Global Health
Development Unit

Cipargamin (KAE609) Severe malaria

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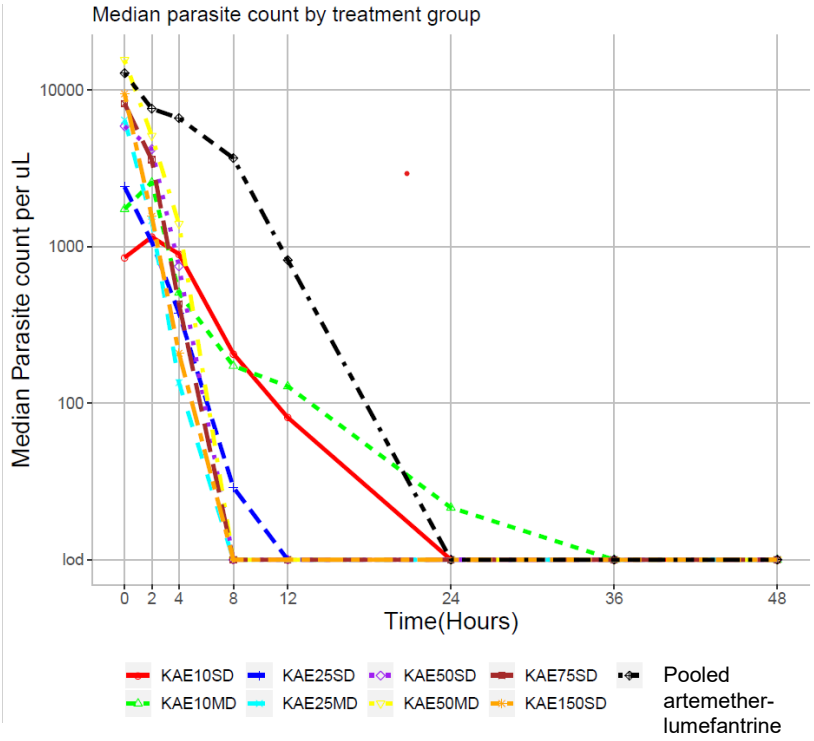
Introduction to Cipargamin (also known as KAE609)

- Cipargamin is a member of a new non-artemisinin (spiroindolone) class of antimalarials
- Cipargamin inhibits PfATP4-associated Na+-ATPase activity and disrupts Na+ homeostasis in the malaria parasite
- A potent, fast acting compound with blood stage and gametocytocidal activity
- Activity demonstrated against *P. falciparum & P.vivax* malaria in patients
- Half life approximately 24.4 – 35.1 h after a single dose; parasite clearance time 8h
- In clinical development as an intravenous formulation for treatment of patients with severe malaria

References: Koehne E et al 2021 Expert Opin Pharmacother; Rosling JEO et al 2018 J Biol Chem; White NJ et al 2014 N Eng J Med; Bouwman SAM et al 2020 Travel Medicine & Infectious disease; Schmitt et al 2021 Clin Infect Dis, https://clinicaltrials.gov/study/NCT04675931?term=NCT04675931&rank=1

Cipargamin early clinical profiling

- Cipargamin at doses of 10mg -150 mg administered orally single dose or once daily for 3 days to patients with malaria due to P. falciparum (Schmitt et al 2021)
  - Median parasite clearance time 12 hours for P. falciparum at doses of 30 mg
  - Rapid parasite clearance observed in 4 patients bearing K13 mutations (White NJ et al 2014)



Adapted from: Schmitt et al 2021 Clin Infect Dis

Reference: White NJ et al 2014 N Eng J Med; Schmitt et al 2021 Clin Infect Dis

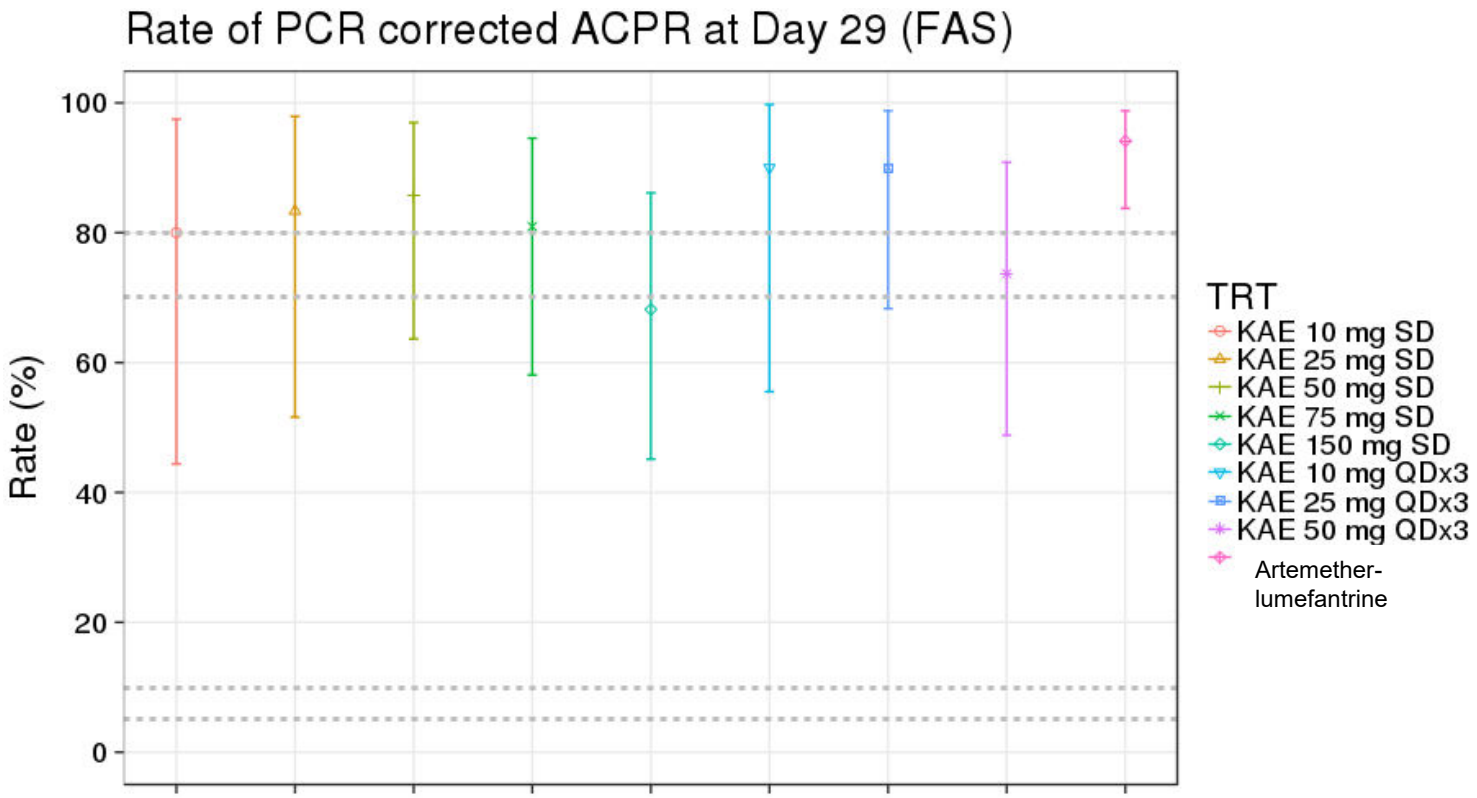
Clinical experience with oral cipargamin in patients with uncomplicated malaria

- Reversible asymptomatic LFT elevation in a human challenge study (healthy volunteers) triggered the conduct of a hepatic safety study in 184 patients
- Single doses and repeat doses up to 150 mg for 3 days were evaluated as monotherapy in adults with *P. falciparum* malaria
- Cipargamin achieved very rapid parasite clearance with median parasite clearance time of 8h with doses of 50 mg or higher
- PCR-corrected ACPR at 28 days of >65%; treatment emergent mutations observed in a few patients
- Frequency of LFT elevations was similar to artemether-lumefantrine control

LFT: liver function tests

References: McCarthy JS 2021 Antimicrob Agents Chemother; Ndayisaba G et al. (2021) Malar J; Schmitt EK et al 2022 Clin Infect Dis

Cipargamin monotherapy dose response for PCR corrected cure rate (day 29)



Reference: Schmitt EK et al 2022 Clin Invest Dis

Treatment groups were balanced in terms of demography and baseline characteristics with the exception of baseline *P. falciparum* density which was higher in Cohort 4 and 5 than in Cohorts 1 to 3

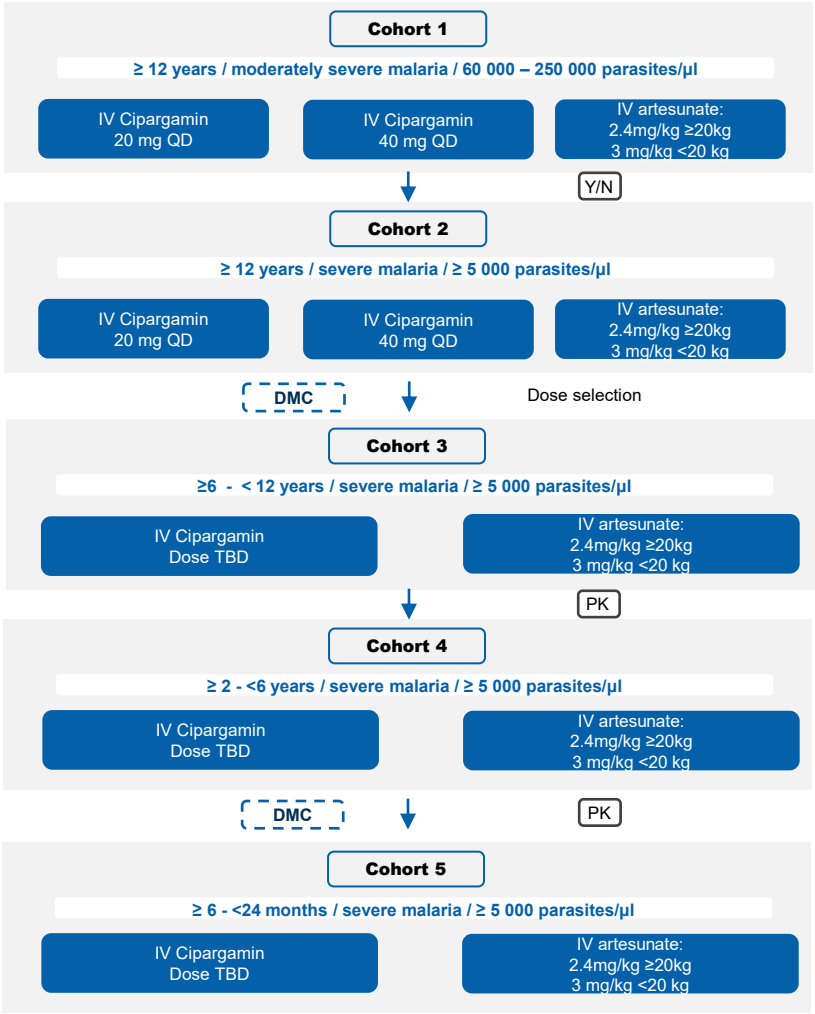
Cipargamin safety profile in acute uncomplicated malaria patients

- KAE609 was considered to have an acceptable hepatic safety profile in the dose range of 10-150 mg single dose and 10-50 mg QDx3 days when compared to artemether-lumefantrine
- KAE609 was generally well-tolerated and there were no particular safety findings of note
- The majority of adverse events were associated with malaria infection

Overall profile and rapid parasite clearance time supports potential use in severe malaria

References: Ndayisaba G et al. (2021) Malar J; Bouwman SAM et al 2020 Travel Medicine & Infectious disease

KARISMA Ph2 study in severe malaria
NCT04675931



- **Study ongoing**
- Moderately severe malaria patients in cohort 1– defined as prostration and/or repeated vomiting
- Cipargamin dose was refined after interim assessment of cohorts 1 & 2
- Cipargamin is administered for 2-3 days; IV artesunate used in accordance with label, followed by oral therapy in all patients
- 252 patients with severe malaria planned
- New clinical success endpoint tested

Y/N: stopping criteria for safety and efficacy (continuously monitored)

PK: exposure will be confirmed in first 6 patients

References: https://clinicaltrials.gov/study/NCT04675931?term=NCT04675931&rank=1, https://pactr.samrc.ac.za/Search.aspx PACTR202102626263606

Future outlook for cipargamin

- Ph2 KARISMA study expected to finish mid-2025
- Plan to develop cipargamin with a partner drug as an intravenous fixed-dose combination to mitigate against development of resistance

References: Schmitt et al 2021 Clin Infect Dis, https://clinicaltrials.gov/study/NCT04675931?term=NCT04675931&rank=1

Our partners in clinical development of Cipargamin

EDCTP

Thank you

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