2 Synopsis

Name of product: KAF156 and LUM-SDF

Protocol identification number: Protocol no. CKAF156A2202, EudraCT no.: 2020-003284-25

Title of study: A Phase 2 interventional, multicenter, randomized open-label study to determine the effective and tolerable dose of KAF156 and lumefantrine Solid Dispersion Formulation in combination, given once daily for 1, 2 and 3 days to adults and children with uncomplicated *Plasmodium falciparum* malaria

Principal or Coordinating Investigator: Martin Peter Grobusch M.D, PhD, FRCP, Centre de Recherches Médicales de Lambaréné, CERMEL, Albert Schweitzer Hospital, BP242 Lambarene, Gabon.

Study center(s): 13 centers in 10 countries: Uganda (2 centers), Kenya (2 centers), Cote d'Ivoire (2 centers), Vietnam, Thailand, Burkina Faso, Gabon, Mozambique, Mali, India

Publication (reference): None

Study period

Study initiation date: 02-Aug-2017 (first patient first visit)

Study completion date: 28-Jun-2021 (last patient last visit)

Phase of development (phase of this clinical study): II

Objectives: The primary objective was to determine the effective doses of KAF156 combined with LUM-SDF given daily over 1, 2, or 3 days for treatment of uncomplicated malaria caused by *P. falciparum*.

The secondary objectives were to evaluate the safety and tolerability of KAF156/LUM-SDF, to further assess the treatment effect of KAF156/LUM-SDF by assessing uncorrected and PCR-corrected ACPR at additional time points, as well as fever and parasite clearance times, and to assess the key pharmacokinetic (PK) parameters of KAF156 and lumefantrine.

The study has been completed as planned.

Methodology: This was a multicenter, open-label, randomized, parallel-group study to determine the most effective and tolerable dose at the shortest dosing regimen (3-, 2- and 1-day regimens) of a combination of KAF156 and a solid dispersion formulation of lumefantrine (LUM-SDF) in adults and children with uncomplicated *P. falciparum* malaria. The study had a PK Run-in part and two main parts: Part A and Part B. In the PK Run-in part, male and female adult/adolescent patients (≥ 12 years old and ≥ 35 kg) were administered a single KAF156/LUM-SDF dose to assess potential PK interactions. In Part A, male and female adult/adolescent patients (≥ 12 years old and ≥ 35 kg) were randomized into one of seven cohorts (six KAF156 and LUM-SDF cohorts and a control arm - Coartem) in a 2:2:2:2:2:2:1 ratio. Patients were admitted to the hospital on Day 1, were dosed on Day 1 only, Days 1 and 2, or Days 1, 2, and 3, depending on the assigned treatment cohort, and were discharged on Day 4. Patients were then followed up until Day 43. Upon completion of Part A, all the dosing groups were evaluated in an interim assessment to determine the effective and tolerated KAF156 and LUM-SDF dosing regimen and dosages to be used in Part B. In Part B, children (2 to < 12 years old and ≥ 10 kg) with uncomplicated *P. falciparum* malaria were randomized to the three selected KAF156 and LUM-SDF cohorts and Coartem in a 2:2:2:1 ratio.

Number of subjects (planned and analyzed): In the PK Run-in part, 12 patients were planned to be enrolled, and 12 patients were enrolled and analyzed. In Part A, approximately 325 patients were planned to be enrolled, and 337 patients were enrolled and analyzed. In Part B, approximately 175 patients were planned to be enrolled, 175 patients were enrolled, and 174 patients were analyzed (1 patient did not receive the study treatment).

Diagnosis and main criteria for inclusion: Male or female patients ≥ 12 years old and ≥ 35 kg (PK Run-in part and Part A) or 2 to < 12 years old and ≥ 10 kg (Part B) with confirmed and uncomplicated *P. falciparum* malaria (microscopic confirmation by Giemsa-stained thick and thin films) and *P. falciparum* counts more than 1000 and less than 150000 parasites/µL at pre-screening, and axillary temperature ≥ 37.5 ºC or oral/tympanic/rectal temperature ≥ 38.0ºC, or similar history of fever during the previous 24 hours.

Duration of treatment: In the PK Run-in part, KAF156/LUM-SDF was administered QD for 1 day. In Part A and Part B, KAF156/LUM-SDF was administered QD for 1 day, 2 days, or 3 days, while Coartem was administered BID for 3 days.

Test and reference therapies, dose and mode of administration, batch number: In the PK Run-in part, KAF156 200 mg and LUM-SDF 960 mg was administered orally. The dosing scheme followed for KAF156/LUM-SDF and Coartem in Part A and Part B is given below:

Part A: KAF156 and LUM-SDF dosing scheme

Cohort	Treatment	Dose	Dosing regimen (oral administration)
1	KAF156/LUM-SDF	400 mg/960 mg	QD for 1 day
2	KAF156/LUM-SDF	800 mg/960 mg	QD for 1 day
3	KAF156/LUM-SDF	400 mg/960 mg	QD for 2 days
4	KAF156/LUM-SDF	200 mg/480 mg	QD for 3 days
5	KAF156/LUM-SDF	400 mg/480 mg	QD for 3 days
6	KAF156/LUM-SDF	400 mg/960 mg	QD for 3 days

Part B: KAF156 and LUM-SDF dosing scheme*

Treatment	Dose	Dosing regimen (oral administration)
KAF156/LUM-SDF	400 mg/960 mg	QD for 1 day
KAF156/LUM-SDF	400 mg/960 mg	QD for 2 days
KAF156/LUM-SDF	400 mg/960 mg	QD for 3 days

Doses for KAF156/LUM-SDF in the table are for patients > 35 kg. For patients with lower body weights, these were adapted as follows: 25 to< 35 kg. 0.75 of the adult dose, 15 to < 25 kg: 0.50 of the adult dose, 10 to < 15 kg: 0.25 of the adult dose. These are the same weight brackets and corrections as for Coartem.

Coartem dosing per weight (Parts A and B)

Weight	Dose (artemether/lumefantrine)	Dosing regimen (oral administration)
≥ 12 years and ≥ 35.0 kg	80/480 mg	BID for 3 days
25.0 to < 35.0 kg	60/360 mg	BID for 3 days
15.0 to < 25.0 kg	40/240 mg	BID for 3 days
10.0 to < 15.0 kg	20/120 mg	BID for 3 days

Criteria for evaluation

Efficacy: Efficacy assessments were based on polymerase chain reaction (PCR)-corrected adequate clinical and parasitological response (ACPR) at Day 29. For parasitemia assessment, thick and thin blood films were evaluated using Giemsa stain and were used to quantify each parasite species and *P. falciparum* gametocytes. Microscopic species identification of parasites was confirmed and determined with PCR-based methods on blood samples.

Pharmacokinetics: Blood samples were collected for rich PK sampling in the PK Run-in Part and in some patients in Part A and sparse PK sampling in Part A (in the rest of the patients not involved in rich PK) and in Part B. Parameters such as AUCinf, AUClast, AUC0-t, Cmax, and Tmax were reported,

where possible for the patients with rich PK data using non-compartmental method of analysis (using Phoenix 6.4 or higher).

Safety: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), along with their severity and relationship to the study treatment. This included physical examination and malaria signs and symptoms, regular monitoring of vital signs, body temperature, laboratory evaluations (hematology, blood chemistry, and urinalysis), electrocardiogram (ECG), pregnancy and assessments of fertility.

Statistical methods: Statistical analyses for the PK Run-in part, Part A, and Part B were performed separately. Subgroups, which included age-groups, baseline weight-groups, sex, and region, were used for descriptive summary of selected efficacy and safety analyses. For key efficacy and safety outcome, pooled analysis was performed by pooling Part B and corresponding cohorts in Part A. Unless described separately, the same statistical method was used for separate analysis and pooled analysis.

Efficacy: The PK Run-in part was analyzed separately. The objective for the PK Run-in part was to investigate the pharmacokinetic interaction potential between KAF156 and lumefantrine.

The primary efficacy variable was PCR-corrected ACPR at Day 29. A patient was considered as PCR-corrected ACPR at Day 29 if the patient did not meet any of the criteria of early treatment failure (up to Day 4), late clinical failure (Day 5 to Day 29) or late parasitological failure (Day 8 to Day 29), and has absence of parasitemia on Day 29 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 (Day 8 or later) was considered as a reinfection only if the original parasitemia cleared 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. Treatment failures after 7 days due to reinfection based on PCR genotyping were not considered as failure for PCR-corrected analyses but were considered as failure for uncorrected analyses.

The statistical null hypothesis was that the ACPR rate at Day 29 is at most 80%. The alternative hypothesis was that the ACPR rate at Day 29 is greater than 80%. The statistical hypothesis was evaluated using the lower limit of 2-sided 95% exact confidence interval (CI) (Clopper-Pearson method) for the ACPR rate at Day 29. If the lower limit of 2-sided 95% exact CI for the ACPR rate at Day 29 is greater than 80%, the null hypothesis is rejected. The statistical hypothesis testing was evaluated separately for each KAF156 and LUM-SDF combination in each part based on the per-protocol set (PPS). There was no adjustment for multiplicity for this Phase II study.

Supportive analysis of the primary endpoint (for the full analysis set; FAS) was performed using the Kaplan-Meier method. In order to assess the impact of reinfections on the PCR-corrected ACPR rate, sensitivity analysis was performed. PCR-corrected ACPR rate was recalculated by excluding the patients with reinfections occurring prior to Day 29. Analyses were based on PPS for Part A and Part B.

Secondary endpoints:

- PCR-corrected ACPR (at Day 15 and 43) and uncorrected ACPR (at Day 15, 29, and 43): At each visit, the mean ACPR rate with 95% CI was provided using Clopper-Pearson method for each treatment group. In addition, PCR-corrected ACPR rate was calculated and plotted using the Kaplan-Meier method for each treatment group in the FAS. For uncorrected ACPR at Day 29, a sensitivity analysis was performed to assess the impact of administration of non-study antimalarial drugs on the PCR uncorrected response rate. The proportion of patients with PCR uncorrected ACPR at Day 29 was recalculated by considering the patients receiving non-study antimalarial drugs (if received before Day 29 visit without being treatment failures i.e. not early treatment failures or late clinical failures or late parasitological failures) as non-responders using FAS. Patients who received concomitant prohibited non-malaria medications with potential impact on efficacy/antimalarial activity (PROH01b) before the Day 29 visit without being treatment failures were also considered as non-responders.
- Treatment failure related parameters: 95% CI were provided for each treatment group using the Clopper-Pearson method for the proportion of patients with parasitemia at 12, 24, and

48 hours after treatment and for the proportion of patients with early treatment failure, late clinical failure, and late parasitological failure.

- Recrudescence and reinfection: Incidence rates of recrudescence (appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline) and reinfection (appearance of asexual parasites after clearance of initial infection with a genotype different from those parasites present at baseline) at Days 15, 29, and 43 were estimated by the Kaplan-Meier method based on the subset of FAS patients who had clearance of initial infection by Day 15. Time to event (recrudescence or reinfection) was calculated from the time of first study medication to the date of first event if a patient experienced the event and was censored at the time of last parasite assessment if a patient did not experience the event.
- Parasite clearance time and fever clearance time: Descriptive statistics were presented using the Kaplan-Meier method. Parasite clearance time was calculated based on uncorrected parasite counts. Patients without parasite clearance for whatever reason were censored at the time of last parasite assessment. Patients who were enrolled on the basis of history of fever and did not subsequently have a fever at pre-dose were not included in the analysis of fever clearance time. Patients without fever clearance for whatever reason were censored at the time of last temperature assessment.

Analyses of ACPRs (PCR-corrected or uncorrected) were based on the FAS and PPS. Analyses of other secondary efficacy variables were based on the FAS.

The following additional analyses were performed for each part and the pooled Part A and Part B:

- For PCR-corrected and uncorrected ACPR rates, the 95% CIs for the difference between each test group (KAF156/LUM-SDF combination) and the control (Coartem) were provided using the Wilson uncorrected method. For the pooled analysis, the treatment differences versus control were evaluated using a Mantel-Haenszel estimate of the common risk difference stratified by part.
- For parasite clearance time and fever clearance time, the difference between each test group and control were evaluated using a log-rank test. Patients who did not experience a clearance were censored at the time of last relevant assessment (parasite or fever). For the pooled analysis, the log-rank test was stratified by Part.

Safety: All safety analyses were performed using the Safety set. The assessment of safety and tolerability was based mainly on the number and percent of patients with treatment-emergent adverse events (AEs), changes in laboratory values (hematology, blood chemistry, and urinalysis), and clinically notable changes in vital signs and ECG.

Pharmacokinetics: Descriptive statistics of pharmacokinetic parameters were calculated using the PK analysis set and included arithmetic and geometric means, standard deviation, median, minimum and maximum. A separate PK analysis was performed for patients providing rich PK data. Parameters such as AUCinf, AUClast, AUC0-t, Cmax and Tmax were reported for the patients with rich PK data using non-compartmental method of analysis (using Phoenix 6.4 or higher). For the PK Run-in part, two sided 90% CI for AUC0-24h, Cmax and Tmax PK parameters of KAF156 and lumefantrine were calculated by Part and treatment group using normal or log-normal approximation as applicable. Non-compartmental PK analysis for patients with sparse data was also conducted and feasible PK parameters were reported. Concentration at a nominal time point of 168 hours post dose or any other time point identified as critical for cure was reported for all patients where feasible.

Summary - Results

Demographic and background characteristics: The patient demographics were comparable across the treatment groups in Part A and Part B, respectively. The majority of patients were Black (Part A: 288 patients, 85.5%; Part B: 173 patients, 98.9%). In Part A, the median age of patients was 16 years (range: 11 to 62 years), median body weight was 51 kg (range: 35 to 89 kgs), and the majority of patients (311 patients, 92.3%) had their body mass index (BMI) in the range of 16 to ≤ 25 kg/m^2; there was a higher proportion of males (182 patients, 54%) compared to females (155 patients, 46%). In Part B, the

median age of patients was 6 years (range: 2 to 11 years), median body weight was 20.1 kg (range: 10.2 to 34.5 kgs), and the BMI was < 16 kg/m^2 for majority of patients (140 patients, 80%); there was a higher proportion of females (95 patients, 54.3%) compared to males (80 patients, 45.7%). In the pooled analysis, (including those treatment groups common in Part A and Part B), the demographic characteristics were similar across the treatment regimens. Of the 356 patients (Part A + Part B), the majority (276 patients; 77.5%) were < 18 years of age. The median age was 11.5 years (range: 2 to 60 years). The median body weight was 35.2 kg (range: 10.2 to 89 kgs), and the BMI ranged from 16 to ≤ 25 kg/m^2 for 203 patients (57%) and was < 16 kg/m^2 for 143 patients (40.2%). There was an equal proportion of males (181 patients, 50.8%) and females (175 patients, 49.2%).

In both, Part A and Part B, patients either had fever at baseline or it was reported as a medical history. In some patients, the mean body temperature at baseline was not indicative of fever as these patients received anti-pyretic drugs. In Part A and Part B, all patients were confirmed to be infected with *P. falciparum* at baseline. Except for one patient in Part B with a baseline parasite count of 399/µL, all patients (Part A and Part B) had a baseline parasite count of > 1000/µL.

Efficacy results:

- **Primary efficacy (by PPS)**:
  - The primary objective of Part A was met, and the null hypothesis was rejected for all KAF156/LUM-SDF treatment groups. At Day 29, for the PCR-corrected ACPR rate, the lower limit of 2-sided 95% exact CI was > 80% (pre-defined primary efficacy success criteria) for all KAF156/LUM-SDF treatment groups.
  - In Part B, only the KAF400 mg/LUM960 mg 3-day regimen met the success criteria of lower limit of 2-sided 95% exact CI being > 80% for ACPR rate (83.1%), whereas in the 1-day and 2-day regimens, the lower limit of 2-sided 95% CI was 62.7% and 79.2%, respectively.
  - For the pooled analysis (Part A + Part B), the PCR-corrected ACPR rate at Day 29 for the KAF156/LUM-SDF treatment regimens was the highest in the 3-day regimen (96.4%), and this was numerically similar to Coartem (97.9%), with a treatment difference of −1.4% (95% CI: −7.2, 4.3). At Day 29, the 2-day regimen showed a PCR-corrected ACPR rate of 94.7% and the 1-day regimen was lower at 84.7%.
  - Subgroup analysis: Overall, for the KAF156/LUM-SDF treatment regimens in the pooled analysis, the PCR-corrected ACPR rate was homogenous and consistent across the subgroups (age group, baseline weight group, gender, and region), with a higher response rate in the 2-day and 3-day regimens compared to the 1-day regimen.
    - For the KAF156/LUM-SDF regimens, the PCR-corrected ACPR rate in the 1-day regimen was lower in younger patients (< 18 years of age) compared to adults (≥ 18 years of age). Most patients with lower PCR-corrected ACPR rates in Part A were < 18 years of age. Overall, for the KAF156/LUM-SDF treatment regimens, lower response rates were observed in the younger patients who were < 12 years of age (78.9% to 100% in patients 2 to < 6 years; 74.2% to 96.3% in patients 6 to < 12 years).
  - Sensitivity analysis: A sensitivity analyses was performed where PCR-corrected ACPR rate was recalculated by excluding patients with reinfections prior to Day 29. Results from the sensitivity analysis were consistent with the primary analysis.
- **Secondary efficacy**:
  - **PCR-corrected ACPR rates by PPS**:
    - At Day 15, for the KAF156/LUM-SDF treatment groups, the PCR-corrected ACPR rate varied from 95.8% to 100% in Part A and from 97.8% to 100% in Part B. For the KAF156/LUM-SDF treatment groups in Part A, higher PCR-corrected ACPR rates were noted in the 2-day and 3-day regimens, and these were numerically similar to Coartem. In Part B, the highest PCR-corrected ACPR rate was noted in the 3-day regimen (100%), and this was numerically identical to Coartem (100%).

- At Day 43, the PCR-corrected ACPR rate varied from 90% to 97.9% in Part A and from 75% to 92.5% in Part B. In Part A, for the KAF156/LUM-SDF treatment groups, higher PCR-corrected ACPR rates were noted in the 2-day and 3-day regimens, and these were numerically similar to Coartem. In Part B, the highest PCR-corrected ACPR rate was noted in the 3-day regimen (92.5%), and this was numerically higher than Coartem (90.9%).
- For the pooled analysis (Part A + Part B), the PCR-corrected ACPR rate for the KAF156/LUM-SDF treatment regimens varied from 96.9% to 100% at Day 15 and 82.7% to 94% at Day 43. For Coartem, it was 100% at Day 15 and 93.6% at Day 43.

- **Uncorrected ACPR rate by FAS**:
  - In Part A, the uncorrected ACPR rate was more than 80% for all KAF156/LUM-SDF treatment groups at Days 15, 29, and 43, except for the 1-day regimen of KAF800 mg/LUM960 mg at Day 29 (78.4%) and Day 43 (70.6%). Generally, the uncorrected ACPR rate was similar across the KAF156/LUM-SDF treatment groups at Days 15, 29, and 43; however, there was a decline in the uncorrected ACPR rate at Day 43 due to recrudescence (11 patients) or reinfections (30 patients). For Coartem, the uncorrected ACPR rate at Days 15, 29, and 43 was 100%, 96.3%, and 70.4%, respectively.
  - The uncorrected ACPR rate was lower in Part B compared to Part A, and sharply declined from Day 15 to Day 43 due to recrudescence (22 patients at Day 43) or reinfection (30 patients at Day 43). For Coartem, the uncorrected ACPR rate at Days 15, 29, and 43 was 100%, 62.5%, and 45.8%, respectively.
  - For the pooled analysis, for the KAF156/LUM-SDF treatment regimens and Coartem, the uncorrected ACPR rate declined from Day 15 to Day 43. At Days 29 and 43, for KAF156/LUM-SDF, the 2-day and 3-day regimens showed a higher response rate compared to the 1-day regimen. At Day 43, the uncorrected ACPR rate in all the KAF156/LUM-SDF regimens was numerically higher than in the Coartem treatment group.
    - Subgroup analysis: At Day 29, higher uncorrected ACPR rate in the KAF156/LUM-SDF 2-day and 3-day regimens compared to the 1-day regimen was seen in all the subgroups (age group, baseline weight group, gender, and region).
    - Sensitivity analysis: A sensitivity analysis for uncorrected ACPR at Day 29 was performed where patients receiving non-study antimalarial drugs in the absence of treatment failure were considered as non-responders. Results from the sensitivity analysis were consistent with the secondary analysis.

- **Treatment failure by FAS**:

In both Part A and Part B:

- No patients were noted with early treatment failure.
- The proportion of patients with late clinical failure was numerically higher in the 1-day regimen of KAF156/LUM-SDF and Coartem than the 3-day and 2-day regimens of KAF156/LUM-SDF (with the exception of KAF400 mg/LUM480 mg – 3-day regimen in Part A, in which 6.3% patients had late clinical failure, which was similar to the 1-day regimens).
- The proportion of patients with late parasitological failure was numerically higher in the Coartem treatment group than in the KAF156/LUM-SDF treatment groups and regimens.

- **Parasitemia by FAS**: For Part A and Part B, the proportion of patients with parasitemia declined from 12 hours to 48 hours after treatment, with a sharp decline noted from 24 hours to 48 hours after treatment. The proportion of patients with parasitemia in the

KAF156/LUM-SDF treatment groups was overall comparable with the Coartem treatment group.

- **Reinfections and recrudescence**: Overall, for Part A and Part B, the incidence rate of reinfections was higher than recrudescence in the KAF156/LUM-SDF treatment groups and Coartem group. Also, the overall rate of recrudescence was higher in Part B compared to Part A.
  - **Recrudescence**:
    - In Part A, for the KAF156/LUM-SDF treatment groups, recrudescence was noted in a total of 11 patients out of 310 patients: 4 patients in KAF400 mg/LUM960 mg (1-day regimen), 3 patients in KAF800 mg/LUM960 mg (1-day regimen), 1 patient in KAF400 mg/LUM960 mg (2-day regimen), 1 patient in KAF200 mg/LUM480 mg (3-day regimen), and 2 patients in KAF400 mg/LUM960 mg (3-day regimen). Recrudescence events occurred up to Day 15 in 1 patient, between Day 15 and Day 29 in 8 patients, and between Day 29 and Day 43 in 2 patients. There were no patients with recrudescence events in the Coartem treatment group.
    - In Part B, for the KAF156/LUM-SDF regimens, recrudescence was noted in a total of 22 out of 150 patients (12 patients in the 1-day regimen, 7 patients in the 2-day regimen, and 3 patients in the 3-day regimen). In KAF156/LUM-SDF treatment groups, recrudescence events occurred up to Day 15 in 1 patient, between Day 15 and Day 29 in 13 patients, and between Day 29 and Day 43 in 8 patients. Recrudescence events were noted in 2 patients in the Coartem treatment group (between Day 15 and Day 29 in 1 patient and between Day 29 and Day 43 in 1 patient).
  - **Reinfection**:
    - In Part A, reinfections were noted in a total of 31 patients in the KAF156/LUM-SDF treatment groups. Reinfections were noted in 10 patients, 4 patients, and 17 patients in the 1-day, 2-day, and 3-day regimens, respectively. Reinfection events occurred between Day 15 and Day 29 in 9 patients, and between Day 29 and Day 43 in 22 patients; no events occurred before Day 15. Reinfection events were noted in 8 patients in the Coartem treatment group (between Day 15 and Day 29 in 1 patient and between Day 29 and Day 43 in 7 patients).
    - In Part B, reinfections were noted in a total of 30 patients in the KAF156/LUM-SDF treatment regimens (11 patients in the 1-day regimen, 10 patients in the 2-day regimen, and 9 patients in the 3-day regimen). Reinfection events were observed between Day 15 and Day 29 in 14 patients and between Day 29 and Day 43 in 16 patients; no events occurred before Day 15. Reinfection events were noted in 10 patients in the Coartem treatment group (between Day 15 and Day 29 in 6 patients and between Day 29 and Day 43 in 4 patients).
- **Parasite clearance time by FAS**:
  - In Part A, the median parasite clearance time ranged from 36.2 hours to 48 hours for the KAF156/LUM-SDF treatment groups and was 36 hours for Coartem.
  - In Part B, the median parasite clearance time in the KAF156/LUM-SDF 1-day, 2-day, 3-day regimens was 36.8 hours, 48 hours, and 36.7 hours, respectively. It was 36 hours for patients treated with Coartem.

Pharmacokinetic results:

- **PK Run-in part**:
  - There was no increase in KAF156 exposure in the presence of lumefantrine.
- **Part A**:
  - In general, AUC0-24h from sparse sampling was comparable to rich sampling for both KAF156 and lumefantrine. KAF156 exposures increased with dose, however, lumefantrine exposures appeared to be under dose proportional.
  - The half-life geo-mean, based on rich PK sampling, ranged from 23.7 hours to 33.1 hours for KAF156 and 30.9 hours to 80.9 hours for lumefantrine.
- **Part A and Part B**: For both KAF156 and lumefantrine:
  - Comparable exposures (Cmax and AUC0-24h) were noted for Part A and Part B. The C168h for KAF156 was lower in Part B compared to Part A.
  - There was no difference noted in exposures (Cmax and AUC0-24h) across similar body weight groups and age-groups.
  - A decreasing trend of C168h was noted in the lower weight groups and lower age-groups for KAF156.

Safety results:

- The most common AEs across the KAF156/LUM-SDF treatment groups and regimens included malaria, upper respiratory tract infection, headache, pyrexia, vomiting, abdominal pain, electrocardiogram QT prolonged, and blood bilirubin increased.
  - In Part A, the proportion of patients with AEs were similar across all KAF156/LUM-SDF regimens (in the range of 64.7% to 78.8%) and the Coartem treatment group (70.4%). The incidence of individual AEs did not show any specific trends across the KAF156/LUM-SDF and Coartem treatment groups; however, the incidence of vomiting was higher in the KAF800 mg/LUM 960 mg (1-day regimen) (8 patients, 15.7%) compared to all other KAF156/LUM-SDF treatment groups and Coartem. Additionally, the AEs of malaria (which were due to reappearance of the parasite), pyrexia, and treatment failure had a higher incidence in the Coartem treatment group than the KAF156/LUM-SDF treatment groups.
  - In Part B, the proportion of patients with AEs in the KAF156/LUM-SDF treatment regimens was in the range of 71.1% to 77.4%, and was 58.3% for the Coartem treatment group. The AEs of malaria, pyrexia, blood bilirubin increased, and blood alkaline phosphatase increased had a higher incidence in the Coartem treatment group compared to the KAF156/LUM-SDF treatment regimens.
  - Overall, for Part A and Part B, the incidence of AEs was consistent across age-groups, with the exception of a few AEs that showed age-specific differences. The AEs with a higher incidence in pediatric populations (< 12 years) compared to adolescents and adults included vomiting, pyrexia, and malaria. The AEs with a higher incidence in adolescents and adults compared to pediatric populations included electrocardiogram QT prolonged and headache.
  - There were no meaningful differences in the safety profile of KAF156/LUM-SDF treatment regimens and Coartem across the subgroups of age, baseline weight, and gender.
- Most of the AEs in the KAF156/LUM-SDF treatment groups and all AEs in the Coartem treatment group were of low grade (grade 1-2) severity.
- Proportion of patients with AEs suspected to be related to the study treatment:
  - In Part A, it ranged from 25.5% to 47.1% in the KAF156/LUM-SDF treatment groups, and was 25.9% in the Coartem treatment group.

  - In Part B, it was 13.5%, 22.6%, 15.6%, and 8.3% in the KAF156/LUM-SDF 1-day, 2-day, 3-day regimens, and Coartem, respectively.
- No patients died during the study.
- Across all treatment groups, SAEs were noted in 9 patients in Part A and 12 patients in Part B (mainly single cases in 1 patient each). Most of the SAEs were grade 1-2 laboratory abnormalities that were reported based on protocol-defined laboratory thresholds.
  - For Part A and Part B, across the treatment groups, a higher proportion of SAEs was noted in the age-group of 2 to < 6 years (13.3% to 18.2% in the KAF156/LUM-SDF treatment regimens, and 20% in the Coartem treatment group) compared to the older age groups. There was no difference in the incidence of SAEs with respect to gender.
- Overall, 8 patients discontinued the study treatment due to the AE of vomiting (Part A: 1 patient in the KAF400 mg/LUM960 mg – 3-day regimen; Part B: 2 patients each in the 1-day and 3-day regimens and 3 patients in the 2-day regimen). Discontinuations due to AE were after the Day 1 dose of KAF156/LUM-SDF in 7 patients and after the Day 2 dose of KAF156/LUM-SDF in 1 patient.
- In Part A and Part B, there were no AEs leading to interruption of the study treatment.
- The adverse events of special interest for KAF156/LUM-SDF included events related to bradycardia, gastrointestinal tolerability, hematological disorders, hepatotoxicity, QTc prolongation, and thyroid hypertrophy and hyperplasia.
  - In Part A, events related to gastrointestinal tolerability were noted in fewer patients treated with Coartem (7.4%) compared to KAF156/LUM-SDF (11.1% to 25.5%). The proportion of patients with hematological disorders was comparable between KAF156/LUM-SDF treatment groups (5.6% to 15.7%) and Coartem (11.1%). The incidence of QTc prolongation was comparable across the KAF156/LUM-SDF treatment groups (9.6% to 17.6%) and Coartem (11.1%). Events potentially indicative of bradycardia were noted only in the KAF156/LUM-SDF treatment group and ranged from 2% to 9.8%. Events potentially indicative of hepatotoxicity were noted in fewer patients treated with KAF156/LUM-SDF (1.9% to 7.8%) compared to Coartem (11.1%). Events potentially indicative of thyroid hypertrophy and hyperplasia were reported only in 1 patient in the KAF400 mg/LUM960 mg – 3-day regimen.
  - In Part B, events related to gastrointestinal tolerability were noted in the KAF156/LUM-SDF regimens (1-day: 13.5%, 2-day: 15.1%; 3-day: 15.6%). The proportion of patients with hematological disorders was < 10% in the KAF156/LUM-SDF treatment regimens (1-day: 9.6%; 2-day: 7.5%; 3-day: 6.7%). Events potentially indicative of potential hepatotoxicity were noted in 5.8%, 7.5%, and 2.2% in the 1-day, 2-day, and 3-day KAF156/LUM-SDF treatment regimens, respectively. Events potentially indicative of QTc prolongation were reported only in the 2-day (1 patient, 1.9%) and 3-day (4 patients, 8.9%) KAF156/LUM-SDF treatment regimens. No AEs indicative of bradycardia and thyroid hypertrophy and hyperplasia was reported in the KAF156/LUM-SDF treatment groups.
- For Part A and Part B (KAF156/LUM-SDF and Coartem groups), generally no clinically meaningful change from baseline until Day 29 or Day 43 was noted for hemoglobin, platelets, and white blood cells.
- For Part A and Part B, for KAF156/LUM-SDF and Coartem groups no clinically meaningful change from baseline until Day 29 or Day 43 was noted for creatinine (serum/plasma), aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin, total bilirubin, alkaline phosphatase, thyrotropin, and free thyroxine.
  - For Part A and Part B, isolated elevations in AST/ALT and total bilirubin were noted in a few patients; however, there was no concurrent increases in these parameters, and no cases of Hy's Law were reported. Of note, in Part B, the proportion of patients with newly occurring liver enzyme abnormalities during the study were higher in the Coartem

treatment group (21 patients) compared to the KAF156/LUM-SDF treatment groups (17 patients).

- In Part A, there were no clinically significant changes in urine parameters post-baseline, except for urine protein. The proportion of patients with proteinuria declined at Day 29 and Day 43 compared to baseline. In Part B, no clinically significant changes in urine parameters were noted post-baseline.
- No significant changes in vital signs were noted in adults (≥ 18 years). However, in patients < 18 years of age (in both Part A and Part B), the frequently reported notable vital signs included high pulse rate, low blood pressure (both systolic and diastolic blood pressure), and high axillary body temperature (≥ 37.5°C). An increase in body weight (> 7% from baseline) was noted in 18 patients in Part A (the AE of weight increased noted in 2 patients in Part A) and in 26 patients in Part B.
- In both, Part A and Part B, most frequently, new QTcF values noted were > 450 ms and ≤ 480 ms; QTcF > 480 ms occurred in only 1 patient in Part A (KAF400 mg/LUM480 mg - 3-day regimen), and none of the patients had QTcF > 500 ms. The majority of changes in QTcF from baseline were ≥ 30 ms and < 60 ms; however, in a few patients, changes in QTcF from baseline ≥ 60 ms were also noted. None of the QT changes were symptomatic.
  - In Part A, the overall frequency of QTcF increase from baseline ≥ 30 ms to < 60 ms was comparable between the KAF156/LUM-SDF treatment groups (33.3% to 48.1%) and Coartem (40.7%), while the proportion of patients with QTcF increase from baseline ≥ 60 ms was generally higher in the KAF156/LUM-SDF groups (3.9% to 13.7%) than in the Coartem treatment group (3.7%), without apparent dose dependency.
  - In Part B, the frequency of QTcF increase from baseline ≥ 30 ms to < 60 ms was comparable between the KAF156/LUM-SDF treatment regimens (15.4% to 46.7%) and Coartem (25%), and was slightly higher in the KAF156/LUM-SDF 3-day regimen (46.7%). The proportion of patients with QTcF increase from baseline ≥ 60 ms was generally higher in the KAF156/LUM-SDF treatment regimens (1.9% to 13.3%) compared to Coartem (0), with an apparent dose proportionality.

Conclusion:

This was the first study to evaluate KAF156/LUM-SDF in patients with uncomplicated *P. falciparum* malaria in Africa and Asia. No clinically significant PK interaction between KAF156 and LUM-SDF was observed. The efficacy and safety data in children (≥ 2 years), adolescents and adults (≥ 12 years) show that KAF156/LUM-SDF is effective and well-tolerated. There was no impact on outcome of parasite resistance markers present at baseline (exploratory resistance markers analysis will be reported separately as data were not available at the time of database lock).

Overall, the positive benefit-risk balance supports the evaluation of the identified effective and safe dose range of KAF156/LUM-SDF in future Phase III studies. KAF156 when given in combination with LUM-SDF to patients with uncomplicated malaria could cover the unmet medical need for antimalarial treatment with a new mechanism of action to counter the emergence of resistance to artemisinin.

History of changes to the synopsis			
Version	Date (content final)	Summary of Changes	Change to overall conclusion
1.0	07-Dec-2021	Original version	