



Clinical trial results:

A Phase 2 interventional, multicenter, randomized, open-label study in three age-descending cohorts to evaluate efficacy, safety and tolerability of KAF156 and Lumefantrine-SDF combination in the treatment of acute uncomplicated Plasmodium falciparum Malaria in a pediatric population

Summary

EudraCT number	2021-003583-27
Trial protocol	Outside EU/EEA
Global end of trial date	28 August 2024

Results information

Result version number	v1 (current)
This version publication date	15 March 2025
First version publication date	15 March 2025

Trial information

Trial identification

Sponsor protocol code	CKAF156A2203
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04546633
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 August 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of KAF156 combined with LUM- Solid dispersion formulation (SDF) compared to Coartem® (non-inferiority trial) for the treatment of uncomplicated malaria caused by *P. falciparum* in children 6 months to < 12 years.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Burkina Faso: 59
Country: Number of subjects enrolled	Congo, The Democratic Republic of the: 1
Country: Number of subjects enrolled	Gabon: 92
Country: Number of subjects enrolled	Mali: 132
Country: Number of subjects enrolled	Côte d'Ivoire: 11
Worldwide total number of subjects	295
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	80
Children (2-11 years)	140

Adolescents (12-17 years)	75
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 10 investigative sites in 5 countries.

Pre-assignment

Screening details:

During pre-screening, a *P. falciparum* parasite count was obtained for all patients. Further screening assessments took place only if the outcome was in the pre-defined range ($\geq 1,000$ and $\leq 150,000$ parasites/ μL in Run-In Cohort and $\geq 1,500$ and $\leq 150,000$ parasites/ μL in Cohort 1 and Cohort 2).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Run-in Cohort-KAF400mg/LUM240mg-QDx2-Fed

Arm description:

KAF156-400 mg and LUM-240 mg-solid dispersion formulation (SDF), once daily (QD) for 2 days in fed condition, via oral.

Arm type	Experimental
Investigational medicinal product name	Lumefantrine Solid Dispersion Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

Administered in combination with KAF156 once daily for 2 days in fed condition at 240mg.

Investigational medicinal product name	KAF156
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered in combination with LUM-SDF once daily for 2 days in fed condition at 400mg.

Arm title	Run-in Cohort-KAF400mg/LUM240mg-QDx2-Fasted
------------------	---------------------------------------------

Arm description:

KAF156-400 mg and LUM-240 mg-SDF once daily for 2 days in fasted condition, via oral.

Arm type	Experimental
Investigational medicinal product name	Lumefantrine Solid Dispersion Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

Administered in combination with KAF156 once daily for 2 days in fasted condition at 240mg.

Investigational medicinal product name	KAF156
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Administered in combination with LUM-SDF once daily for 2 days in fasted condition at 400mg.	
Arm title	Run-in Cohort-KAF400mg/LUM480mg-QDx2-Fed
Arm description:	
KAF156-400 mg and LUM-480 mg-SDF once daily for 2 days in fed condition, via oral.	
Arm type	Experimental
Investigational medicinal product name	Lumefantrine Solid Dispersion Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use
Dosage and administration details:	
Administered in combination with KAF156 once daily for 2 days in fed condition at 480mg.	
Investigational medicinal product name	KAF156
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Administered in combination with LUM-SDF once daily for 2 days in fed condition at 400mg.	
Arm title	Run-in Cohort-KAF400mg/LUM480mg-QDx2-Fasted
Arm description:	
KAF156-400 mg and LUM-480 mg-SDF once daily for 2 days in fasted condition, via oral.	
Arm type	Experimental
Investigational medicinal product name	Lumefantrine Solid Dispersion Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use
Dosage and administration details:	
Administered in combination with KAF156 once daily for 2 days in fasted condition at 480mg.	
Investigational medicinal product name	KAF156
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Administered in combination with LUM-SDF once daily for 2 days in fasted condition at 400mg.	
Arm title	Cohort 1/2-KAF400mg/LUM480mg-QDx3
Arm description:	
KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight.	
Arm type	Experimental

Investigational medicinal product name	Lumefantrine Solid Dispersion Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

Administered in combination with KAF156 once daily for 3 days with a light meal and the full dose was adjusted based on patient's body weight.

Investigational medicinal product name	KAF156
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered in combination with LUM-SDF once daily for 3 days with a light meal and the full dose was adjusted based on patient's body weight.

Arm title	Cohort 1/2-Artemether80mg/LUM480mg
------------------	------------------------------------

Arm description:

Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label.

Arm type	Experimental
Investigational medicinal product name	Artemether80mg/LUM480mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Administered with food and the doses were based on patient's body weight as per product label, twice daily for 3 days.

Number of subjects in period 1	Run-in Cohort- KAF400mg/LUM240 mg-QDx2-Fed	Run-in Cohort- KAF400mg/LUM240 mg-QDx2-Fasted	Run-in Cohort- KAF400mg/LUM480 mg-QDx2-Fed
Started	25	26	11
Completed	23	26	11
Not completed	2	0	0
Lost to follow-up	1	-	-
Guardian decision	1	-	-

Number of subjects in period 1	Run-in Cohort- KAF400mg/LUM480 mg-QDx2-Fasted	Cohort 1/2- KAF400mg/LUM480 mg-QDx3	Cohort 1/2- Artemether80mg/LU M480mg
Started	13	110	110
Completed	13	104	102
Not completed	0	6	8
Lost to follow-up	-	4	4
Guardian decision	-	2	4

Baseline characteristics

Reporting groups

Reporting group title	Run-in Cohort-KAF400mg/LUM240mg-QDx2-Fed
Reporting group description: KAF156-400 mg and LUM-240 mg-solid dispersion formulation (SDF), once daily (QD) for 2 days in fed condition, via oral.	
Reporting group title	Run-in Cohort-KAF400mg/LUM240mg-QDx2-Fasted
Reporting group description: KAF156-400 mg and LUM-240 mg-SDF once daily for 2 days in fasted condition, via oral.	
Reporting group title	Run-in Cohort-KAF400mg/LUM480mg-QDx2-Fed
Reporting group description: KAF156-400 mg and LUM-480 mg-SDF once daily for 2 days in fed condition, via oral.	
Reporting group title	Run-in Cohort-KAF400mg/LUM480mg-QDx2-Fasted
Reporting group description: KAF156-400 mg and LUM-480 mg-SDF once daily for 2 days in fasted condition, via oral.	
Reporting group title	Cohort 1/2-KAF400mg/LUM480mg-QDx3
Reporting group description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight.	
Reporting group title	Cohort 1/2-Artemether80mg/LUM480mg
Reporting group description: Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label.	

Reporting group values	Run-in Cohort-KAF400mg/LUM240 mg-QDx2-Fed	Run-in Cohort-KAF400mg/LUM240 mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LUM480 mg-QDx2-Fed
Number of subjects	25	26	11
Age Categorical Units:			
<=18 years	25	26	11
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous Units: years			
arithmetic mean	14.08	13.62	14.36
standard deviation	± 1.382	± 1.416	± 1.859
Sex: Female, Male Units: participants			
Female	15	12	8
Male	10	14	3
Race/Ethnicity, Customized Units: Subjects			
Black or African American	25	26	11

Reporting group values	Run-in Cohort-KAF400mg/LUM480 mg-QDx2-Fasted	Cohort 1/2-KAF400mg/LUM480 mg-QDx3	Cohort 1/2-Artemether80mg/LUM480mg
Number of subjects	13	110	110

Age Categorical Units:			
<=18 years	13	110	110
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous Units: years			
arithmetic mean	14.85	4.86	4.58
standard deviation	± 1.573	± 3.464	± 3.251
Sex: Female, Male Units: participants			
Female	4	60	42
Male	9	50	68
Race/Ethnicity, Customized Units: Subjects			
Black or African American	13	110	110

Reporting group values	Total		
Number of subjects	295		
Age Categorical Units:			
<=18 years	295		
Between 18 and 65 years	0		
>=65 years	0		
Age Continuous Units: years			
arithmetic mean	-		
standard deviation	-		
Sex: Female, Male Units: participants			
Female	141		
Male	154		
Race/Ethnicity, Customized Units: Subjects			
Black or African American	295		

Subject analysis sets

Subject analysis set title	Cohort 1-KAF400mg/LUM480mg-QDx3
Subject analysis set type	Sub-group analysis
Subject analysis set description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 1 participants age 2 to <12 years.	
Subject analysis set title	Cohort 2-KAF400mg/LUM480mg-QDx3
Subject analysis set type	Sub-group analysis
Subject analysis set description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 2 participants ages 6 months to <2 years.	
Subject analysis set title	Cohort 1-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 1 participants age 2 to <12 years.

Subject analysis set title	Cohort 2-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 2 participants ages 6 months to <2 years.

Subject analysis set title	Cohort 2-KAF400mg/LUM480mg-QDx3Edit
Subject analysis set type	Sub-group analysis

Subject analysis set description:

KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 2 participants ages 6 months to <2 years.

Subject analysis set title	Cohort 1-KAF400mg/LUM480mg-QDx3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 1 participants age 2 to <12 years.

Subject analysis set title	Cohort 1-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 1 participants age 2 to <12 years.

Subject analysis set title	Cohort 2-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 2 participants ages 6 months to <2 years.

Reporting group values	Cohort 1- KAF400mg/LUM480 mg-QDx3	Cohort 2- KAF400mg/LUM480 mg-QDx3	Cohort 1- Artemether80mg/LU M480mg
Number of subjects	65	31	53
Age Categorical Units:			
<=18 years			
Between 18 and 65 years			
>=65 years			
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Sex: Female, Male Units: participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Black or African American	65	31	53

Reporting group values	Cohort 2- Artemether80mg/LU	Cohort 2- KAF400mg/LUM480	Cohort 1- KAF400mg/LUM480
------------------------	--------------------------------	------------------------------	------------------------------

	M480mg	mg-QDx3Edit	mg-QDx3
Number of subjects	31	31	68
Age Categorical Units:			
<=18 years			
Between 18 and 65 years			
>=65 years			
Age Continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male Units: participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Black or African American	31	31	68

Reporting group values	Cohort 1- Artemether80mg/LU M480mg	Cohort 2- Artemether80mg/LU M480mg	
Number of subjects	65	35	
Age Categorical Units:			
<=18 years			
Between 18 and 65 years			
>=65 years			
Age Continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Sex: Female, Male Units: participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Black or African American	65	35	

End points

End points reporting groups

Reporting group title	Run-in Cohort-KAF400mg/LUM240mg-QDx2-Fed
Reporting group description: KAF156-400 mg and LUM-240 mg-solid dispersion formulation (SDF), once daily (QD) for 2 days in fed condition, via oral.	
Reporting group title	Run-in Cohort-KAF400mg/LUM240mg-QDx2-Fasted
Reporting group description: KAF156-400 mg and LUM-240 mg-SDF once daily for 2 days in fasted condition, via oral.	
Reporting group title	Run-in Cohort-KAF400mg/LUM480mg-QDx2-Fed
Reporting group description: KAF156-400 mg and LUM-480 mg-SDF once daily for 2 days in fed condition, via oral.	
Reporting group title	Run-in Cohort-KAF400mg/LUM480mg-QDx2-Fasted
Reporting group description: KAF156-400 mg and LUM-480 mg-SDF once daily for 2 days in fasted condition, via oral.	
Reporting group title	Cohort 1/2-KAF400mg/LUM480mg-QDx3
Reporting group description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight.	
Reporting group title	Cohort 1/2-Artemether80mg/LUM480mg
Reporting group description: Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label.	
Subject analysis set title	Cohort 1-KAF400mg/LUM480mg-QDx3
Subject analysis set type	Sub-group analysis
Subject analysis set description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 1 participants age 2 to <12 years.	
Subject analysis set title	Cohort 2-KAF400mg/LUM480mg-QDx3
Subject analysis set type	Sub-group analysis
Subject analysis set description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 2 participants ages 6 months to <2 years.	
Subject analysis set title	Cohort 1-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 1 participants age 2 to <12 years.	
Subject analysis set title	Cohort 2-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 2 participants ages 6 months to <2 years.	
Subject analysis set title	Cohort 2-KAF400mg/LUM480mg-QDx3Edit
Subject analysis set type	Sub-group analysis
Subject analysis set description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 2 participants ages 6 months to <2 years.	
Subject analysis set title	Cohort 1-KAF400mg/LUM480mg-QDx3

Subject analysis set type	Sub-group analysis
Subject analysis set description: KAF156-400mg and LUM-480 mg-SDF once daily for 3 days, via oral. It was administered with a light meal and the full dose was adjusted based on patient's body weight. Cohort 1 participants age 2 to <12 years.	
Subject analysis set title	Cohort 1-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 1 participants age 2 to <12 years.	
Subject analysis set title	Cohort 2-Artemether80mg/LUM480mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Artemether-80mg/LUM-480 mg, twice daily for 3 days, it was administered with food and the doses were based on patient's body weight as per product label. Cohort 2 participants ages 6 months to <2 years.	

Primary: Polymerase Chain Reaction (PCR)-corrected adequate clinical and parasitological response (ACPR) - Cohorts 1 and 2 pooled

End point title	Polymerase Chain Reaction (PCR)-corrected adequate clinical and parasitological response (ACPR) - Cohorts 1 and 2 pooled ^[1]
End point description: PCR-corrected ACPR, defined as the absence of parasitemia(PS),was evaluated on Day29. Microscopic species identification was confirmed and determined by PCR genotyping methods to establish malaria recrudescence/reinfection.A participant was considered as PCR corrected ACPR at Day29 if the participant did not meet any of the criteria of early treatment failure (up to Day4), late clinical failure(Day5 to Day29) or late parasitological failure(Day8 to Day29), and had absence of PS on Day29 irrespective of axillary temperature unless the presence of PS after 7days(Day8 or later) was due to reinfection based on PCR genotyping.A presence of PS after 7days of treatment initiation was considered as a reinfection only if the PS was clear before Day8 and none of the parasite strain(s) detected on Day8 or later match with the parasite strain at baseline based on PCR genotyping.Given the age-independent symptoms of acute malaria, and to increase statistical power,the cohorts 1 and 2 were pooled.	
End point type	Primary
End point timeframe: Day 29	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This Endpoint is not analyzed for all arms

End point values	Cohort 1/2-KAF400mg/LUM480mg-QDx3	Cohort 1/2-Artemether80mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	99		
Units: Percentage of participants				
number (confidence interval 95%)	99.0 (94.4 to 100.0)	99.0 (94.5 to 100.0)		

Statistical analyses

Statistical analysis title	PCR-ACPR
Comparison groups	Cohort 1/2-KAF400mg/LUM480mg-QDx3 v Cohort 1/2-Artemether80mg/LUM480mg

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	2.8

Secondary: PCR-corrected and uncorrected Adequate Clinical and Parasitological Response (ACPR)

End point title	PCR-corrected and uncorrected Adequate Clinical and Parasitological Response (ACPR)
End point description:	
<p>PCR-corrected ACPR, defined as the absence of parasitemia, was evaluated. Microscopic species identification was confirmed and determined by polymerase chain reaction (PCR) genotyping methods to establish malaria recrudescence/reinfection.</p> <p>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. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2).</p>	
End point type	Secondary
End point timeframe:	
Corrected ACPR: Day 15, Day 43; Uncorrected ACPR: Day 15, Day 29 and Day 43	

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	22	8	13
Units: Percentage of participants				
number (confidence interval 95%)				
Day 15-corrected ACPR	100.0 (71.5 to 100.0)	100.0 (84.6 to 100.0)	100.0 (63.1 to 100.0)	100.0 (75.3 to 100.0)
Day 43-corrected ACPR	100.0 (71.5 to 100.0)	100.0 (84.6 to 100.0)	87.5 (47.3 to 99.7)	92.3 (64.0 to 99.8)
Day 15-uncorrected ACPR	100.0 (71.5 to 100.0)	100.0 (84.6 to 100.0)	100.0 (63.1 to 100.0)	100.0 (75.3 to 100.0)
Day 29-uncorrected ACPR	90.9 (58.7 to 99.8)	95.5 (77.2 to 99.9)	87.5 (47.3 to 99.7)	100.0 (75.3 to 100.0)
Day 43-uncorrected ACPR	81.8 (48.2 to 97.7)	86.4 (65.1 to 97.1)	62.5 (24.5 to 91.5)	76.9 (46.2 to 95.0)

End point values	Cohort 1/2- KAF400mg/LU M480mg-QDx3	Cohort 1/2- Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	99		
Units: Percentage of participants				
number (confidence interval 95%)				
Day 15-corrected ACPR	100.0 (96.3 to 100.0)	100.0 (96.3 to 100.0)		
Day 43-corrected ACPR	94.9 (88.5 to 98.3)	96.0 (90.0 to 98.9)		
Day 15-uncorrected ACPR	100.0 (96.3 to 100.0)	100.0 (96.3 to 100.0)		
Day 29-uncorrected ACPR	96.9 (91.3 to 99.4)	94.9 (88.6 to 98.3)		
Day 43-uncorrected ACPR	85.7 (77.2 to 92.0)	85.9 (77.4 to 92.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: PCR-corrected Adequate Clinical and Parasitological Response (ACPR) - Run-in Cohort

End point title	PCR-corrected Adequate Clinical and Parasitological Response (ACPR) - Run-in Cohort ^[2]
-----------------	----------------------------------------------------------------------------------------------------

End point description:

PCR-corrected ACPR, defined as the absence of parasitemia, was evaluated on Day 29. 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 at Day 29 if the participant did not meet any of the criteria of early treatment failure (ETF) (up to Day 4), late clinical failure (LCF) (Day 5 to Day 29) or late parasitological failure (LPF) (Day 8 to Day 29), and had absence of parasitaemia on Day 29 irrespective of axillary temperature unless the presence of parasitaemia after 7 days (Day 8 or later) was due to reinfection based on PCR genotyping. A presence of parasitaemia after 7 days of treatment initiation was considered as a reinfection only if the parasitaemia was clear before Day 8 and none of the parasite strain(s) detected on Day 8 or later match with the parasite strain at baseline based on PCR genotyping.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 29

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This Endpoint is not analyzed for all arms

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	22	8	13
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (71.5 to 100.0)	100.0 (84.6 to 100.0)	100.0 (63.1 to 100.0)	100.0 (75.3 to 100.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Fever clearance Times (FCT)

End point title	Fever clearance Times (FCT)
End point 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. FCT was calculated using the Kaplan-Meier method. Participants who received any antimalarial medication (including rescue medication) before fever clearance are censored at the first use of antimalarial medication. Participants without fever clearance are censored at the time of last fever assessment. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2). Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.	
End point type	Secondary
End point timeframe:	
up to 43 days	

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	3	2
Units: hours				
median (confidence interval 95%)	23.5 (23.3 to 999)	23.9 (23.6 to 999)	23.8 (23.7 to 999)	27.1 (23.9 to 999)

End point values	Cohort 1/2-KAF400mg/LU M480mg-QDx3	Cohort 1/2-Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	36		
Units: hours				
median (confidence interval 95%)	23.9 (23.4 to 24.3)	23.7 (23.5 to 23.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parasite Clearance Time (PCT)

End point title	Parasite Clearance Time (PCT)
-----------------	-------------------------------

End point 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. PCT was calculated using the Kaplan-Meier method. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2).

End point type	Secondary
----------------	-----------

End point timeframe:

up to 43 days

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	11	13
Units: hours				
median (confidence interval 95%)	48.1 (36.1 to 48.2)	36.2 (36.0 to 71.9)	48.0 (36.0 to 48.2)	48.0 (24.0 to 48.2)

End point values	Cohort 1/2-KAF400mg/LU M480mg-QDx3	Cohort 1/2-Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: hours				
median (confidence interval 95%)	47.5 (36.2 to 47.8)	35.9 (35.6 to 36.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Early Treatment Failure (ETF)

End point title	Percentage Early Treatment Failure (ETF)
-----------------	------------------------------------------

End point description:

Participants were defined as early treatment failures (ETFs) if they developed danger signs or severe malaria on Day 2, Day 3, or Day 4 in the presence of parasitemia, parasitemia on Day 3 with a count higher than the Day 1 count irrespective of axillary temperature, parasitemia on Day 4 with axillary temperature $\geq 37.5^{\circ}\text{C}$, or parasitemia on Day 4 with a count equal to or more than 25% of the count on Day 1. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2).

End point type	Secondary
----------------	-----------

End point timeframe:

From Day 1 to Day 4

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	26	11	13
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 14.3)	0.0 (0.0 to 13.2)	0.0 (0.0 to 28.5)	0.0 (0.0 to 24.7)

End point values	Cohort 1/2-KAF400mg/LU M480mg-QDx3	Cohort 1/2-Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	110		
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 3.4)	0.0 (0.0 to 3.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Late Clinical Failure (LCF)

End point title	Percentage Late Clinical Failure (LCF)
-----------------	----------------------------------------

End point description:

Participants were defined as late clinical failures (LCFs) if they developed danger signs or severe malaria on any day from Day 5 to Day 43 in the presence of parasitemia without previously meeting any of the criteria of ETF, or if they had parasitemia and an axillary temperature of $\geq 37.5^{\circ}\text{C}$ on any day from Day 5 to Day 43 without previously meeting any of the criteria of ETF. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2).

End point type	Secondary
----------------	-----------

End point timeframe:

Day 5 to Day 43

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	26	11	13
Units: Percentage of participants				
number (confidence interval 95%)	8.7 (1.1 to 28.0)	0.0 (0.0 to 13.2)	0.0 (0.0 to 28.5)	7.7 (0.2 to 36.0)

End point values	Cohort 1/2-KAF400mg/LU M480mg-QDx3	Cohort 1/2-Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	102		
Units: Percentage of participants				
number (confidence interval 95%)	8.7 (4.0 to 15.8)	3.9 (1.1 to 9.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Late Parasitological Failure (LPF)

End point title	Percentage Late Parasitological Failure (LPF)
End point description:	
Participants were defined as late parasitological failures (LPFs) if they had parasitemia on any day from Day 8 to Day 43 and an axillary temperature < 37.5°C without previously meeting any of the criteria of ETF or LCF. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2).	
End point type	Secondary
End point timeframe:	
Day 8 to Day 43	

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	26	11	12
Units: Percentage of participants				
number (confidence interval 95%)	19.0 (5.5 to 41.9)	19.2 (6.6 to 39.4)	54.5 (23.4 to 83.3)	16.7 (2.1 to 48.4)

End point values	Cohort 1/2-KAF400mg/LU	Cohort 1/2-Artemether80		
------------------	------------------------	-------------------------	--	--

	M480mg-QDx3	mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	98		
Units: Percentage of participants				
number (confidence interval 95%)	4.2 (1.2 to 10.4)	11.2 (5.7 to 19.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new infections events

End point title	Number of participants with new infections events
-----------------	---------------------------------------------------

End point 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. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2).

End point type	Secondary
----------------	-----------

End point timeframe:

Day 15, Day 29 and Day 43

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	11	13
Units: participants				
Day 15	0	0	0	0
Day 29	1	0	2	0
Day 43	3	3	3	2

End point values	Cohort 1/2-KAF400mg/LU M480mg-QDx3	Cohort 1/2-Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: participants				
Day 15	0	0		
Day 29	3	4		
Day 43	7	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with recrudescence events

End point title	Number of participants with recrudescence events
End point 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. Given the age-independent symptoms of acute malaria, and to increase statistical power, the cohorts 1 and 2 were pooled (cohort 1/2).	
End point type	Secondary
End point timeframe: Day 15, Day 29 and Day 43	

End point values	Run-in Cohort- KAF400mg/LU M240mg- QDx2-Fed	Run-in Cohort- KAF400mg/LU M240mg- QDx2-Fasted	Run-in Cohort- KAF400mg/LU M480mg- QDx2-Fed	Run-in Cohort- KAF400mg/LU M480mg- QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	11	13
Units: participants				
Day 15	0	0	0	0
Day 29	1	0	0	0
Day 43	1	0	0	1

End point values	Cohort 1/2- KAF400mg/LU M480mg-QDx3	Cohort 1/2- Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: participants				
Day 15	0	0		
Day 29	1	1		
Day 43	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)
End point description: Number of participants with treatment emergent adverse events (any AE regardless of seriousness), and SAEs. Given the age-independent symptoms of acute malaria, and to increase statistical power, the	

cohorts 1 and 2 were pooled (cohort 1/2).

End point type	Secondary
----------------	-----------

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment up to a maximum duration of approximately 43 days.

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	11	13
Units: participants				
Adverse Events	15	13	10	9
Serious Adverse Events	1	0	0	1

End point values	Cohort 1/2-KAF400mg/LU M480mg-QDx3	Cohort 1/2-Artemether80 mg/LUM480mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: participants				
Adverse Events	74	61		
Serious Adverse Events	0	4		

Statistical analyses

No statistical analyses for this end point

Secondary: KAF156 and Lumefantrine (LUM) Cmax

End point title	KAF156 and Lumefantrine (LUM) Cmax ^[3]
-----------------	---------------------------------------------------

End point description:

Cmax is the maximum observed plasma concentration following drug administration. PK parameters are calculated from plasma concentration-time data using non-compartmental methods. Analyte KAF156 is not applicable for Artemether80mg/LUM480mg arm. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
----------------	-----------

End point timeframe:

Run-in Cohort:Pre-dose,1,3,4,5,6,8,24,25,27,28,29,30,32,48,72,168 hours; PK sampling 6-12 years: 3,6,24,48,51,54,72,168 hours; 6 months -< 6 years: 24,48,51,54,72,168 hours; Coartem arm:24,48,68,168 hours.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK Endpoint not analyzed for participants on placebo

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	23	8	13
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
KAF156	1520 (± 27.1)	1460 (± 26.5)	1610 (± 17.7)	1320 (± 24.6)
LUM	11600 (± 59.1)	7850 (± 64.4)	25900 (± 51.1)	10900 (± 86.7)

End point values	Cohort 1-KAF400mg/LU M480mg-QDx3	Cohort 2-KAF400mg/LU M480mg-QDx3	Cohort 1-Artemether80 mg/LUM480mg	Cohort 2-Artemether80 mg/LUM480mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	31	53	31
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
KAF156	1240 (± 60.4)	741 (± 56.6)	999 (± 999)	999 (± 999)
LUM	21300 (± 52.5)	9020 (± 135.5)	6510 (± 63.3)	3300 (± 142)

Statistical analyses

No statistical analyses for this end point

Secondary: KAF156 and Lumefantrine Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast)

End point title	KAF156 and Lumefantrine Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) ^[4]
-----------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------

End point description:

AUC is the area under the plasma concentration-time curve. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. For Cohort 1/2 - Artemether80mg/LUM480mg arms enough plasma samples were not collected to calculate AUC parameters.

End point type	Secondary
----------------	-----------

End point timeframe:

Run-in Cohort: Pre-dose, 1, 3, 4, 5, 6, 8, 24, 25, 27, 28, 29, 30, 32, 48, 72, 168 hours; PK sampling 6-12 years: 3, 6, 24, 48, 51, 54, 72, 168 hours; 6 months - < 6 years: 24, 48, 51, 54, 72, 168 hours; Coartem arm: 24, 48, 68, 168 hours.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK Endpoint not analyzed for participants on placebo

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	23	8	13
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
KAF156	45900 (± 21.2)	44100 (± 30.7)	53000 (± 29.1)	44000 (± 27.4)
LUM	389000 (± 60.4)	207000 (± 86.5)	934000 (± 49.7)	342000 (± 80.3)

End point values	Cohort 1-KAF400mg/LU M480mg-QDx3	Cohort 2-KAF400mg/LU M480mg-QDx3Edit		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	31		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
KAF156	44100 (± 66.8)	25600 (± 71.6)		
LUM	970000 (± 59.6)	383000 (± 182.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: KAF156 and Lumefantrine time to reach the maximum plasma concentration after drug administration (Tmax)

End point title	KAF156 and Lumefantrine time to reach the maximum plasma concentration after drug administration (Tmax) ^[5]
-----------------	------------------------------------------------------------------------------------------------------------------------

End point description:

Tmax is the time to reach maximum plasma concentration following drug administration. PK parameters are calculated from plasma concentration-time data using non-compartmental methods. For Cohort 1/2 -Artemether80mg/LUM480mg arms enough plasma samples were not collected to calculate Tmax parameter.

End point type	Secondary
----------------	-----------

End point timeframe:

Run-in Cohort:Pre-dose,1,3,4,5,6,8,24,25,27,28,29,30,32,48,72,168 hours; PK sampling 6-12 years: 3,6,24,48,51,54,72,168 hours; 6 months -< 6 years: 24,48,51,54,72,168 hours; Coartem arm:24,48,68,168 hours.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK Endpoint not analyzed for participants on placebo

End point values	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M240mg-QDx2-Fasted	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fed	Run-in Cohort-KAF400mg/LU M480mg-QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	23	8	13
Units: hours				
median (full range (min-max))				
KAF156	3.92 (2.65 to 7.93)	3.58 (1.35 to 5.88)	4.46 (3.87 to 5.97)	4.18 (2.85 to 7.98)
LUM	7.67 (4.02 to 8.12)	7.7 (0.967 to 8.23)	7.02 (5.9 to 24.1)	6.05 (5.05 to 24.2)

End point values	Cohort 1-KAF400mg/LU M480mg-QDx3	Cohort 2-KAF400mg/LU M480mg-QDx3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	31		
Units: hours				
median (full range (min-max))				
KAF156	3.03 (0 to 23.5)	2.95 (0 to 23.5)		
LUM	5.97 (0 to 23.9)	6.02 (0 to 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: KAF156 and Lumefantrine plasma drug concentration 168 hours post first dose administration (C168h)

End point title	KAF156 and Lumefantrine plasma drug concentration 168 hours post first dose administration (C168h) ^[6]
-----------------	-------------------------------------------------------------------------------------------------------------------

End point description:

C168h is the plasma concentration at 168h post first dose administration. PK parameters are calculated from plasma concentration-time data using non-compartmental methods. Analyte KAF156 is not applicable for Artemether80mg/LUM480mg arm. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
----------------	-----------

End point timeframe:

at 168 hours

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK Endpoint not analyzed for participants on placebo

End point values	Run-in Cohort- KAF400mg/LU M240mg- QDx2-Fed	Run-in Cohort- KAF400mg/LU M240mg- QDx2-Fasted	Run-in Cohort- KAF400mg/LU M480mg- QDx2-Fed	Run-in Cohort- KAF400mg/LU M480mg- QDx2-Fasted
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	23	8	13
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
KAF156	23.9 (± 38.7)	21.8 (± 62.5)	14.9 (± 62.7)	25.3 (± 55.9)
LUM	429 (± 50.1)	189 (± 106.1)	679 (± 36.5)	332 (± 73.5)

End point values	Cohort 2- KAF400mg/LU M480mg-QDx3	Cohort 1- KAF400mg/LU M480mg-QDx3	Cohort 1- Artemether80 mg/LUM480mg	Cohort 2- Artemether80 mg/LUM480mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	68	65	35
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
KAF156	11 (± 87.5)	24.8 (± 120.8)	999 (± 999)	999 (± 999)
LUM	574 (± 135.8)	1320 (± 92.4)	438 (± 80.9)	297 (± 89.1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment up to a maximum duration of approximately 43 days.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	27.0
--------------------	------

Reporting groups

Reporting group title	KAF400mg/LUM240mg-QDx2-Fed
-----------------------	----------------------------

Reporting group description:

KAF400mg/LUM240mg-QDx2-Fed

Reporting group title	Coartem
-----------------------	---------

Reporting group description:

Coartem

Reporting group title	KAF400mg/LUM480mg-QDx2-Fasted
-----------------------	-------------------------------

Reporting group description:

KAF400mg/LUM480mg-QDx2-Fasted

Reporting group title	KAF400mg/LUM480mg-QDx3
-----------------------	------------------------

Reporting group description:

KAF400mg/LUM480mg-QDx3

Reporting group title	KAF400mg/LUM240mg-QDx2-Fasted
-----------------------	-------------------------------

Reporting group description:

KAF400mg/LUM240mg-QDx2-Fasted

Reporting group title	KAF400mg/LUM480mg-QDx2-Fed
-----------------------	----------------------------

Reporting group description:

KAF400mg/LUM480mg-QDx2-Fed

Serious adverse events	KAF400mg/LUM240mg-QDx2-Fed	Coartem	KAF400mg/LUM480mg-QDx2-Fasted
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	4 / 110 (3.64%)	1 / 13 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 25 (0.00%)	2 / 110 (1.82%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			

subjects affected / exposed	1 / 25 (4.00%)	1 / 110 (0.91%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 110 (0.91%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	KAF400mg/LUM480 mg-QDx3	KAF400mg/LUM240 mg-QDx2-Fasted	KAF400mg/LUM480 mg-QDx2-Fed
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 110 (0.00%)	0 / 26 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	KAF400mg/LUM240 mg-QDx2-Fed	Coartem	KAF400mg/LUM480 mg-QDx2-Fasted
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 25 (48.00%)	55 / 110 (50.00%)	9 / 13 (69.23%)
Investigations			

Bilirubin conjugated increased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	0 / 13 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	1 / 13 (7.69%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 110 (0.00%) 0	0 / 13 (0.00%) 0
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	6 / 110 (5.45%) 6	1 / 13 (7.69%) 1
Heart rate decreased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	1 / 13 (7.69%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 110 (0.91%) 1	3 / 13 (23.08%) 3
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 110 (0.91%) 1	1 / 13 (7.69%) 1
Anaemia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	6 / 110 (5.45%) 6	1 / 13 (7.69%) 1
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	12 / 110 (10.91%) 12	3 / 13 (23.08%) 3
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 110 (0.00%) 0	0 / 13 (0.00%) 0
Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	3 / 110 (2.73%) 3	1 / 13 (7.69%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	2 / 13 (15.38%) 2
Toothache subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	0 / 13 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	12 / 110 (10.91%) 12	0 / 13 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	4 / 110 (3.64%) 4	1 / 13 (7.69%) 1
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	0 / 13 (0.00%) 0
Infections and infestations Furuncle subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	1 / 13 (7.69%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 110 (0.00%) 0	0 / 13 (0.00%) 0
Malaria subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 6	15 / 110 (13.64%) 15	3 / 13 (23.08%) 3
Schistosomiasis subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 110 (0.91%) 1	1 / 13 (7.69%) 1
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	16 / 110 (14.55%) 19	0 / 13 (0.00%) 0

Non-serious adverse events	KAF400mg/LUM480 mg-QDx3	KAF400mg/LUM240 mg-QDx2-Fasted	KAF400mg/LUM480 mg-QDx2-Fed
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 110 (62.73%)	12 / 26 (46.15%)	10 / 11 (90.91%)
Investigations			
Bilirubin conjugated increased			
subjects affected / exposed	1 / 110 (0.91%)	0 / 26 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 110 (0.00%)	1 / 26 (3.85%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 110 (0.91%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	18 / 110 (16.36%)	1 / 26 (3.85%)	4 / 11 (36.36%)
occurrences (all)	18	1	6
Heart rate decreased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 110 (0.91%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 110 (1.82%)	0 / 26 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Anaemia			
subjects affected / exposed	5 / 110 (4.55%)	1 / 26 (3.85%)	1 / 11 (9.09%)
occurrences (all)	5	1	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	16 / 110 (14.55%)	1 / 26 (3.85%)	2 / 11 (18.18%)
occurrences (all)	16	1	2
Gastrointestinal disorders			

Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	2 / 26 (7.69%) 2	0 / 11 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 2	0 / 26 (0.00%) 0	1 / 11 (9.09%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 26 (0.00%) 0	0 / 11 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 26 (0.00%) 0	1 / 11 (9.09%) 1
Vomiting subjects affected / exposed occurrences (all)	32 / 110 (29.09%) 32	2 / 26 (7.69%) 2	1 / 11 (9.09%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 6	1 / 26 (3.85%) 1	0 / 11 (0.00%) 0
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 26 (0.00%) 0	1 / 11 (9.09%) 1
Infections and infestations Furuncle subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 26 (0.00%) 0	0 / 11 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 26 (0.00%) 0	1 / 11 (9.09%) 1
Malaria subjects affected / exposed occurrences (all)	13 / 110 (11.82%) 13	5 / 26 (19.23%) 6	6 / 11 (54.55%) 7
Schistosomiasis subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 26 (0.00%) 0	1 / 11 (9.09%) 1

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	27 / 110 (24.55%)	1 / 26 (3.85%)	0 / 11 (0.00%)
occurrences (all)	29	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2021	Changes have been implemented due to the availability of data from another ongoing study (CKAF156A2202). The changes are related to safety and efficacy data of KAF156 combined with LUM-SDF in pediatric patients (2 to <12 years of age).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported