not associated with clinical symptoms. Similar findings have been previously reported in both adults and children, and were judged as not relevant cardiac risks for patients treated with artemether-lumefantrine.^{7,8,31} In this context, we point out that recovery from malaria is associated with a consistent reduction in heart rate and lengthening of the QT interval as a result of decreased autonomic tone, which seems to be independent of antimalarial treatment.¹⁰ Overall, our safety data did not show any increased risk of adverse events in the treatment with the dispersible formulation.

Our study was done under supervised conditions and may therefore not entirely represent normal outpatient practice, which could be a limitation of the trial. Additionally, the relative acceptability of the dispersible versus the crushed formulation was not assessed because it was not an objective of this study. Finally, the trial was done in one continent, which carries the largest burden of *P. falciparum* malaria. No formal meta-analysis of previous trial data could be undertaken because this is the first therapeutic study comparing these two formulations.

Artemisinin-based combination treatments have the potential to lower the emergence and spread of drug resistance, and delay in decisions to adopt them as treatment is likely to increase morbidity and mortality.³² Implementation of artemether-lumefantrine in Africa can reduce total expenditure on malaria treatment.³³ A recent cost-effectiveness analysis of artemether-lumefantrine for treatment of uncomplicated malaria in an area of Africa with high drug resistance showed that the use of this combination is clearly justifiable on both economic and public-health grounds. The high treatment success rate, less demand for second-line treatment, and reduction in the prevalence of severe malaria, associated with a decreased need for hospital care, have led to cost savings.³⁴

Since we found that the dispersible formulation was similar in efficacy and safety to the standard formulation, cost savings are also likely with its use, with the potential benefit of improving acceptability of the combination once on the market. The price of the dispersible tablets has not yet been decided but the manufacturers have indicated that it is likely to be similar to the existing formulation. Most countries in sub-Saharan Africa that have adopted artemisinin combination therapies have chosen artemether-lumefantrine as first-line treatment for uncomplicated *P. falciparum* malaria because it has recently become more affordable and, according to the manufacturer, 120 million of 160 million courses of treatment provided so far through the public health-care system for children. The dispersible formulation is easy to administer, gives compliance and effective treatment; and hence facilitates adoption in malaria control programmes.

Contributors

All authors contributed to the design of the study and assisted with data interpretation. IS, SB, UDA, QB, RG, MH, BO, AB, and SA coordinated the study and supervised the enrolment and follow-up of patients. KA, MC, and GL participated in data entry, collection, and analysis of data. All authors participated in the preparation of the report and approved the final version.

Conflict of interest statement

SA, IS, SB, RG, MH, BO, AM, JL, HM, PS, AN, QB, EJ, AB, HPB, and ZP received payments to attend meetings related to the trial. IS, ZP, UDA, and BO received payments from Novartis Pharma to attend meetings related to malaria. SA, UDA, BO, and PS received payments for travel expenses or speaking engagements. KA, MC, and GL are employees of Novartis Pharma and hold stock ownership with Novartis. DU is an employee of Medicines for Malaria Venture.

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