Artemeter-Lumefantrine therapeutic efficacy, safety and plasma levels in patients with uncomplicated falciparum malaria from the Colombian Pacific region

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Abstract
Introduction: In Colombia, the published studies for the treatment of uncomplicated Plasmodium falciparum malaria with Artemether-Lumefantrine are scarce. The aim of the study was to evaluate the therapeutic efficacy and safety profile of this combination.

Methods: A clinical trial was performed in adults with uncomplicated P. falciparum malaria using the 28-day World Health Organization validated protocol. Patients received supervised antimalarial treatment and the primary efficacy endpoint was the clinical and parasitological response. Safety was assessed through adverse events surveillance and plasmatic levels of antimalarial drugs were measured.

Results: 88 patients were included. Adequate clinical and parasitological response rate of 100% on day 28 was achieved in 84 patients, diagnosed by thick blood smear examination. There were four parasitological therapeutic failures (5%) detected by polymerase chain reaction.

Discussion: Therapeutic efficacy similar to previous studies was established with a slight increase in therapeutic failure. The serum levels of the antimalarials were adequate and the few cases of therapeutic failure were not related.

Conclusion: Treatment of uncomplicated P. falciparum malaria with Artemeter-Lumefantrine was effective and safe in the study population. All patients reached adequate plasma concentrations of the drugs; therapeutic failures were not associated with low blood levels of the drug clinical trial.

Keywords: Malaria, Plasmodium falciparum, Artemeter-Lumefantrine, Efficacy, Safety, Plasmatic levels,
Introduction

Malaria is widespread in tropical areas worldwide and has a high morbidity burden. The emergence of parasite resistance to antimalarial medicines is considered part of the challenges impeding countries’ abilities to advance towards elimination; these include lack of sustainable funding, risks posed by conflict in malaria endemic zones, and mosquito resistance to insecticides.

Approximately 216 million malaria cases were reported globally in 2016 and the disease was considered endemic in 91 countries and territories. For this same year, the most prevalent species in Colombia were *P. falciparum* and *P. vivax* with 57,515 cases confirmed with microscopy and 5,655 with rapid diagnostic tests, and a total of 18 reported deaths in 2015. Previous national data about the infections showed a higher incidence of *P. vivax* infections over *P. falciparum* infections from years 2000 to 2013. In the last years the proportion of *P. falciparum* cases reported is increasing; 50.6% were *P. falciparum* infections between 40,763 cases in 2014, and 59.8% between 51,594 cases in 2015. In the recent years, malaria transmission was focalized in Chocó region.

Artemisinin Combination Therapies (ACTs) have been integrated into the recent success of global malaria control, and protecting their efficacy for the treatment of *P. falciparum* malaria is a global health priority. In Colombia, antimalarial treatment for uncomplicated falciparum malaria is based on ACTs in accordance with the World Health Organization recommendation for regions with resistance to antimalarials. First line treatment is based on fixed-dose co-formulation tablets of Artemeter-Lumefantrine (AL). The majority of the studies analyzing efficacy of this antimalarial regimen are conducted in high transmission regions, and selection of mutations that could possibly confer *P. falciparum* resistance to ACT has been reported both in vivo and ex-vivo. The advice for government health programs is to closely monitor parasite genotypic, phenotypic and clinical dynamics of *P. falciparum* infections in response to ACTs, despite its continued efficacy.

Although multidrug resistance, including Artemisinin, has been reported in five countries of the Greater Mekong sub region (GMS) in America efficacy studies are scarce. A study conducted in Suriname in 2011 detected a 9% treatment failure rate with AL. Other studies conducted in the period 2010–2016 showed effective first-line treatment for *P. falciparum* (treatment failure rates 0%) (1). In Colombia a study in 2008 with Artesunate-Amodiaquine (AS-AQ) regimen vs. AL regimen, found no early treatment failure (ETF) or late clinical failures (LCF) in either group and one late parasitological treatment failure (LPTF) in the AL group.

Considering the acute and chronic morbidity of falciparum malaria, the national epidemiologic shift towards *P. falciparum* predominance seen in the last years, the lack of studies about AL efficacy in Latin America and reports of emergent resistance around the globe it is pertinent to further study the efficacy of the first line treatment used in the country. The objectives of this study were to assess the parasitological and clinical efficacy in patients with non-complicated *P. falciparum* malaria treated with Artemeter-Lumefantrine, to evaluate the safety of this combination and the correlation of the treatment response with both blood antimalarial drug concentrations.

Patients and methods

Study design and site

This was a therapeutic efficacy study with an one-arm prospective evaluation of the clinical and parasitological response to supervised treatment for uncomplicated Plasmodium falciparum malaria. It was based on the 2009 WHO therapeutic efficacy studies protocol.

The study was conducted in the municipality of Quibdó, Chocó (Lat. 05°41′41″N; Long. 76°39′40″W); recruitment during 2013 (8 months), laboratory procedures during 2013-January 2014. Quibdó it is located on the Atrato River, in a warm and humid climate between 43 and 53 meters above sea level with an average temperature of 28°C, a total area of 3,337,5 km² and near 100,000 inhabitants, and 35% living in rural locations. Malaria is endemic in the state with a 2013 Annual Parasitic Index of 28.4 and 13,095 reported cases, 4,232 of them in the municipality of Quibdó.

Study population and inclusion criteria

Patients with uncomplicated falciparum malaria seeking care at the malaria diagnostic post (outpatient service) in the Ismael Roldan Hospital. Patients were eligible if diagnosed with *P. falciparum* mono infection (confirmed by molecular diagnosis – PCR- in blood collected on day 0), ages 5 to 65 years, parasiteemia between 250-50,000/µl of asexual forms, and axillary temperature of ≥37.5°C in the absence of another cause of fever. Exclusion criteria comprised danger signs (Extreme weakness, Signs of respiratory distress, Hyperpyrexia, Repeated vomiting, Repeated Diarrhea, Signs of severe dehydration, Spontaneous bleeding. Dark urine, Hyperparasitemia), severe malnutrition, known underlying chronic or severe diseases (cardiac, renal, hepatic diseases, HIV/AIDS), confirmed pregnancy and hypersensitivity to the medications tested.

Sample size

According WHO recommendation a classical statistical method for determining sample size was applied. In the case of a medicine with an expected failure rate of 5%, a confidence interval of 95% and a precision level of 5%, a minimum of 73 patients should be enrolled. The sample size estimated was 88 subjects; it included a 20% increase to allow for losses to follow-up. Sampling was done for convenience, in order of arrival at the malaria post among patients who met the entry criteria.
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Procedures during inclusion and follow-up

After obtaining the informed written consent, a complete medical history (symptoms, current medications and previous use of anti-malarial drugs), biographic and contact details were noted. A complete physical examination was performed and a case record form was filled in for each patient. Body weight was recorded at day 0; temperature was measured using a thermometer with a precision of 0.1°C at baseline and on follow-up days, and additionally measured as clinically indicated. On each follow-up, clinical signs and symptoms were recorded, including vital signs (axillary temperature, heart and respiratory rate, blood pressure), symptoms (including fever, headache, chills and abdominal pain, among 17 evaluated) and clinical signs (including pallor, jaundice, signs of bleeding and hepatomegaly, among 18 evaluated); blood smears were performed for detecting malaria parasites, and filter-paper spot samples were taken for molecular diagnosis.

Microscopic Blood Examination and quality control. Thick and thin blood films were prepared and stained with Giemsa for screening and subsequent species diagnosis and parasitemia calculation on days 0, 1, 2, 3, 7, 14, 21 and 28 or if reassessment was required. Parasite counts were done on thick films and the number of parasites per 200 white blood cells (WBCs) were counted by light microscopy. Parasite density, expressed as the number of asexual parasites per μL of blood, was calculated by dividing the number of asexual parasites by the number of WBCs counted, and then multiplying it by an assumed WBC density of typically 8,000 per μL. A blood-slide sample was considered negative when examination of 200 fields containing at least ten WBCs per field revealed no asexual parasites. The presence of gametocytes on the day the patient was enrolled or on the day of follow-up was also recorded.

Two independent lecturers examined Blood smears of enrolled patients; one microscopist at the study site and a professional in microbiology at the Malaria Group Laboratory. If the first two readings varied by more than 25% a third independent in microbiology was performed. Each reader was blinded to the results of the others.

Hemoglobin and antimalarial drug blood concentration. Hemoglobin was determined on days 0 and 28 in 10µL of capillary blood sample with the HemoCue blood Hemoglobin system. A 5 ml blood sample was obtained 1 hour and 120 hours after the fifth medication dose to determine AL blood levels. Specimens were be labeled anonymously (study number, day of follow-up, date).

Antimalarial treatment. All enrolled patients were treated with AL on site, by directly observed treatment and monitored for 28 days. Patients were given the fixed-dose AL regimen (Artemether – ARM – 20mg + Lumefantrine – LU-120mg per tablet, “Coartem®” from NOVARTIS) adjusted to measured weight (1.7/12 mg/kg body weight of ARM and LF, respectively). The AL schedule consisted of twice-daily doses over 3 days (Day 0 to 2). After supervised administration of the drug, patients were observed during 30 minutes for adverse events or vomiting. Patients who vomited within this period were then provided with another dose of the study drugs and were observed for 30 additional minutes. If a second vomiting episode occurred, the patient was excluded from the study and offered parenteral rescue therapy. Concomitant treatment with acetaminophen was permitted to patients presenting axillary temperature ≥38°C. In case of a first line therapeutic failure, patients received quinine sulfate (10 mg/kg, administered at 8-h intervals during 7 days) plus clindamycin (10 mg/kg administered at 12-h intervals during 7 days).

Follow-up and loss

Follow-up visits and procedures were scheduled per protocol on days 1, 2, 3, 7, 14, 21, and 28. Patients were instructed to return to the health center at any time if they had fever or any general danger signs as described under exclusion criteria. Where clinically indicated, patients were evaluated out of schedule and treated appropriately. The study team made home visits as follow-ups for study participants that were late for their scheduled visits. Patients who failed to return on days 1 or 2 and missed one dose of the treatment or enrolled patients who could not attend scheduled visits were considered lost to follow-up and excluded from study.

Outcomes

Treatment outcomes were assessed based on parasitological and clinical results and were classified according to the WHO protocol as:13

- Early Treatment Failure (ETF): Development of danger signs or severe malaria on day 1, day 2 or day 3 in the presence of parasitemia;
  - Parasitemia on day 2 higher than day 0 count irrespective of axillary temperature;
  - Parasitemia on day 3 with axillary temperature ≥ 37.5 °C;
  - Parasitemia on day 3 ≥ 25% of count on day 0.
- Late Clinical Failure (LCF)
  - Development of danger signs or severe malaria on any day from day 4 to day 28 in the presence of parasitemia, without previously meeting any of the criteria of Early Treatment Failure;
  - Presence of parasitemia and axillary temperature ≥ 37.5 °C (or history of fever) on any day from day 4 to day 28, without previously meeting any of the criteria of Early Treatment Failure.
- Late Parasitological Failure (LPF)
  - Presence of parasitemia on any day from day 7 to day 28 and axillary temperature < 37.5 °C, without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure.
- Adequate Clinical and Parasitological Response (ACPR): Absence of parasitemia on day 28 irrespective of axillary temperature without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure or Late Parasitological Failure.

**PCR testing for Plasmodium infection**

We did PCR testing in order to determine parasitemia, confirm the plasmodium species and the mono-infection. Blood spots were collected on filter paper (Whatman No. 3) on days 0 and 28 and on a different day from participants with recurrent parasitemia. Blood samples were dried at ambient temperature before storage in individual plastic bags with silica gel. DNA samples were extracted from filter paper with blood spots by the saponin-Chelex method and they were analyzed using the nested PCR protocol described by Singh et al described briefly: a first amplification reaction with primers rPLU1 126 and rPLU5 for the fragment of the 18s-rRNA ribosomal subunit of the Plasmodium 127 genus parasites. This PCR product was used for the second reaction (nested PCR) 128 with primers rVIV 1 and rVIV 2 for the identification of *P. vivax* and rFAL1 and rFAL 129 2 for the detection of *P. falciparum*.

**Antimalarial drugs concentration**

Quantification of ARM, LF and Dihydroartemisinin (DHA) in plasma. The separation of DHA, ARM and LF was carried out by liquid chromatography using a chromatographic column ZORBAX Eclipse XDB-Pheny 4.6x150mm, 5μ and a mobile phase composed of MeOH: CH3COOH 0.2%: H2O: CH3COOH 0, 2% at a constant flow of 1ml/min and with programming by gradient. The detection of the analytes was performed with a simple quadrupole mass detector, monitoring the ratios m/z 323, 307 and 267 for DHA; for ARM m/z 321 and 267, and for LF m/z 528 and 530. Liquid-liquid extraction was performed to obtain the analytes from plasma. Each curve was made in triplicate and Artesunate (ART) was assumed at each level as an internal standard for DHA and ARM at a fixed concentration of 1,500 ng/ml. All the parameters of quantification were checked in this way: linearity, accuracy, precision and recovery.

**Statistical Analysis**

IBM’s statistical software SPSS (17th version) was used for data management and analysis. Data was analyzed using two methods: the Kaplan-Meier analysis and the per protocol analysis.

The description of demographic and clinical characteristics are shown as proportions for categorical variables and mean (medians) values for continuous variables. The treatment outcomes at 28 day are presented for both thick smear and PCR results as absolute numbers and proportions. The plasmatic concentration of drugs on days 2 and 7 are presented as media (95% C.I.), median and range. The Mann Whitney U-test was done to evaluate differences in the antimalarial drugs blood concentration on day 2 among patients with a negative PCR on day 28 and those with a positive result. Statistical significance was defined as P < 0.05

**Ethical considerations**

The Ethical Committee of the Faculty of Medicine of the University of Antioquia approved the study protocol. The trial was conducted according to good clinical practice guidelines. Written consent was obtained from all adult patients and from the parents or guardians of the children who participated in the study. Children over 12 years of age signed an informed assent form. The principal investigators had no affiliation with any of the malaria diagnostic centers where the study was conducted.

**Results**

**Baseline characteristics of participants**

During the study period, 143 patients were screened; 2 participants were excluded because of the parasitemia was above 50,000 parasites/µl, 10 presented clinical danger signs and 43 living outside the study area. Finally were included 88 patients; during follow-up 4 patients were lost and 84 completed the study. Demographic and laboratory baseline data of the participants is summarized in Table 1.

**Efficacy results**

The treatment outcomes are summarized in Table 2. On day 1, parasitemia was identified in 78 patients, with an average parasite load of 756 parasites/µl (SD = 2.004, median = 157); five patients were positive on day 2, with an average of 49 parasites/µl (SD = 21.9, median = 39). On day 3, all patients had cleared parasitemia. An adequate clinical and parasitological response, defined by a negative thick blood smear on day 28, was found in 100% of cases, and no treatment failures were detected. No serious adverse events were registered. The PCR results for 4 patients were positive for *P. falciparum* on day 28; comparisons between day 0 and 28 were not performed. The PCR-corrected per-protocol analysis (4 lost patients) showed an adequate clinical and parasitological response for 95.2%; the cure rate (Kaplan-Meier) was 90.7–99.8%. The median of the parasitemia on the initial day did not differ statistically (P > 0.05; Mann Whitney U test) between patients with ACPR (median =4,235) and those considered with parasitological failure using PCR (median =3,625).

**Antimalarial drugs blood concentration**

The plasmatic concentrations are presented in Table 3. The amount of blood was not sufficient to perform the measurements in all patients; however, measurements were made for the three analytes in 56 participants (67%) on day 2.

The median values of DHA on day 2 among patients with a negative PCR on day 28 and those with a positive result were 85.9 ng/ml and 113.8 ng/ml, respectively. The median values of ARM on day 2 among patients with a negative PCR on day 28 and those with a positive result were 100.9 ng/ml and 113.8 ng/ml, respectively. The median values of LF on day 2 among patients with a negative PCR on day 28 and those with a positive result were 100.9 ng/ml and 113.8 ng/ml, respectively.
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Table 1. Demographic and clinical characteristics of 88 patients included.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Age, years, mean (median)</td>
<td>24.7 (20)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>48</td>
<td>54.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African descent</td>
<td>75</td>
<td>85.2</td>
</tr>
<tr>
<td>Mestizo</td>
<td>9</td>
<td>10.2</td>
</tr>
<tr>
<td>Native Americans</td>
<td>4</td>
<td>4.5</td>
</tr>
<tr>
<td>Malaria, episodes last year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>71</td>
<td>80.7</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>10.2</td>
</tr>
<tr>
<td>2-4</td>
<td>8</td>
<td>9.1</td>
</tr>
<tr>
<td>Characteristics of current malaria episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria evolution time, days, mean (median)</td>
<td>4.5 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Parasitemia day 0, asexual forms/µl, mean (median)</td>
<td>9,873 (4,109)</td>
<td></td>
</tr>
<tr>
<td>Symptoms during current malaria episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>88</td>
<td>100.0</td>
</tr>
<tr>
<td>Cephalea</td>
<td>88</td>
<td>100.0</td>
</tr>
<tr>
<td>Shivers</td>
<td>88</td>
<td>100.0</td>
</tr>
<tr>
<td>Diaphoresia</td>
<td>86</td>
<td>97.7</td>
</tr>
<tr>
<td>Osteomuscular pain</td>
<td>82</td>
<td>93.2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>41</td>
<td>46.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>41</td>
<td>46.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>14.8</td>
</tr>
</tbody>
</table>

Numbers were 200.1 and 1,019.5. No significant differences were found between these values (Mann Whitney U-test; p>0.05).

Discussion

A therapeutic efficacy of 100% after a 28 days follow-up was established, evaluated by microscopic examination. The detection of submicroscopic parasitemia in four cases (5%) on day 28 by PCR may reflect a reduction in susceptibility to AL in the region, however reinfections could not be ruled out as the cause for these findings. In the analysis, these cases were considered as therapeutic failures in accordance with findings in the same area in 2009 where a late failure of 1% was evidenced. From the comparison of this data and the findings in the previous study, we infer that the crude and PCR-corrected ACPR rates found in the Colombian Pacific region are similar. Even though AL is the standard treatment for uncomplicated P. falciparum malaria in Colombia, the literature discussing its efficacy is scarce.

Several studies have shown that high parasite density is associated with treatment failure; in this study, not statistically significant difference was found in the initial parasitaemia between those who presented ACPR and therapeutic failure determined by PCR.

The treatment was generally well tolerated and no serious adverse events were observed. This finding is consistent with other studies in which no serious adverse effects were reported.

Antimalarial drug’s efficacy depends not only on the parasite susceptibility to the drug and on its blood concentration but also on the host’s immunity. All patients reached adequate therapeutic concentrations. The concentration of the analytes was within the normality ranges expected, which include: for ARM a Cmax of 66.2 ± 54.3 ng/ml and Cmin of 6.7 ± 8.5 ng/ml; for DHA a Cmax of 205 ± 102 ng/ml and a Cmin of 13.4 ± 12.1 ng/ml; for LF, pharmacokinetics are reported as highly variable, but a study in Thailand suggests that the maximum concentrations after reaching the maximum absorption time range between 1,100 ng/ml and 19,000 ng/ml. For these reasons, it can be proposed as a hypothesis that the therapeutic failures are due to resistance of the parasite to the AL combination.

Studies conducted in Colombia have shown high efficacy of therapeutic combinations that include artemisinin derivatives. In the region of Urabá, the therapeutic efficacy of different combinations with ACT was evaluated in 2002-2006 through microscopy; ACPR of 96% was found with Artesunate-Sulfadoxine/pyrimethamine, 100% with Artesunate-Amodiaquine and 100% with Artesunate-Mefloquine. Findings in 2007 have reported similar results, of 100% mean (95% CI: 89.1%-100%) PCR-adjusted ACPR rates for ACT treatment (AS-AQ) in the Colombian Pacific region. Additionally uncorrected Day-42 cure rates for other ACTs were observed in the Pacific region (Tumaco) in 2008: 97.5% for AL and 98.1% for Artesunate-Mefloquine.

Recurrences of parasitaemia by P. falciparum may be due to a recrudescence (a repeated attack of malaria due to the survival of parasites in red blood cells) or a reinfection. The first ones are due to a therapeutic failure and therefore it is recommended to try to differentiate between both situations, which can be attempted through the genetic characterization of the parasites. In this study, genotyping was not carried out, which constitutes a limitation. However, in Colombia has been described the presence of many identical or closely related genotypes of P. falciparum that difficult to achieve this differentiation.

In conclusion this study showed very high therapeutic effi-

Table 2. Treatment outcomes at 28 day in 84 patients.

<table>
<thead>
<tr>
<th>Treatment outcomes</th>
<th>Thick blood film</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate clinical and parasitological response</td>
<td>84</td>
<td>100%</td>
</tr>
<tr>
<td>Early treatment failure</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Late clinical failure</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Late parasitological failure</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
cacy and safety of the AL combination in the municipality of Quibdó, for the treatment of uncomplicated malaria by *Plasmodium falciparum*, with 100% of adequate clinical and parasitological response evaluated by microscopy and 95% when molecular diagnosis is applied. All patients achieved the therapeutic concentrations of Artemether and Lumefantrine. The therapeutic failures established by PCR were not associated with low levels of the drug in blood. As evidenced by other studies in the country, the treatment of uncomplicated malaria by *P. falciparum* with combinations that include derivatives of artemisinin has very high efficacy.

Studies should be carried out to separately evaluate the drugs that are part of the combinations commonly used in order to ensure the useful life of these ACTs, since it is not known if the cases of failure are due to the appearance of parasites resistant to artemisinin derivatives. In addition, genotyping must be done to interpret the type of recurrence that occurs. Regular monitoring of AL is required in view of malaria elimination initiatives, which will be largely dependent on therapeutic interventions and regular surveillance.

**Acknowledgments**

Thanks to the Quibdó community and to the directors of the Ismael Roldán Hospital who allowed access to their facilities.

**Ethical responsibilities**

**Protection of human subjects.** The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors obtained the informed consent of the patients mentioned in the article. The author for correspondence is in possession of these documents.

### Table 3. Plasma concentration of antimalarials on days 2 and 7

<table>
<thead>
<tr>
<th>Analyte</th>
<th>n</th>
<th>Media (95% C.I.)</th>
<th>Median</th>
<th>Lower-Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA Dihydro-artemisinin day 2 ng/ml</td>
<td>57</td>
<td>131.2 (73.9-188.6)</td>
<td>92.2</td>
<td>1.4 – 1,374</td>
</tr>
<tr>
<td>ARM Artemisinin day 2 ng/ml</td>
<td>56</td>
<td>131.3 (99.9-162.7)</td>
<td>100.9</td>
<td>14.9 – 640.9</td>
</tr>
<tr>
<td>LF Lumefantrine day 2 ng/ml</td>
<td>58</td>
<td>1,565.2 (1,323-1,807)</td>
<td>1,389.4</td>
<td>84.8-4,358.4</td>
</tr>
<tr>
<td>LF Lumefantrine day 7 ng/ml</td>
<td>37</td>
<td>293.6 (72.7-1,947.6)</td>
<td>200.1</td>
<td>72.7-1,947.6</td>
</tr>
</tbody>
</table>

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