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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Artemether-lumefantrine (COA566)

Trial Indication(s)

Acute uncomplicated *Plasmodium falciparum* malaria

Protocol Number

CCOA566B2307

Protocol Title

Multicenter, open-label, single-arm study to evaluate the PK, safety, tolerability and efficacy of a new artemether:lumefantrine (2.5 mg:30 mg) dispersible tablet in the treatment of infants and neonates <5 kg body weight with acute uncomplicated *Plasmodium falciparum* malaria

Clinical Trial Phase

Phase 2/Phase 3

Phase of Drug Development

Phase 4 (artemether:lumefantrine 20 mg:120 mg)

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Study Start/End Dates

Study Start Date: December 21, 2020 (Actual)
Primary Completion Date: July 02, 2023 (Actual)
Study Completion Date: May 10, 2024 (Actual)

Reason for Termination (If applicable)

The study team decided to stop further enrollment in the study after 6 patients had been recruited in Cohort 2. The decision to terminate the core part of the study was made consequent to the difficulty in recruiting patients in the youngest age group (0–28 days) and was not due to any safety concerns or lack of efficacy.

Study Design/Methodology

This Phase II/III multicenter, open-label, single-arm, adaptive study evaluated the pharmacokinetics (PK), safety, tolerability, and efficacy of a new artemether-lumefantrine (2.5 mg:30 mg) dispersible tablet in the treatment of infants and neonates <5 kg body weight with acute uncomplicated *P. falciparum* malaria.

The study had two sequential and age-descending cohorts. Cohort 1 enrolled patients >28 days of age and patients with 1 to ≤28 days of age were enrolled in Cohort 2. The core study duration was 43 days. Patients attended a long-term safety follow-up visit when they reached 12 months of age.

Centers

3 centers in 2 countries: Burkina Faso(2), Democratic Republic of the Congo(1)

Objectives:

The primary objective was to assess the key pharmacokinetics (PK) parameter of artemether in infants and neonates < 5 kg body weight dosed with the new formulation of artemether-lumefantrine dispersible tablet.

The secondary objectives were:

- To assess other key PK parameters of artemether, dihydroartemisinin (DHA) and lumefantrine in infants and neonates <5 kg body weight dosed with the new formulation of artemether-lumefantrine dispersible tablet.
- To evaluate the safety and tolerability of the new formulation of artemether-lumefantrine dispersible tablet in infants and neonates <5 kg body weight with acute uncomplicated *P. falciparum* malaria.
- To determine the efficacy of the new formulation of artemether-lumefantrine dispersible tablet for treatment of acute uncomplicated *P. falciparum* malaria in infants and neonates <5 kg body weight

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational product was artemether-lumefantrine 2.5 mg:30 mg (COA566 2.5 mg:30 mg), supplied in the form of oral dispersible tablets.

The study treatment for all 28 patients in the study was 2 oral dispersible tablets (i.e. artemether-lumefantrine 5 mg:60 mg), twice daily, for 3 days.

Statistical Methods

For primary PK endpoint, the 90% 2-sided confidence intervals (CIs) of geometric mean for artemether (ART) Cmax were presented by cohort using the PK set. Calculation was based on the log normal distribution. The study objective was considered to have been met if 90% CIs for ART Cmax contained the desired values based on historical data especially those from children 5 to <15 kg body weight in a previous clinical trial, i.e. 101 ng/mL (Study CCOA566B2303).

The key secondary endpoint was Day 8 (168h) lumefantrine concentration (LUM C168h), the 90% 2-sided CI of geometric mean was calculated for Day 8 (168h) lumefantrine concentration based on the log normal distribution by cohort and treatment group using the PK set.

For polymerase chain reaction (PCR)-corrected adequate clinical and parasitological response (ACPR) at Day 15, Day 29 and Day 43, the ACPR rate with 95% 2-sided CIs was assessed using the Clopper-Pearson method for each treatment group by cohort using Per-Protocol Set (PPS) and Full Analysis Set (FAS), and FAS was used for PCR-uncorrected analysis.

Incidence rates of recrudescence and new infection at Days 15, 29 and 43 were estimated by Kaplan Meier method based on the subset of FAS patients who had clearance of initial infection by Day 7.

Descriptive statistics were presented for parasite clearance time (PCT) and fever clearance times (FCT) by cohort using the Kaplan-Meier method based on the FAS.

The following analysis sets were used in this study:

- The Full Analysis Set (FAS) comprised of all patients that received any study treatment and had *P. falciparum* present at Screening visit.
- The PK set was a subset of the FAS who had evaluable PK parameter data.
- The Safety Set included all patients who received at least one dose of study treatment. The Safety Set was used for safety analyses while FAS was used for other analyses.
- The Per-Protocol Set (PPS) was a subset of patients of the FAS and was characterized by the following criteria:
  - Did not have important protocol deviations affecting efficacy
  - Took at least 80% of study medication
  - PCR corrected cure status at Day 29 could be defined

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Male or female neonates/infants
2. Body weight <5 kg but ≥ 2 kg
3. In Cohort 1, infants aged >28 days; in Cohort 2, neonates aged 1 to ≤28 days
4. Microscopically confirmed diagnosis of P. falciparum malaria (or mixed infections):

- in Cohort 1 of ≥500 and <100,000 parasites/µL asexual *P. falciparum* parasitemia
- in Cohort 2 of ≥100 and <100,000 parasites/µL asexual *P. falciparum* parasitemia
- either congenital or neonatal
- either symptomatic or asymptomatic

Exclusion Criteria:

1. Head circumference < - 2 SD z-score in cm following WHO age and sex-specific reference curves (suspicion of microcephaly)
2. Presence of severe malaria (according to WHO 2015 definition)
3. HIV status :
   - in Cohort 1, patient's or patient's mother's current treatment with ARV
   - in Cohort 2, mother's known HIV positive status at patient's birth or mother's current treatment with ARV
4. Presence of the following signs of a critical condition: apnea-bradycardia, sustained bradycardia, tachycardia, desaturation, hypotension, hypothermia; or other severely deteriorated general condition (based on IMCI criteria in sick infants) (WHO 2005)
5. Presence of any clinically significant neurological condition:
   - any episode of convulsion during the present illness (in keeping with the IMCI list of general danger signs)
   - known neurological disorders (e.g. chronic seizure disorders, cerebral palsy)
6. Presence of clinically significant abnormality of the hepatic and renal systems
7. Patients unable to swallow or whose drinking is impaired

8. Known hypersensitivity of the patient or either patient's parent to artemether, lumefantrine, any of the excipients of Coartem®/Riamet® Dispersible tablet, or to drugs of similar chemical classes
9. History of malabsorption or previous gastrointestinal surgery, or history of radiation therapy that could affect drug absorption or metabolism, or any other disorder or history of a condition that could interfere with drug absorption, distribution, metabolism, or excretion
10. Known family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to be associated with prolongation of the QTc interval such as history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease
11. Disturbances of electrolyte balance (e.g. hypokalaemia or hypomagnesaemia)
12. Presence of any age-adjusted clinically or hematologically relevant laboratory and blood chemistry abnormalities
13. Patients who received any antimalarial drug, including antibiotics with antimalarial activity, within 14 days of trial start, or any other prohibited drug
14. Patients who received an investigational drug within 5 half-lives of enrollment or participated in an investigational study or within 30 days, whichever is longer

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Participant Flow Table

Overall Study

	Cohort 1	Cohort 2	Total
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	
Started	22	6	28
Full Analysis Set (FAS)	22	6	28
Per-Protocol Set (PPS)	17	6	23
PK Set	22	6	28
Completed treatment phase	22	6	28
Completed Core follow-up (43 days)	22	6	28
Completed Long-term follow-up	21	6	27
Not Completed	1	0	1
Lost to Follow-up	1	0	1

Baseline Characteristics

	Cohort 1	Cohort 2	Total
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	
Number of Participants [units: participants]	22	6	28

Baseline Analysis Population Description

Age Continuous (units: days) Analysis Population Type: Participants Median (Full Range)			
	96.0 (53.0 to 157.0)	22.5 (1.0 to 26.0)	83.0 (1.0 to 157.0)
Age, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
1-7 days	0	1	1
8-14 days	0	0	0
15-28 days	0	5	5
>28 days	22	0	22
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	15	3	18
Male	7	3	10
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Black or African American	22	6	28
Study Specific Characteristic **Weight** (units: kilograms) Analysis Population Type: Participants Median (Full Range)			

	4.82 (3.89 to 4.98)	3.50 (2.80 to 4.24)	4.76 (2.80 to 4.98)
Study Specific Characteristic **Plasmodium species** (units: participants) Description: Parasitemia determinations were performed in peripheral blood. Microscopic species determination was confirmed with polymerase chain reaction (PCR)-based methods. The assessments were performed at a central reference laboratory. Analysis Population Type: Participants Count of Participants (Not Applicable)			
P. falciparum asexual forms	21	6	27
P. falciparum gametocytes	4	1	5
P. vivax	0	0	0
P. ovale	0	0	0
P. malariae	1	0	1
P. knowlesi	0	0	0
Study Specific Characteristic **Plasmodium falciparum density** (units: parasites/µL) Description: Parasitemia determinations were performed in peripheral blood. Giemsa stained thick fields were examined at a central reference laboratory. The parasite density was calculated according to the following formula: (number of Plasmodium falciparum parasites * actual leukocytes)/number of leucocytes counted (200 thick films fields examined) Analysis Population Type: Participants Median (Full Range)			
	8400 (748 to 156400)	3660 (384 to 52700)	7020 (384 to 156400)

Primary Outcome Result(s)

Artemether Cmax after first dose

Description: Artemether Cmax represents the highest concentration between the concentrations at 1 hour and 2 hours after first dose. Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on artemether plasma concentrations.

Time Frame	1 and 2 hours after first dose (Day 1)
Analysis Population Description	Participants in the PK set who had an available value for the outcome measure.

	Cohort 1	Cohort 2
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	20	5
Artemether Cmax after first dose (units: ng/mL)	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**
	68.0 (45.1 to 103)	62.2 (33.6 to 115)

Secondary Outcome Result(s)

Lumefantrine Day 8 concentration (C168h)

Description	Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on lumefantrine plasma concentrations. Dosing times were 0, 8, 24, 36, 48 and 60 hours.
Time Frame	168 hours after first dose (corresponding to 108 hours after last dose)
Analysis Population Description	Participants in the PK set who had an available value for the outcome measure.

	Cohort 1	Cohort 2

Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
Lumefantrine Day 8 concentration (C168h) (units: ng/mL)	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**
	353 (250 to 498)	480 (265 to 870)

Lumefantrine Cmax after last dose

Description	Lumefantrine Cmax represents the highest concentration among four sampling time points after last dose. Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on lumefantrine plasma concentrations. Dosing times were 0, 8, 24, 36, 48 and 60 hours.
Time Frame	62, 66, 68 and 84 hours after first dose (corresponding to 2, 6, 8 and 24 hours after last dose)
Analysis Population Description	Participants in the PK set who had an available value for the outcome measure.

	Cohort 1	**Cohort 2**
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
Lumefantrine Cmax after last dose (units: ng/mL)	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**
	3180 (2530 to 4000)	3510 (1880 to 6540)

DHA Cmax after first dose

Description	Dihydroartemisinin (DHA) is an active metabolite of artemether. DHA Cmax represents the highest concentration between the concentrations at 1 hour and 2 hours after first dose. Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on DHA plasma concentrations.
Time Frame	1 and 2 hours after first dose (Day 1)
Analysis Population Description	Participants in the PK set who had an available value for the outcome measure.

	Cohort 1	**Cohort 2**
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	20	5
DHA Cmax after first dose (units: ng/mL)	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**
	11.5 (7.58 to 17.4)	15.7 (8.53 to 28.9)

Parasite Clearance Time (PCT)

Description	PCT is defined as time from the first dose until the first total and continued disappearance of asexual parasite forms which remained at least a further 48 hours. PCT is based on uncorrected parasite counts. Patients who received rescue medication before parasite clearance were censored at the first use of rescue medication. Patients without parasite clearance were censored at the time of last parasite assessment. PCT was calculated using the Kaplan-Meier method.
Time Frame	Up to 48 hours after first dose
Analysis Population Description	Full Analysis Set (FAS)

	Cohort 1	Cohort 2
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
Parasite Clearance Time (PCT) (units: hours)	**Median** **(Inter-Quartile Range)**	**Median** **(Inter-Quartile Range)**
	35.0 (24.0 to 35.8)	30.6 (23.8 to 47.6)

Fever clearance Times (FCT)

Description	FCT is defined as time from the first dose until the first time the axillary body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours. Patients who received rescue medication before fever clearance were censored at the first use of rescue medication. Patients without fever clearance were censored at the time of last parasite assessment. FCT was calculated using the Kaplan-Meier method.
Time Frame	Up to 36 hours after first dose
Analysis Population Description	Participants in the Full Analysis Set (FAS) who had fever at baseline

	Cohort 1	Cohort 2
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	4	1
Fever clearance Times (FCT) (units: hours)	**Median** **(Inter-Quartile Range)**	**Median** **(Inter-Quartile Range)**
	15.7 (3.9 to 29.7)	7.6 (7.6 to 7.6)

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PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – PPS analysis

Description	PCR-corrected ACPR, defined as the absence of parasitemia, was evaluated on Days 15, 29 and 43. Microscopic species identification was confirmed and determined by polymerase chain reaction (PCR) genotyping methods to establish malaria recrudescence/reinfection. A participant was considered as PCR-corrected ACPR if the participant did not meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure and had absence of parasitemia on Days 15, 29 or 43 irrespective of axillary temperature unless the presence of parasitemia after 7 days was due to reinfection based on PCR. A presence of parasitemia after 7 days of treatment initiation was considered as a reinfection only if the parasitemia was clear before Day 8 and none of the parasite strain(s) detected on Day 8 or later matched with the parasite strain at baseline based on PCR.
Time Frame	Days 15, 29 and 43
Analysis Population Description	Per-Protocol Set (PPS). Five patients in Cohort 1 were excluded from the PPS due to the use of prohibited concomitant medication, i.e. erythromycin.

	Cohort 1	**Cohort 2**
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	17	6
PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – PPS analysis (units: percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
Day 15 (n=17, 6)	100 (80.49 to 100)	100 (54.07 to 100)
Day 29 (n=17, 6)	100 (80.49 to 100)	100 (54.07 to 100)
Day 43 (n=17, 6)	94.1 (71.31 to 99.85)	100 (54.07 to 100)

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PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – FAS analysis

Description	PCR-corrected ACPR, defined as the absence of parasitemia, was evaluated on Days 15, 29 and 43. Microscopic species identification was confirmed and determined by polymerase chain reaction (PCR) genotyping methods to establish malaria recrudescence/reinfection. A participant was considered as PCR-corrected ACPR if the participant did not meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure and had absence of parasitemia on Days 15, 29 or 43 irrespective of axillary temperature unless the presence of parasitemia after 7 days was due to reinfection based on PCR. A presence of parasitemia after 7 days of treatment initiation was considered as a reinfection only if the parasitemia was clear before Day 8 and none of the parasite strain(s) detected on Day 8 or later matched with the parasite strain at baseline based on PCR.
Time Frame	Days 15, 29 and 43
Analysis Population Description	Full Analysis Set (FAS)

	Cohort 1	**Cohort 2**
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – FAS analysis (units: percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
Day 15 (n=22, 6)	100 (84.56 to 100)	100 (54.07 to 100)
Day 29 (n=22, 6)	95.5 (77.16 to 99.88)	100 (54.07 to 100)
Day 43 (n=22, 6)	90.9 (70.84 to 98.88)	100 (54.07 to 100)

PCR-uncorrected Adequate Clinical and Parasitological Response (ACPR)

Description	PCR-uncorrected ACPR, defined as the absence of parasitemia, was evaluated on Days 8, 15, 29 and 43. A participant was considered as PCR-uncorrected ACPR if the participant did not meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure and had absence of parasitemia on Days 8, 15, 29 or 43 irrespective of axillary temperature.
Time Frame	Days 8, 15, 29 and 43
Analysis Population Description	Full Analysis Set (FAS)

	Cohort 1	Cohort 2
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
PCR-uncorrected Adequate Clinical and Parasitological Response (ACPR) (units: percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
Day 8 (n=22, 6)	100 (84.56 to 100)	100 (54.07 to 100)
Day 15 (n=22, 6)	100 (84.56 to 100)	100 (54.07 to 100)
Day 29 (n=22, 6)	77.3 (54.63 to 92.18)	100 (54.07 to 100)
Day 43 (n=22, 6)	63.6 (40.66 to 82.80)	100 (54.07 to 100)

Number of participants with recrudescence events

Description	Recrudescence is defined as appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline. Recrudescence had to be confirmed by PCR analysis.
Time Frame	Days 15, 29 and 43

Analysis Population Description	Full Analysis Set (FAS)

	Cohort 1	Cohort 2
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
Number of participants with recrudescence events (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
Day 15 (n=22, 6)	0 (%)	0 (%)
Day 29 (n=22, 6)	1 (4.55%)	0 (%)
Day 43 (n=22, 6)	1 (4.55%)	0 (%)

Number of participants with new infections events

Description	New infection is defined as appearance of asexual parasites after clearance of initial infection with a genotype different from those parasites present at baseline. New infection had to be confirmed by PCR analysis.
Time Frame	Days 15, 29 and 43
Analysis Population Description	Full Analysis Set (FAS)

	Cohort 1	Cohort 2

Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
Number of participants with new infections events (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
Day 15 (n=22, 6)	0 (%)	0 (%)
Day 29 (n=22, 6)	4 (18.18%)	0 (%)
Day 43 (n=22, 6)	2 (9.09%)	0 (%)

Number of participants with Adverse Events (AEs)

Description	Number of participants with adverse events (any AEs regardless of seriousness), including changes in laboratory results qualifying and reported as adverse events.
Time Frame	From first dose of study treatment until Day 43
Analysis Population Description	Safety Set, including all patients who received at least one dose of study treatment

	Cohort 1	**Cohort 2**
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
Number of participants with Adverse Events (AEs) (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
	17 (77.27%)	4 (66.67%)

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Number of participants with Serious Adverse Events (SAEs)

Description	Number of participants with serious adverse events (SAEs), including changes in laboratory results qualifying and reported as serious adverse events.
Time Frame	From first dose of study treatment until 12 months of age (assessed up to maximum 1 year)
Analysis Population Description	Safety Set, including all patients who received at least one dose of study treatment

	Cohort 1	**Cohort 2**
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days
Number of Participants Analyzed [units: participants]	22	6
Number of participants with Serious Adverse Events (SAEs) (units: participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	0 (%)	0 (%)

Safety Results

Time Frame	Non-serious adverse events were collected from first dose of study treatment until Day 43. Deaths and serious adverse events were collected from first dose of study treatment until 1 year of age (assessed up to maximum 1 year).
Additional Description	Adverse events are assessed in the Safety Set, including all patients who received at least one dose of study treatment.

Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Cohort 1 N = 22	Cohort 2 N = 6	Pooled Cohort N = 28
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	All infants and neonates who received at least one dose of artemether-lumefantrine
Total Number Affected	0	0	0
Total Number At Risk	22	6	28

Serious Adverse Events

Time Frame	Non-serious adverse events were collected from first dose of study treatment until Day 43. Deaths and serious adverse events were collected from first dose of study treatment until 1 year of age (assessed up to maximum 1 year).
Additional Description	Adverse events are assessed in the Safety Set, including all patients who received at least one dose of study treatment.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

No serious adverse events were reported.

Other (Not Including Serious) Adverse Events

Time Frame	Non-serious adverse events were collected from first dose of study treatment until Day 43. Deaths and serious adverse events were collected from first dose of study treatment until 1 year of age (assessed up to maximum 1 year).
Additional Description	Adverse events are assessed in the Safety Set, including all patients who received at least one dose of study treatment.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Cohort 1 N = 22	**Cohort 2 N = 6**	**Pooled Cohort N = 28**
Arm/Group Description	Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	All infants and neonates who received at least one dose of artemether-lumefantrine
Total # Affected by any Other Adverse Event	17	4	21
Total # at Risk by any Other Adverse Event	22	6	28

Blood and lymphatic system disorders			
Anaemia	7 (31.82%)	1 (16.67%)	8 (28.57%)
Gastrointestinal disorders			
Abdominal pain	0 (0.00%)	1 (16.67%)	1 (3.57%)
Vomiting	6 (27.27%)	1 (16.67%)	7 (25.00%)
General disorders and administration site conditions			
Pyrexia	8 (36.36%)	2 (33.33%)	10 (35.71%)
Infections and infestations			
Bacterial rhinitis	2 (9.09%)	0 (0.00%)	2 (7.14%)
Ear infection	0 (0.00%)	1 (16.67%)	1 (3.57%)
Gastrointestinal fungal infection	0 (0.00%)	1 (16.67%)	1 (3.57%)
Malaria	9 (40.91%)	0 (0.00%)	9 (32.14%)
Rhinitis	0 (0.00%)	1 (16.67%)	1 (3.57%)

Conclusion:

The objective of this Phase II/III study was to test the new artemether-lumefantrine dispersible tablet formulation to determine exposure to artemether, DHA and lumefantrine as well as its safety, tolerability and efficacy in patients <5 kg with uncomplicated *P. falciparum* malaria. The results of artemether and lumefantrine concentration are in same ranges as in patients ≥5 kg as per historical data from Study COA566B2303, which is also reflected in efficacy and safety outcomes. The PCR-corrected ACPR and overall efficacy was consistent with historical data.

The safety profile was consistent with the known safety profile of artemether and lumefantrine. There were no new or unexpected safety signals reported during this study. Neurodevelopmental assessments showed no significant adverse findings in the small sample studied; however, results must be viewed with caution.

In conclusion, the results of this study demonstrate the exposures, safety and efficacy of artemether-lumefantrine 2.5 mg:30 mg dispersible tablet formulation at a twice daily dose of 5 mg:60 mg in infants weighing less than 5 kg with acute uncomplicated *P. falciparum* malaria are similar as previously observed in the pivotal Study COA566B2303, and thus, this dose is found appropriate for the treatment of patients <5 kg.

Date of Clinical Trial Report

19-March-2024 (Primary Clinical Study Report) and 28-Aug-2024 (Final Clinical Study Report).