zac00815/zac4220d15z | xppws | S=1 | 6/4/15 | 5:41 | Facing: 3-4 | ArtID: 00014-15 | NLM: review-article | CE: jtc

Editor: Milhous | Section: Minireview | Designation: R

AAC Journals.ASM.org

MINIREVIEW

Tailoring a Pediatric Formulation of Artemether-Lumefantrine for Treatment of *Plasmodium falciparum* Malaria

Quique Bassat,[a,b] Bernhards Ogutu,[c] Abdoulaye Djimde,[d] Kirstin Stricker,[e] Kamal Hamed[f]

ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic—Universitat de Barcelona, Barcelona, Spain[a]; Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique[b]; Centre for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya[c]; Malaria Research and Training Center, University of Science, Techniques and Technologies of Bamako, Bamako, Mali[d]; Novartis Pharma AG, Basel, Switzerland[e]; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA[f]

Specially created pediatric formulations have the potential to improve the acceptability, effectiveness, and accuracy of dosing of artemisinin-based combination therapy (ACT) in young children, a patient group that is inherently vulnerable to malaria. Artemether-lumefantrine (AL) Dispersible is a pediatric formulation of AL that is specifically tailored for the treatment of children with uncomplicated *Plasmodium falciparum* malaria, offering benefits relating to efficacy, convenience and acceptance, accuracy of dosing, safety, sterility, and stability and a pharmacokinetic profile and bioequivalence similar to those of crushed and intact AL tablets. However, despite being the first pediatric antimalarial to meet World Health Organization (WHO) specifications for use in infants and children who are ≥5 kg in body weight and its inclusion in WHO Guidelines, there are very few publications that focus on AL Dispersible. Based on a systematic review of the recent literature, this paper provides a comprehensive overview of the clinical experience with AL Dispersible to date. A randomized, phase 3 study that compared the efficacy and safety of AL Dispersible to those of crushed AL tablets in 899 African children reported high PCR-corrected cure rates at day 28 (97.8% and 98.5% for AL Dispersible and crushed tablets, respectively), and the results of several subanalyses of these data indicate that this activity is observed regardless of patient weight, food intake, and maximum plasma concentrations of artemether or its active metabolite, dihydroartemisinin. These and other clinical data support the continued use of pediatric antimalarial formulations in all children <5 years of age with uncomplicated malaria when accompanied by continued monitoring for the emergence of resistance.

Approximately 198 million cases of malaria occurred globally in 2013, resulting in an estimated 584,000 deaths. The vast majority of these cases (82%) and deaths (90%) occurred in sub-Saharan Africa (1). Young children are inherently vulnerable to malaria; of all malaria deaths in 2013, 78% were of children under 5 years of age. This equated to 453,000 young children who lost their lives to malaria in a single year (1).

Artemisinin-based combination therapy (ACT) is the recommended standard first-line treatment for individuals with uncomplicated malaria (2). ACT has been adopted in all African countries of malaria endemicity as it is effective, has a good safety profile, and reduces the risk of antimalarial resistance compared with monotherapies (1), which are now formally prohibited. ACT is typically provided in tablet form, which can be problematic when treating young children who are typically unable to swallow pills (3, 4). To facilitate administration of ACT to children, tablets may be crushed and mixed with water. However, this process can result in loss of active ingredients and lead to underdosing. Crushed tablets can also be unpalatable as they have a bitter taste and often remain difficult to swallow, causing children to spit them out, thus adding to the risk of uncertain and/or subtherapeutic dosing (3, 4).

Dry powders intended for suspension in water have been developed for pediatric use but are often substandard relative to tablets, may contain ineffective or incorrect amounts of preservatives, and are also prone to contamination when reconstituted (5, 6). While liquid formulations such as syrups may be among the pediatric formulations preferred by some health professionals, their stability is often limited, particularly in hot climates. Distribution and storage can also be challenging with these formulations due to their high volume and weight (7), which also adds to the cost of freight.

As recognized by the World Health Organization (WHO), the use of specially created pediatric formulations has the potential to improve the effectiveness and accuracy of ACT dosing in young children (2). To address the potential risks associated with the availability in many countries of substandard medication that does not have proven quality and may therefore represent a potential risk for the development of resistance, the WHO instigated its Prequalification of Medicines Programme in 2001. This initiative aims to ensure that medicines supplied by procurement agencies meet acceptable standards of quality, safety, and efficacy (8). Good manufacturing process (GMP) guidelines must also be followed to help ensure the quality of any new product, including pediatric formulations of an existing medicine. Although many countries have developed local requirements, many also rely on the WHO-recommended GMP guidelines for pharmaceutical products (9).

Before new formulations of existing drugs are licensed, it is also usually necessary to perform bioequivalence studies to show that

Accepted manuscript posted online 26 May 2015

Citation Bassat Q, Ogutu B, Djimde A, Stricker K, Hamed K. 2015. Tailoring a pediatric formulation of artemether-lumefantrine for treatment of *Plasmodium falciparum* malaria. Antimicrob Agents Chemother 59:000–000. doi:10.1128/AAC.00014-15.

Address correspondence to Quique Bassat, quique.bassat@isglobal.org.

doi:10.1128/AAC.00014-15

the bioavailabilities of the new and original formulations (in terms of peak and total exposures) are similar to such a degree that their effects can be expected to be essentially the same after administration of the same molar dose under the same conditions (10). A number of guidelines provide instructions on how these bioequivalence studies should be carried out (10–12).

DEVELOPMENT OF AL DISPERSIBLE

Artemether-lumefantrine (AL) (Coartem; Novartis Pharma AG) is a fixed-dose ACT that meets the WHO prequalification criteria for efficacy, quality, and safety and has demonstrated consistently high (>95%) 28-day PCR-corrected cure rates (13–18). In order to overcome the challenges associated with dry powder and liquid formulations discussed above, Novartis, in partnership with the Medicines for Malaria Venture (MMV), has developed a dispersible tablet formulation of AL that is specifically tailored for the treatment of children with uncomplicated *Plasmodium falciparum* malaria (19). Its cherry flavor makes it more child-friendly than conventional tablets, which are bitter and are often spat out by children.

AL Dispersible (Novartis Pharma AG) is the first pediatric antimalarial to meet WHO specifications for use in infants and children who are ≥5 kg in body weight (8), has received Swissmedic approval, and is recommended for use in the relevant WHO guidelines (2). Since its launch in 2009, more than 250 million AL Dispersible treatments have been delivered to 50 countries of malaria endemicity (http://www.chemeurope.com/en/associations/34537/medicines-for-malaria-venture-mmv.html [accessed 20 May 2015]).

Despite the WHO recommendation and extensive experience with AL Dispersible over the last 5 years, there are very few publications that focus on this pediatric formulation. In an effort to address this, we have developed a comprehensive and up-to-date overview of clinical experience with AL Dispersible based on a systematic review of the recent literature.

LITERATURE SEARCH STRATEGY

Literature searches were conducted using PubMed, Ovid, and clinical trial registries for the period 1 January 2008 to 30 April 2014, using search terms that included coartem OR riamet OR CGP56697 OR CGP 56697 OR CGP-56697 OR coartemether OR exafal, artemether-lumefantrine OR artemether OR lumefantrine OR benflumelol OR benflumetol, *Plasmodium falciparum* OR malaria OR falciparum, and *Plasmodium vivax* OR vivax OR malaria. Searches were limited to include only the relevant age groups (e.g., infant, child, preschool, and adolescent). Search outputs were screened and assessed for reports of AL Dispersible clinical trials, including reviews discussing the clinical data.

Information extracted from each data source included study design and location, patient numbers, and mean age and age groups studied. The main efficacy endpoint reported in the identified trials was the PCR-corrected cure rate on day 28; secondary efficacy endpoints included the PCR-corrected cure rate on day 42, uncorrected cure rates on days 28 and 42, and time to clearance of parasites and fever. Safety data, pharmacokinetics, and outcomes relating to adherence to treatment and acceptability were also extracted and summarized.

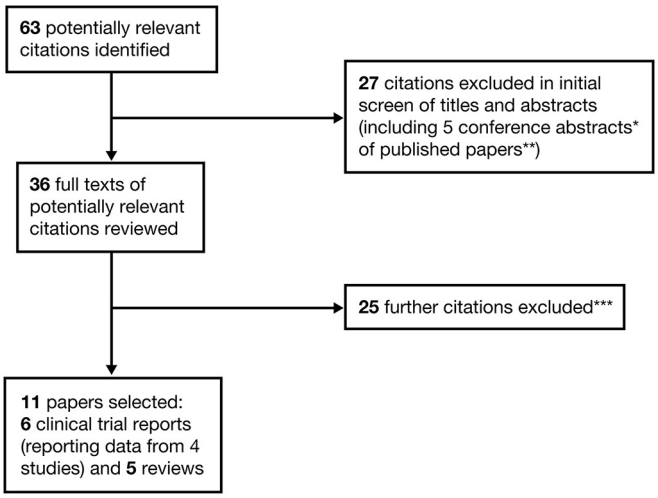

FIG 1 Summary of publication selection process following literature searches using PubMed, Ovid, and clinical trial registries for the period 1 January 2008 to 30 April 2014. *, due to duplication and screening studies not considered relevant for inclusion; **, due to duplication with published papers; ***, due to lack of AL Dispersible data (data on crushed AL tablets [$n = 7$], intact AL tablets [$n = 15$]), undeclared formulation ($n = 2$), and non-falciparum malaria ($n = 1$).

LITERATURE SEARCH RESULTS

Of 63 potentially relevant papers, 6 original papers reporting data from four clinical trials of AL Dispersible (19–24) and five relevant reviews were identified (3, 4, 25–27). A total of 52 records, including studies with data duplication, a lack of data on the AL Dispersible formulation (e.g., papers that focused on crushed or intact AL tablets), and undeclared AL formulation, studies in non-falciparum malaria patients, and screening studies considered not relevant for inclusion within the present paper, were discarded (Fig. 1). F1

Data from the identified clinical trials are discussed in detail in the following sections and are summarized in Table 1. T1

PALATABILITY AND BIOAVAILABILITY IN HEALTHY SUBJECTS

Data from two studies performed in healthy subjects during early development of AL Dispersible were reported in a single publication (20). The first of these studies was performed in order to select the flavor of the AL Dispersible tablet, an important consideration for encouraging children to adhere to treatment. A total of 48 healthy children in Tanzania tasted (without swallowing) differently flavored oral AL suspensions offered in a randomized, single-blind, crossover fashion. Although no statistically significant differences in visual analogue scale-assessed palatability scores between strawberry-, orange-, and cherry-flavored suspensions were observed, cherry had the highest score in several ratings, including overall liking and flavor. The cherry flavor was thus adopted for use in AL Dispersible.

The second of the studies reported in this minireview (20) was performed in order to meet the regulatory requirement to demonstrate bioequivalence of AL Dispersible and AL intact tablets. This study recruited 48 healthy adults and showed that single doses of AL Dispersible and AL intact tablets delivered bioequivalent systemic exposures of artemether, dihydroartemisinin (DHA [active metabolite of artemether]) and lumefantrine.

TABLE 1 Summary of clinical data reported for AL Dispersible from four clinical trials (identified from studies and analyses published between 1 January 2008 and 30 April 2014)[a]

Clinical trial or subanalysis	Reference	Study design and location	Population	Key efficacy data	Key safety data	Other outcomes/author comments
1	Abdulla et al. 2010 (20)	Palatability study: strawberry, orange and cherry flavors tested in a randomized, single-blind, crossover study in Tanzania	48 healthy schoolchildren (mean age, 8.6 yrs)	No efficacy data	No safety data	No statistically significant differences among the three flavors in VAS scores, but cherry had the highest score in several ratings (particularly for overall liking)
2	Abdulla et al. 2010 (20)	Bioavailability study: single doses administered with food in an open, randomized crossover study in France	48 healthy male and female adults (mean age, 33.1 yrs)	No efficacy data	No safety data	AL Dispersible and crushed tablets delivered bioequivalent artemether, DHA, and lumefantrine systemic exposures; mean ± SD $AUC_{0\text{-to-last}}$ values were 208 ± 113 vs 195 ± 93 h · ng/ml for artemether, 206 ± 81 vs 199 ± 84 h · ng/ml for DHA, and 262 ± 107 vs 291 ± 106 h · μg/ml for lumefantrine
3	Abdulla et al. 2008 (19)	AL Dispersible vs crushed tablets: randomized, single-blind, multicenter, controlled phase 3 study performed for 42 days in 5 countries of sub-Saharan Africa (Benin, Kenya, Mali, Mozambique, Tanzania)	899 children (median age in both treatment groups, 3.0 yrs) (group given AL Dispersible, 447; group given crushed tablets, 452)	For AL Dispersible vs crushed tablets, day 28 PCR-corrected cure rates (primary study objective), 97.8% vs 98.5%; day 42 PCR-corrected cure rates, 96.0% vs 96.9%; median times to fever clearance (h), 7.9 vs 7.8; median parasite clearance times (h), 34.3 vs 34.9; parasite clearance within 24 h, 38.5% vs 37.4%; parasite clearance within 48 h, 88.5% vs 89.4%; ACPR, 79.0% vs 75.7%; uncorrected day 28 cure rates, 92.1% vs 90.5%; uncorrected day 42 cure rates, 77.7% vs 74.5%	Overall frequencies of AEs, 68.7% vs 70.4%; the most-frequent drug-related AE for AL Dispersible vs crushed tablets was vomiting (7.4% vs 9.3%)	Ease of administration, compliance, and effectiveness facilitate adoption of AL Dispersible in malaria control programs; cost savings mentioned as being likely with use of AL Dispersible
Subanalyses of Abdulla et al. 2008 trial						
a	Bassat et al. 2011 (21)	Analysis by body wt: study design as described above	mITT populations (n = 812 children): 5 to <10 kg, 143 (17.6%; mean age, 14.4 mo); 10 to <15 kg, 334 (41.1%; mean age, 35.9 mo); 15 to <25 kg, 277 (34.1%; mean age, 71.7 mo); 25 to <35 kg, 8 (7%; mean age, 119.3 mo)	For body wt groups 5 to <10 kg, 10 to <15 kg, 15 to <25 kg, 25 to <35 kg, day 28 PCR-corrected cure rates (%), 97.2, 98.8, 97.8, 98.3; day 42 PCR-corrected cure rates (%), 95.3, 97.9, 95.8, 94.3; median times to fever clearance (h), 8.2, 7.8, 7.8, 7.7; median parasite clearance times (h), 35.6, 35.0, 25.8, 25.8	Incidence of most-frequent AEs by body wt group (5 to <10 kg, 10 to <15 kg, 15 to <25 kg, 25 to <35 kg): pyrexia (%), 42.3, 38.3, 34.9, 23.8; vomiting (%), 32.1, 16.4, 11.4, 3.2; *P. falciparum* malaria (%), 16.7, 20.1, 23.2, 25.4; headache (%), 0.6, 3.7, 13.5, 19.0; overall (%), 74.4, 69.9, 67.8, 61.9	Similar efficacies of AL Dispersible across body wt groups; no clinically relevant between-group difference in peak plasma concn for artemether or DHA, but lumefantrine concn appeared higher in 15-to-<25-kg group than in 5-to-<15-kg group
b	Borrmann et al. 2010 (22)	Food effect on bioavailability: study design as described above	PK analysis population (mean age, 4.1 yrs) (n = 621 children): AL Dispersible, 308; crushed tablets, 313	AL Dispersible vs crushed tablets (evaluable population): day 28 PCR-corrected cure rates, 99.0% vs 99.3%	Published in Abdulla et al. 2008 (19)	PK analysis confirmed that consumption of milk or regional diet during treatment enhanced absorption of and exposure to lumefantrine in children by factors ranging from 1.57 to 2.74 (artemether and DHA not measured)

c	Djimdé et al. 2011 (23)	PK and PD analysis: study design as described above	899 children (AL Dispersible, 447; crushed tablets, 452): 5 to <15 kg, 60.8%; 15 to <25 kg, 32.2%; 25 to <35 kg, 7.0%	Published in Abdulla et al. 2008 (19)	Published in Abdulla et al. 2008 (19)	PK analysis of AL Dispersible vs crushed tablet by body wt group (5 to <15 kg, 15 to <25 kg, 25 to <35 kg): mean artemether C_{max} (ng/ml), 196, 150, 134 vs 188, 198, 174; mean DHA C_{max} (ng/ml), 62.0, 66.5, 73.9 vs 54.7, 79.8, 68.4; mean lumefantrine C_{max} (μg/ml), 5.2, 8.0, NA vs 6.1, 9.4, NA (too few patients to determine data in highest-body-wt group); no correlation between artemether and DHA maximum concn and parasite clearance time or treatment-associated AEs was observed (no relationship could be investigated for lumefantrine)
4	Ogutu et al. 2014 (24)	AL Dispersible vs DHA-PPQ Pediatric: randomized, open-label, single-center study performed for 42 days in Kenya	454 children (AL Dispersible, 227; DHA-PPQ Pediatric, 227) (mean age, AL Dispersible, 29.6 mo, DHA-PPQ Pediatric, 32.0 mo)	AL Dispersible vs DHA-PPQ Pediatric: corrected day 28 ACPR rates (primary study objective), 97.8% vs 99.1%; uncorrected day 28 ACPR rates, 81.1% vs 87.7%; corrected day 42 ACPR rates, 96.8% vs 98.7%; uncorrected day 42 ACPR rates, 67.8% vs 70.5%; parasite clearance within 24 h, 50% vs 50%; parasite clearance within 40 h, 90% vs 90%; treatment failure (*n*) at day 28 for baseline parasite densities of <50,000/μl and >50,000/μl, 23 and 20 vs 12 and 14; treatment failure (*n*) at day 28 for baseline parasite densities of <100,000/μl and >100,000/μl, 31 and 12 vs 23 and 5	Incidence of most-frequent AEs for AL Dispersible vs DHA-PPQ Pediatric: malaria, 25.6% vs 18.2%; cough, 15.5% vs 17.3%; anemia, 4.2% vs 3.5%; fever, 2.9% vs 6.1%; overall, 65.5% vs 67.5%; one SAE (severe malaria) noted in AL Dispersible arm (not related to study drug)	Acceptability of AL Dispersible vs DHA-PPQ Pediatric: use of medication considered simple or very simple, 82.4% vs 67.0%, $P = 0.007$; taste of medication liked or liked very much, 72% vs 56.4, $P = 0.001$

[a] ACPR, adequate clinical and parasitological response; DHA, dihydroartemisinin; DHA-PPQ, dihydroartemisinin-piperaquine; AE, adverse event; mITT, modified intent to treat; NA, not applicable; PD, pharmacodynamic; PK, pharmacokinetic; SAE, serious adverse event; VAS, visual analogue scale.

zac00815/zac4220d15z xppws S=1 6/4/15 5:42 Facing: 3-4 ArtID: 00014-15 NLM: review-article CE: jtc

AL DISPERSIBLE VERSUS AL CRUSHED TABLETS

The first publication relating to the use of AL Dispersible in children and infants with malaria describes a pivotal randomized, single-blind, multicenter, controlled phase 3 study conducted in five countries of sub-Saharan Africa from August 2006 to March 2007 (19). The efficacy and safety of AL Dispersible versus crushed AL tablets were evaluated in 899 African children with uncomplicated malaria (Table 1). Median age, mean body weight, mean patient temperature, and median parasite density were 3.0 years, 14.4 kg, 38.0°C, and 26,364 asexual parasites/μl, respectively, for the dispersible-tablet population ($n = 447$) and 3.0 years, 14.5 kg, 38.0°C, and 32,288 asexual parasites/μl for the crushed-tablet population ($n = 452$) (19).

The 28-day PCR-corrected cure rates were 97.8% in the AL Dispersible group versus 98.5% in the crushed-tablet group (19). PCR-corrected cure rates at days 14 (99.5% versus 99.8%, respectively) and 42 (96.0 versus 96.9%, respectively) were also similar for the two formulations, as were the proportions of patients in the dispersible and crushed groups achieving parasite clearance within 24 h (38.5% versus 37.4%) and 48 h (88.5% versus 89.4%) (19). Other efficacy data from the trial are summarized in Table 1.

The pharmacokinetic profile of AL Dispersible was similar to that of crushed tablets; maximum concentrations of drug in plasma (C_{max}) in the AL Dispersible group versus the crushed-tablet group, respectively, were 175 versus 211 μg/liter for artemether, 68.0 versus 63.7 μg/liter for DHA, and 6.3 versus 7.7 mg/liter for lumefantrine. Similar lumefantrine concentration-time profiles were also obtained following the two treatments (574 versus 636 mg · h/liter, respectively) (19).

There was no clinically relevant difference in the maximum plasma concentration of artemether versus that of DHA across different body weight subgroups, although lumefantrine C_{max} and area under the curve (AUC) values appeared higher in the 15-to-<25-kg group than in the 5-to-<15-kg group (19). Plasma levels of artemether, DHA, and lumefantrine in all body weight groups, including the smallest children (5 to <10 kg), remained within the ranges reported in adult patients (21).

Both treatment groups tolerated the drug, with similar overall frequencies of adverse events (AE) observed (68.7% for the AL Dispersible group versus 70.4% for the crushed-tablet group). The most commonly reported AEs (across the total study population) were associated with malaria signs or symptoms such as pyrexia (36.9%) and coughing (24.2%), and the most frequent drug-related AE was vomiting (8.3%). A slight increase in the QTc interval (corrected measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) was observed in both treatment groups. There were no reports of hemolytic anemia (19).

AQ: D

AL DISPERSIBLE VERSUS AL CRUSHED TABLETS: SUBANALYSES

Body weight. AL is dosed according to body weight, such that patients weighing 5 to <15 kg, 15 to <25 kg, 25 to <35 kg, or >35 kg receive 1, 2, 3, or 4 tablets per dose, respectively. Patients receive six doses at 0, 8, 24, 36, 48, and 60 h (i.e., two doses each on days 1, 2, and 3 of treatment). Bassat (21) analyzed data from the pivotal multicenter, controlled phase 3 study described above to evaluate the effect of body weight on the efficacy and safety of AL Dispersible (Table 1) and to address the issue of whether those at the lower or upper end of a weight category were at risk of over- or underdosing (21).

The modified intent-to-treat (mITT) population ($n = 812$) comprised 143 children who were 5 to <10 kg in body weight, 334 children who were 10 to <15 kg, 277 children who were 15 to <25 kg, and 58 children who were 25 to <35 kg. The 28-day PCR cure rates (97.2%, 98.9%, 97.8%, and 98.3%, respectively), representing the primary endpoint, were comparable across the four body weight groups. There were no clinically relevant differences in safety or tolerability between body weight groups, although an increased incidence of vomiting and pyrexia and a decreased incidence of headache and *P. falciparum* infection were associated with lower body weights (21). In the three AL body weight dosing groups (5 to <15 kg, 15 to <25 kg, and 25 to <35 kg), 80% of patients were aged 10 to 50 months, 46 to 100 months, and 90 to 147 months, respectively (21).

Food consumption. The effect of food consumption on the efficacy of AL and lumefantrine pharmacokinetics was evaluated in African children with uncomplicated malaria, using data obtained during the pivotal phase 3 study (Table 1) (22). The overall 28-day PCR-corrected cure rate in the evaluable pharmacokinetic population ($n = 587$) was 99.1%, and the cure rates seen with the AL Dispersible and crushed-tablet groups were similar (99.0% versus 99.3%). Efficacy was not related to food intake; patients who consumed no food near the time of dosing ($n = 35$) had a 28-day PCR-corrected cure rate of 100% (22). Consumption of milk or a low-fat meal increased lumefantrine bioavailability compared to the bioavailability seen in the absence of food intake (Fig. 2). This increase was greater in older children than in younger children (22).

F2

Pharmacokinetic/pharmacodynamic comparison. A detailed pharmacokinetic/pharmacodynamic comparison of AL Dispersible versus crushed AL tablets has also been reported on the basis of data from the pivotal phase 3 study population (23). No clinically meaningful correlation was found between artemether or DHA C_{max} values and parasite clearance time or occurrence of treatment-related AEs for either treatment (23).

AL DISPERSIBLE VERSUS DHA-PPQ PEDIATRIC COMPARATOR STUDY

An open-label, randomized, single-center comparator study was conducted in Kenya from March 2010 to November 2011 to compare AL Dispersible and dihydroartemisinin-piperaquine (DHA-PPQ) Pediatric. DHA-PPQ Pediatric consisted of a standard dose combining 2.25 mg/kg DHA and 18 mg/kg piperaquine, with the tablets crushed and dispersed in a small volume of water or milk. The efficacy and safety of AL Dispersible ($n = 227$) and DHA-PPQ Pediatric tablets ($n = 227$) were evaluated in 454 Kenyan children with uncomplicated malaria (Table 1). The mean ages of the AL Dispersible and DHA-PPQ Pediatric populations were 29.6 and 32.0 months, respectively. Mean body weights, temperatures, and parasite densities for the AL Dispersible and DHA-PPQ Pediatric populations were 12.2 kg, 38.3°C, and 38,202/μl and 12.3 kg, 38.3°C, and 38,546/μl, respectively (24).

No significant differences in PCR-corrected adequate clinical and parasitological response (ACPR) rates between the AL Dispersible and DHA-PPQ Pediatric groups were observed at day 28 (97.8% versus 99.1%), day 14 (100% versus 100%), and day 42 (96.8% versus 98.7%). Times to parasite clearance were

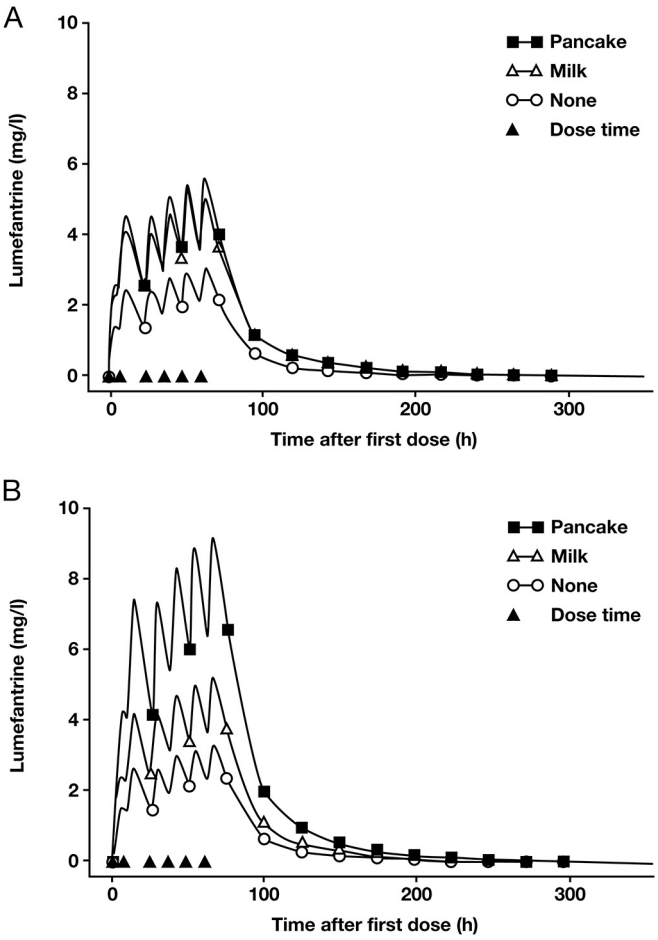

FIG 2 Predicted plasma lumefantrine concentration versus time after first dose by treatment and meal type for AL Dispersible (A) and crushed AL tablets (B) in African children with uncomplicated malaria. (Reprinted from reference 22 with permission of the publisher.)

also similar in the two groups, with 50% parasite clearance achieved in 24 h and 90% parasite clearance at 40 h for both treatment arms.

Both treatments were generally well tolerated; the overall incidences of AEs in the AL Dispersible and DHA-PPQ Pediatric treatment groups were similar at 65.5% and 67.5%, respectively. The most commonly occurring AEs were related to malarial infection and included cough (15.5% and 17.3%, respectively) and anemia (4.2% and 3.5%, respectively) (24).

Acceptability of treatment was higher for AL Dispersible than for DHA-PPQ Pediatric, as determined by a caregiver questionnaire. The taste of AL Dispersible was "liked" or "liked very much" by 72% of respondents compared with 56% for DHA-PPQ Pediatric ($P = 0.001$). Administration of the drug was considered "simple" or "very simple" by 82% of the patients on AL Dispersible and 67% on DHA-PPQ Pediatric ($P = 0.007$). Adherence to treatment was also higher for AL Dispersible (93.6% versus 85.6%; $P = 0.089$) (24).

DISCUSSION

Since its launch in 2009, more than 250 million AL Dispersible treatments have been delivered to 50 countries of malaria endemicity (http://www.chemeurope.com/en/associations/34537/medicines-for-malaria-venture-mmv.html; accessed 20 May 2015). Despite the scaling up of its use in recent years, it remains efficacious as a first-line treatment for uncomplicated malaria, with no current evidence that development of resistance has occurred in sub-Saharan Africa (4). AL Dispersible was specifically tailored for the pediatric population and offers several benefits, including efficacy, convenience and acceptance, accurate dosing, safety, sterility and stability, and pharmacokinetic profile and bioequivalence similar to those of crushed and intact AL tablets (19, 23, 25).

The efficacy of AL Dispersible has been shown to be maintained over time; the regimen consistently achieves PCR-corrected cure rates of >95% at day 28 after administration, and the cure rate is not affected by body weight (21). Efficacy is comparable to that achieved with standard crushed AL tablets in children and infants (19), although the dispersible formulation has additional benefits. AL Dispersible tablets take less than 1 min to disperse in a small volume of liquid, forming a sweet-tasting medicine that appeals to children (20). Because of its pleasant, sweet taste, AL Dispersible is not disliked by children to the same extent as conventional tablets, which have a bitter taste when crushed; this in turn encourages adherence to the complete treatment regimen and presents parents/guardians and health workers with the advantages of a convenient and well-accepted formulation, despite the relative inconvenience of a twice-daily dosing schedule (24, 26). Importantly, the efficacy of AL Dispersible does not appear to be affected by intake of food (22). Furthermore, there is no requirement for routine electrocardiogram (ECG) assessment with AL Dispersible (28), unlike other antimalarials, such as those containing piperaquine, where ECG monitoring is recommended in those considered to be at risk of developing arrhythmia related to QTc prolongation (specifically, female and elderly patients and young children who have vomited) (29).

AL Dispersible tablets contain an accurate dose of the active antimalarial ingredient, and the formulation ensures that the full and appropriate dose is administered to the patient. This is an advantage over crushed tablets, where loss of some of the pill can lead to suboptimal dosing, and also over dry powder and syrup formulations, where accurate dosing requires precise volume measuring in the field (3). In addition, stability cannot be guaranteed when syrups and powders are reconstituted, particularly in hot climates (5). AL Dispersible tablets are provided in dose blister packs that offer protection from contamination and also from humidity and damage (30).

The safety profile of AL Dispersible is comparable to the safety profiles of standard AL and crushed AL tablets (13, 19, 31); the most common AEs are associated with symptoms of malaria and include pyrexia, headache, anorexia, dizziness, asthenia, arthralgia, myalgia, and nausea.

The development of WHO-prequalified pediatric ACT formulations such as AL Dispersible addresses a key unmet need in malaria treatment. Unfortunately, there are several drugs available on the market that are not WHO prequalified and therefore have unproven quality. Such drugs represent a risk to affected patients and threaten efforts to control malaria. The reality of this issue is highlighted by the recent withdrawal from the U.S. market of certain generic drugs due to inappropriate manufacturing in China and India (32).

Several pediatric ACT formulations are currently approved for

use in treatment of uncomplicated *P. falciparum* malaria, although only two ACT treatments, in addition to AL Dispersible, are currently WHO prequalified and considered appropriate for children in the relevant doses. A fixed-dose combination (FDC) of artesunate and amodiaquine (ASAQ FDC [Coarsucam]; ASAQ Winthrop) is one such treatment developed by Sanofi and the Drugs for Neglected Diseases initiative (DNDi). ASAQ FDC is provided as a soluble tablet formulation for children unable to swallow pills and has day 42 (97.3% ASAQ versus 94.2% AL) and day 28 (99.3% ASAQ versus 97.9 AL) PCR-corrected cure rates similar to those seen with the standard-formulation AL crushed tablets administered with a high-fat cookie, which were well above the WHO-recommended 90% threshold for treatments in use (33).

An artesunate-mefloquine fixed-dose combination (ASMQ FDC) produced by Cephalon/Mepha and DNDi has also been WHO prequalified. The pediatric dose (25 mg/55 mg) of this drug easily disintegrates in a small volume of water to ease administration to children (34). The PCR-corrected cure rates for ASMQ FDC and AL tablets (standard formulation crushed and mixed with water) were 96.2% and 93.7%, respectively, in children with uncomplicated malaria, indicating comparable efficacies (35). In the same study, no serious AEs were reported; the most common AE was vomiting (reported in 30% and 36% of children in the ASMQ and AL arms, respectively). ASMQ has a strong posttreatment prophylactic effect (36).

Another pediatric antimalarial expected to be submitted shortly for WHO prequalification is a granule formulation of pyronaridine-artesunate (Pyramax; Shin Poong Pharmaceutical Co. Ltd. and Medicines for Malaria Venture), which shows efficacy, tolerability, and pharmacokinetic characteristics similar to those seen with standard tablet formulations and is also taste-masked to appeal to children (37).

It should be noted that there are no data from comparator studies performed with AL Dispersible for the pediatric formulations described above; these formulations have been compared with AL crushed tablets, which, as discussed, may be unpalatable (due to their bitter taste), leading to subtherapeutic dosing and poor treatment compliance.

A further pediatric ACT formulation (not currently WHO prequalified but expected to be submitted for prequalification status very soon) is the nondispersible DHA-PPQ Pediatric (8). DHA-PPQ Pediatric is currently used in some countries as a rescue and/or alternative treatment following initial AL Dispersible therapy. It has benefits similar to those seen with AL Dispersible, such as ease of use and accurate dosing, and requires only a single daily dose. Nevertheless, when the two formulations were directly compared, AL Dispersible was better accepted and tolerated and considered easier to use and better tasting (24). In high-transmission settings, the use of DHA-PPQ Pediatric may be more attractive owing to the longer half-life of piperaquine (3 to 4 weeks) compared with that of lumefantrine (3 to 6 days). The longer half-life results in a longer posttherapeutic prophylactic effect and a decreased reinfection rate in the first 28 days compared with AL (38). However, theoretically, the longer half-life could also potentially increase the risk of selection of resistance to piperaquine (39).

Finally, a DHA-PPQ pediatric dispersible formulation has been developed by Sigma Tau (Italy) and is currently being tested in a phase 2 study against *P. falciparum* malaria in different sites in Africa (ClinicalTrials registration no. NCT01992900).

A randomized trial in 298 children aged 6 months to 10 years compared the efficacies of intact tablet formulations of AL and DHA-PPQ and showed that, despite similar overall PCR-corrected efficacies, gametocyte carriage and malaria transmission to mosquitoes were lower after AL treatment than after DHA-PPQ treatment; the proportion of mosquitoes that became infected after feeding on blood from AL-treated children was 1.88% (43 of 2,293), compared with 3.50% (83 of 2,371) for those that fed on blood from DHA-PPQ-treated children ($P = 0.06$) (40). The effects of AL on gametocyte carriage have recently been reviewed by Makanga (41). Decreased gametocyte carriage following AL treatment was observed across all reviewed studies, suggesting that AL could have an important role in limiting disease transmission.

Additional data on the efficacy of AL have recently been reported in a pooled analysis of clinical trials involving a total of 14,327 patients with *P. falciparum* malaria. The analysis was performed in order to investigate the influence of dosing strategy on the efficacy of various AL formulations (only 431 patients [3%; all in Africa] received AL Dispersible). In this analysis, which captured 61 trials, the overall PCR-adjusted cure rates were 97.6% at day 28 and 96.0% at day 42. The efficacy of AL was reliably high in all age and weight categories. Notably, however, cure rates appeared to be lowest in young children from Asia and young underweight children from Africa; PCR-adjusted cure rates in these groups were 91.7% and 94.3%, respectively. While patient numbers were relatively small within these subgroups, the authors concluded that a higher-dose regimen should be evaluated in these patients (42).

In conclusion, the data reviewed above provide a strong argument for specifically tailoring antimalarial formulations to children, the most vulnerable patients, who are in serious need of effective treatment. Given the well-documented comparable data on efficacy, safety, and pharmacokinetics, plus the greater acceptability, tolerability, and palatability observed with AL Dispersible compared with AL crushed tablets and other ACTs, it is our opinion that this highly efficacious formulation should be made more readily available to all children <5 years of age with uncomplicated malaria. As with any antimalarial treatment, continued sensitivity monitoring of AL Dispersible for emergence of resistance is also required.

ACKNOWLEDGMENTS

Medical writing support was provided by Rachel Mason, Certified Medical Publication Professional (CMPP), at Seren Communications (Tytherington, United Kingdom) and was funded by Novartis.

Q.B. has received speaker's fees and travel grants from Sigma Tau in relation to dihydroartemisinin-piperaquine and has worked as an investigator on studies of dihydroartemisinin-piperaquine sponsored by both Sigma-Tau and Medicines for Malaria Venture. He has also worked as an investigator in studies of artemether-lumefantrine and has previously received speaker's fees and travel grants from Novartis. Q.B. has a fellowship from the program Miguel Servet of the ISCIII (Plan Nacional de I+D+I 2008-2011, grant CP11/00269). B.O. has worked as an investigator on studies of artemether-lumefantrine and dihydroartemisinin-piperaquine sponsored by the WHO, Bill and Melinda Gates Foundation, Novartis and MMV. He has previously received speaker's fees and travel grants from Novartis. A.D. has worked as an investigator in studies of artemether-lumefantrine funded by EDCTP and MMV and has previously received speaker's fees from Novartis. K.S. is an employee of Novartis Pharma AG,

Basel, Switzerland. K.H. is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

REFERENCES

1. **WHO.** 2014. World malaria report 2014. World Health Organization, Geneva, Switzerland.
2. **WHO.** 2015. Guidelines for the treatment of malaria, 3rd ed. World Health Organization, Geneva, Switzerland.
3. **Abdulla S, Sagara I.** 2009. Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children. Malar J **8:**S7. http://dx.doi.org/10.1186/1475-2875-8-S1-S7.
4. **Ogutu B.** 2013. Artemether and lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa. Expert Opin Pharmacother **14:**643–654. http://dx.doi.org/10.1517/14656566.2013.771167.
5. **Atemnkeng M, De Cock K, Plaizier-Vercammen J.** 2007. Post-marketing assessment of content and efficacy of preservatives in artemisinin-derived antimalarial dry suspensions for paediatric use. Malar J **6:**12. http://dx.doi.org/10.1186/1475-2875-6-12.
6. **Atemnkeng MA, De Cock K, Plaizier-Vercammen J.** 2007. Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and DR Congo. Trop Med Int Health **12:**68–74. http://dx.doi.org/10.1111/j.1365-3156.2006.01769.x.
7. **Agnandji S, Kurth F, Fernandes J, Soulanoudjingar S, Abossolo B, Mombo-Ngoma G, Basra A, Gonzalez R, Kizito G, Mayengue P, Auer-Hackenberg L, Issifou S, Lell B, Adegnika A, Ramharter M.** 2011. The use of paediatric artemisinin combinations in sub-Saharan Africa: a snapshot questionnaire survey of health care personnel. Malar J **10:**365. http://dx.doi.org/10.1186/1475-2875-10-365.
8. **WHO.** 2013. The WHO prequalification project. World Health Organization, Geneva, Switzerland.
9. **WHO Expert Committee on Specifications for Pharmaceutical Preparations.** 2014. Good manufacturing practices for pharmaceutical products: main principles. Annex 2. Forty-eighth report. WHO technical report series no. 986. World Health Organization, Geneva, Switzerland. http://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf?ua=1. Accessed 20 May 2015.
10. **US Department of Health and Human Services Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER).** 2014. Guidance for industry. Bioavailability and bioequivalence studies submitted in NDAs or INDs-general considerations. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf. Accessed 20 May 2015.
11. **European Medicines Agency.** 2010. Guideline on the investigation of bioequivalence. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed 20 May 2015.
12. **Swissmedic.** 2009. Instructions for application and authorisation for generics. Swissmedic, Bern, Switzerland.
13. **Makanga M, Bassat Q, Falade CO, Premji ZG, Krudsood S, Hunt P, Walter V, Beck H-P, Marrast A-C, Cousin M, Rosenthal PJ.** 2011. Efficacy and safety of artemether-lumefantrine in the treatment of acute, uncomplicated Plasmodium falciparum malaria: a pooled analysis. Am J Trop Med Hyg **85:**793–804. http://dx.doi.org/10.4269/ajtmh.2011.11-0069.
14. **Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, Ruzagira E, Babigumira J, Kigozi I, Kiguli J, Kyomuhendo J, Ferradini L, Taylor W, Checchi F, Guthmann J-P.** 2005. Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated Plasmodium falciparum malaria in Mbarara, Uganda: a randomised trial. Lancet **365:**1467–1473. http://dx.doi.org/10.1016/S0140-6736(05)66416-1.
15. **Makanga M, Premji Z, Falade C, Karbwang J, Mueller EA, Andriano K, Hunt P, De Palacios PI.** 2006. Efficacy and safety of the six-dose regimen of artemether-lumefantrine in pediatrics with uncomplicated Plasmodium falciparum malaria: a pooled analysis of individual patient data. Am J Trop Med Hyg **74:**991–998.
16. **Eshetu T, Abdo N, Bedru K, Fekadu S, Wieser A, Pritsch M, Loscher T, Berens-Riha N.** 2012. Open-label trial with artemether-lumefantrine against uncomplicated Plasmodium falciparum malaria three years after its broad introduction in Jimma Zone, Ethiopia. Malar J **11:**240. http://dx.doi.org/10.1186/1475-2875-11-240.
17. **Kamugisha E, Jing S, Minde M, Kataraihya J, Kongola G, Kironde F, Swedberg G.** 2012. Efficacy of artemether-lumefantrine in treatment of malaria among under-fives and prevalence of drug resistance markers in Igombe-Mwanza, north-western Tanzania. Malar J **11:**58. http://dx.doi.org/10.1186/1475-2875-11-58.
18. **Mayxay M, Khanthavong M, Chanthongthip O, Imwong M, Pongvongsa T, Hongvanthong B, Phompida S, Vanisaveth V, White N, Newton P.** 2012. Efficacy of artemether-lumefantrine, the nationally-recommended artemisinin combination for the treatment of uncomplicated falciparum malaria, in southern Laos. Malar J **11:**184. http://dx.doi.org/10.1186/1475-2875-11-184.
19. **Abdulla S, Sagara I, Borrmann S, D'Alessandro U, González R, Hamel M, Ogutu B, Mårtensson A, Lyimo J, Maiga H, Sasi P, Nahum A, Bassat Q, Juma E, Otieno L, Björkman A, Beck HP, Andriano K, Cousin M, Lefèvre G, Ubben D, Premji Z.** 2008. 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. Lancet **372:**1819–1827. http://dx.doi.org/10.1016/S0140-6736(08)61492-0.
20. **Abdulla S, Amuri B, Kabanywanyi A, Ubben D, Reynolds C, Pascoe S, Fitoussi S, Yeh C-M, Nuortti M, Sechaud R, Kaiser G, Lefevre G.** 2010. Early clinical development of artemether-lumefantrine dispersible tablet: palatability of three flavours and bioavailability in healthy subjects. Malar J **9:**253. http://dx.doi.org/10.1186/1475-2875-9-253.
21. **Bassat Q, Gonzalez R, Machevo S, Nahum A, Lyimo J, Maiga H, Martensson A, Bashraheil M, Ouma P, Ubben D, Walter V, Nwaiwu O, Kipkeu C, Lefevre G, Ogutu B, Menendez C.** 2011. Similar efficacy and safety of artemether-lumefantrine (Coartem) in African infants and children with uncomplicated falciparum malaria across different body weight ranges. Malar J **10:**369. http://dx.doi.org/10.1186/1475-2875-10-369.
22. **Borrmann S, Sallas WM, Machevo S, González R, Björkman A, Mårtensson A, Hamel M, Juma E, Peshu J, Ogutu B, Djimdé A, D'Alessandro U, Marrast A-C, Lefèvre G, Kern SE.** 2010. The effect of food consumption on lumefantrine bioavailability in African children receiving artemether-lumefantrine crushed or dispersible tablets (Coartem) for acute uncomplicated Plasmodium falciparum malaria. Trop Med Int Health **15:**434–441. http://dx.doi.org/10.1111/j.1365-3156.2010.02477.x.
23. **Djimdé AA, Tekete M, Abdulla S, Lyimo J, Bassat Q, Mandomando I, Lefèvre G, Borrmann S, B2303 Study Group.** 2011. Pharmacokinetic and pharmacodynamic characteristics of a new pediatric formulation of artemether-lumefantrine in African children with uncomplicated Plasmodium falciparum malaria. Antimicrob Agents Chemother **55:**3994–3999. http://dx.doi.org/10.1128/AAC.01115-10.
24. **Ogutu B, Onyango KO, Koskei N, Omondi EK, Ongecha JM, Otieno GA, Obonyo C, Otieno L, Eyase F, Johnson JD, Omollo R, Perkins DJ, Akhwale W, Juma E.** 2014. Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated Plasmodium falciparum malaria in Kenyan children aged less than five years: results of an open-label, randomized, single-centre study. Malar J **13:**33. http://dx.doi.org/10.1186/1475-2875-13-33.
25. **Djimde A, Lefevre G.** 2009. Understanding the pharmacokinetics of Coartem. Malar J **8:**S4. http://dx.doi.org/10.1186/1475-2875-8-S1-S4.
26. **Hamed K, Grueninger H.** 2012. Coartem: a decade of patient-centric malaria management. Expert Rev Anti Infect Ther **10:**645–659. http://dx.doi.org/10.1586/eri.12.51.
27. **Kurth F, Bélard S, Adegnika AA, Gaye O, Kremsner PG, Ramharter M.** 2010. Do paediatric drug formulations of artemisinin combination therapies improve the treatment of children with malaria? A systematic review and meta-analysis. Lancet Infect Dis **10:**125–132. http://dx.doi.org/10.1016/S1473-3099(09)70327-5.
28. **WHO.** 2011. Riamet Dispersible/Coartem Dispersible: summary of product characteristics. WHOPAR Part 4. WHO, Geneva, Switzerland. http://apps.who.int/prequal/whopar/whoparproducts/MA069part4v1.pdf. AQ: G
29. **●●●.** 2011. Eurartesim: summary of product characteristics. **●●●.** AQ: H
30. **International Pharmaceutical Industry (IPI).** 2009. Innovation in malaria drug packaging: Coartem and Coartem Dispersible. International Pharmaceutical Industry, London, United Kingdom.
31. **Falade C, Makanga M, Premji Z, Ortmann C-E, Stockmeyer M, de Palacios PI.** 2005. Efficacy and safety of artemether–lumefantrine (Coartem) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria. Trans R Soc Trop Med Hyg **99:**459–467. http://dx.doi.org/10.1016/j.trstmh.2004.09.013.
32. **Consume Reports.** 2014. Are drugs like Apotex medication made in India safe? FDA sanctions against some Indian drug plants raise concerns about

AQ: F

the U.S. generic-drug supply. http://www.consumerreports.org/cro/news/2014/04/are-generic-drugs-made-in-india-safe/index.htm. Accessed 20 May 2015)

33. **Schramm B, Valeh P, Baudin E, Mazinda C, Smith R, Pinoges L, Dhorda M, Boum Y, Sundaygar T, Zolia Y, Jones J, Comte E, Houze P, Jullien V, Carn G, Kiechel J-R, Ashley E, Guerin P.** 2013. Efficacy of artesunate-amodiaquine and artemether-lumefantrine fixed-dose combinations for the treatment of uncomplicated Plasmodium falciparum malaria among children aged six to 59 months in Nimba County, Liberia: an open-label randomized non-inferiority trial. Malar J **12:**251. http://dx.doi.org/10.1186/1475-2875-12-251.
34. **Drugs for Neglected Diseases initiative (DNDi).** 2012. The fixed-dose combination of artesunate and mefloquine: a new, effective tool in the fight against malaria—executive report. Drugs for Neglected Diseases Initiative, Geneva, Switzerland.
35. **Faye B, Ndiaye JL, Tine R, Sylla K, Gueye A, Lô AC, Gaye O.** 2010. A randomized trial of artesunate-mefloquine versus artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Senegalese children. Am J Trop Med Hyg **82:**140–144. http://dx.doi.org/10.4269/ajtmh.2010.09-0265.
36. **Smithuis F, Kyaw MK, Phe O, Win T, Aung PP, Oo APP, Naing AL, Nyo MY, Myint NZH, Imwong M, Ashley E, Lee SJ, White NJ.** 2010. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. Lancet Infect Dis **10:**673–681. http://dx.doi.org/10.1016/S1473-3099(10)70187-0.
37. **Ramharter M, Kurth F, Schreier AC, Nemeth J, von Glasenapp I, Bélard S, Schlie M, Kammer J, Koumba Koumba P, Cisse B, Mordmüller B, Lell B, Issifou S, Oeuvray C, Fleckenstein L, Kremsner PG.** 2008. Fixed-dose pyronaridine-artesunate combination for treatment of uncomplicated falciparum malaria in pediatric patients in Gabon. J Infect Dis **198:**911–919. http://dx.doi.org/10.1086/591096.
38. **Zongo I, Dorsey G, Rouamba N, Dokomajilar C, Séré Y, Rosenthal PJ, Ouédraogo JB.** 2007. Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in Burkina Faso. Clin Infect Dis **45:**1453–1461. http://dx.doi.org/10.1086/522985.
39. **Agarwal A, McMorrow M, Onyango P, Otieno K, Odero C, Williamson J, Kariuki S, Kachur S, Slutsker L, Desai M.** 2013. A randomized trial of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated malaria among children in western Kenya. Malar J **12:**254. http://dx.doi.org/10.1186/1475-2875-12-254.
40. **Sawa P, Shekalaghe SA, Drakeley CJ, Sutherland CJ, Mweresa CK, Baidjoe AY, Manjurano A, Kavishe RA, Beshir KB, Yussuf RU, Omar SA, Hermsen CC, Okell L, Schallig HD, Sauerwein RW, Hallett RL, Bousema T.** 2013. Malaria transmission after artemether-lumefantrine and dihydroartemisinin-piperaquine: a randomized trial. J Infect Dis **207:**1637–1645. http://dx.doi.org/10.1093/infdis/jit077.
41. **Makanga M.** 2014. A review of the effects of artemether-lumefantrine on gametocyte carriage and disease transmission. Malar J **13:**291. http://dx.doi.org/10.1186/1475-2875-13-291.
42. **Worldwide Antimalarial Resistance Network (WWARN) AL Dose Impact Study Group.** 16 March 2015, posting date. The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data. Lancet Infect Dis http://dx.doi.org/10.1016/S1473-3099(15)70024-1.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 1

AQau—Please confirm the given-names and surnames are identified properly by the colors.
■= Given-Name, ■= Surname

AQau—An ORCID ID was provided for at least one author during submission. Please click the name associated with the ORCID ID icon (iD) in the byline to verify that the link is working and that it links to the correct author.

AQaff—Please confirm the following full affiliations or correct here as necessary. This is what will appear in the online HTML version:

[a]ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic—Universitat de Barcelona, Barcelona, Spain
[b]Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique
[c]Centre for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya
[d]Malaria Research and Training Center, University of Science, Techniques and Technologies of Bamako, Bamako, Mali
[e]Novartis Pharma AG, Basel, Switzerland
[f]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

AQaff—This affiliation line will appear in the PDF version of the article and matches that on page 1 of the proof; corrections to this affiliation line may be made here **or** on page 1 of the proof:

ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic—Universitat de Barcelona, Barcelona, Spain[a]; Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique[b]; Centre for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya[c]; Malaria Research and Training Center, University of Science, Techniques and Technologies of Bamako, Bamako, Mali[d]; Novartis Pharma AG, Basel, Switzerland[e]; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA[f]

AQA—The title was edited for concision per AAC journal style.

AQB—The heading "Rationale for AL Dispersible" has been deleted per ASM style, which does not allow a heading between the abstract and text in a minireview.

AQC—Former reference 20 has been moved to the text per ASM style. To ensure sequential order, references have been renumbered in the text and References. Please check and correct the renumbering if necessary. If any reference should be deleted from the References list, please mark "Reference deleted" in the margin next to that entry; do not renumber subsequent references.

AQD—Please check introductions of abbreviations throughout.

AQE—The use of italics for emphasis has been disallowed per ASM style.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 2

AQF—Please provide a digital object identifier (DOI) number if available for reference 15.

AQG—If reference 29 has not been edited as meant, please correct.

AQH—Please provide the missing publication information for reference 30 (e.g., manufacturer name and location).