Global Health Development Unit

Ganaplacide-Lumefantrine SDF investigational product

RBM Case management meeting
September 2024

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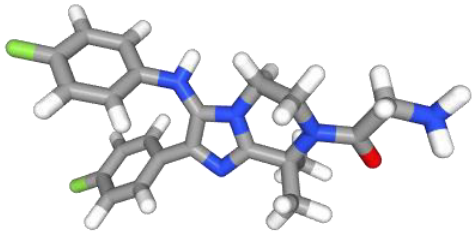
Ganaplacide (also known as KAF156)

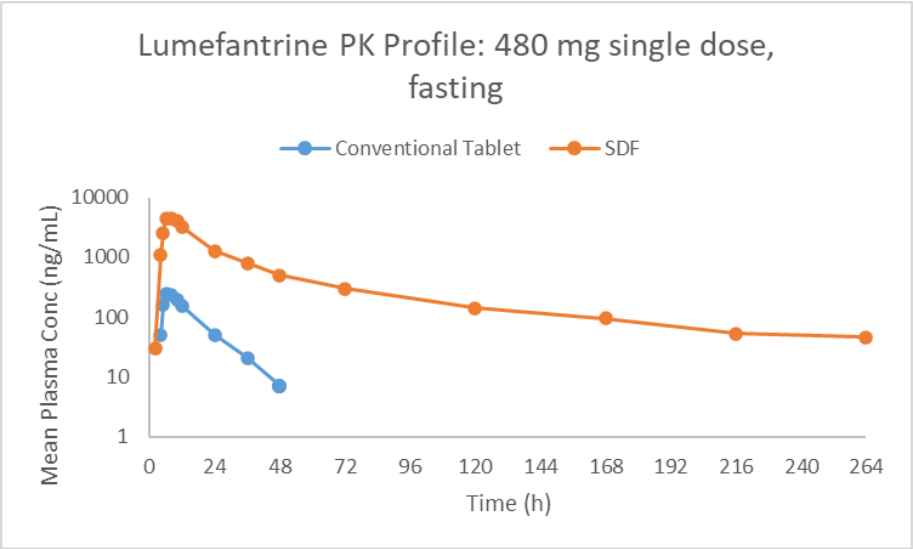
- New non-artemisinin antimalarial of the imidazolopiperazine class
- Novel mechanism of action, likely via Plasmodium intracellular secretory pathway*
- Fast-acting; half-life in patients estimated to be around 40-50 h
- Active against all **blood forms** of *P. falciparum* and *P. vivax**
- Active against all currently known **drug-resistant parasites** in vitro including K13 mutants*
- Potent activity against male and female **gametocytes** in vitro*
- **Causal prophylactic** activity in rodent malaria model*



*References: Meister-S et al. Science 2011, Kuhen KL et al AAC 2014, Leong FJ et al AAC 2014, Lim MY et al Nat Microbiol 2016, NJ White et al, 2016 NEJM, Lamonte et al 2020

Ganaplacide is combined with a new once daily formulation of Lumefantrine (LUM-SDF)

- > 10-fold increase in bio-availability of new LUM-SDF formulation compared to conventional lumefantrine
- Allows simplified once daily dosing



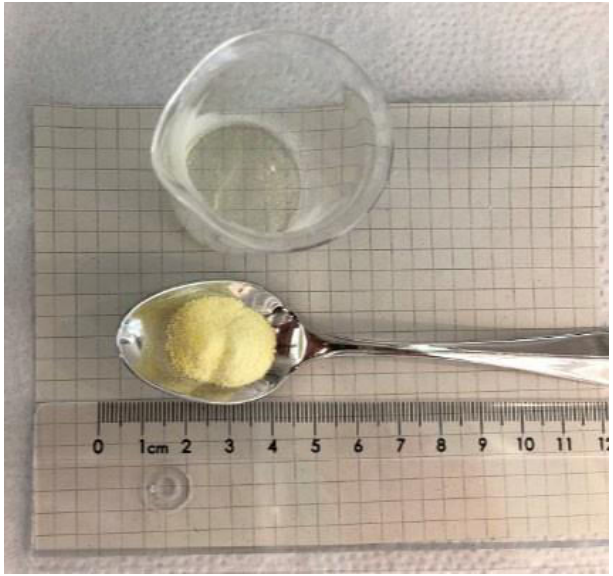
Adapted from: Jain JP et al, 2017. A logarithmic scale was used in this representation of the data.

SDF: solid dispersion formulations

References: Jain JP et al, 2017 Antimicrob Agents Chemother.

Ganaplacide/LUM-SDF in profile

- Oral granules in sachet fixed dose formulation
- 400mg ganaplacide with 480 mg LUM-SDF under evaluation for adults
- Weight-based categories planned for children using 25%, 50%, 75% of adult dose (as for artemether-lumefantrine)
- Once daily treatment over 3 days with food



Please note: This image was taken from Novartis Lab

SDF: solid dispersion formulations
Reference: B Ogutu et al, 2023 The Lancet; https://clinicaltrials.gov/study/NCT04546633?term=NCT04546633&rank=1

Ganaplacide/LUM-SDF clinical program in acute uncomplicated malaria

Study	Outcome
Ph2 monotherapy study in *P. falciparum* & *P. vivax*[1]	Rapid clearance and 13*/21 Day 28 cure of single 800mg dose Activity demonstrated vs P. falciparum and P.vivax blood stages
Ph2b Dose finding study in patients with acute uncomplicated *P. falciparum* (artemether-lumefantrine control)[2]	1-3D QD dose regimens of KAF/LUM-SDF were compared to artemether-lumefantrine in patients >12yrs 3D QD 400mg/960mg (fasted) comparable in patients 2-12yrs
'KALUMI' Ph2b i) Food effect & ii) efficacy, safety and tolerability of KAF/LUM-SDF 2 or 3 days QD in adolescents and children with *P. falciparum* (artemether-lumefantrine control) NCT04546633	Completed
'KALUMA' Ph 3 confirmatory efficacy, safety and tolerability in 1500 adults and children with *P. falciparum* +/- mixed infection (artemether-lumefantrine control) & extension phase NCT05842954	Ongoing

** includes one new infection*
SDF: solid dispersion formulations
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Similar clearance time of parasites with and without K13 mutations* after ganaplacide treatment

Treatment group		Number of samples	Mutations present	Mean PCT (hr)
400 mg KAF156 OD for 3 days	K13 variant	10	C580Y (n=7) P574L (n=1) G538V (n=1) G533A (n-1)	**46.8**
	Wild type	0		
800 mg KAF156	K13 variant		C580Y (n=3) P574L (n=1)	**52.3**
	Wild type	17		**47.2**

This study was conducted in two parts. During part 1 patients received 400 mg KAF156 OD for 3 days, while patients in part 2 received a single dose of 800 mg KAF156.

NJ White et al, 2016 N Engl J Med

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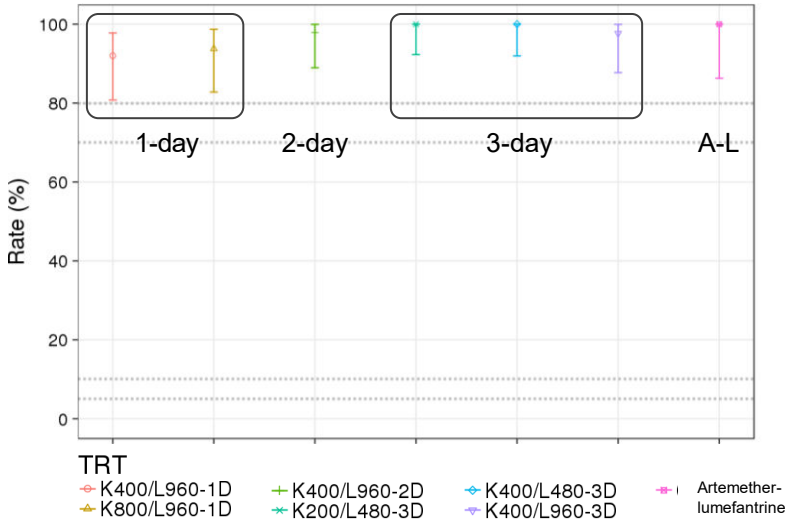
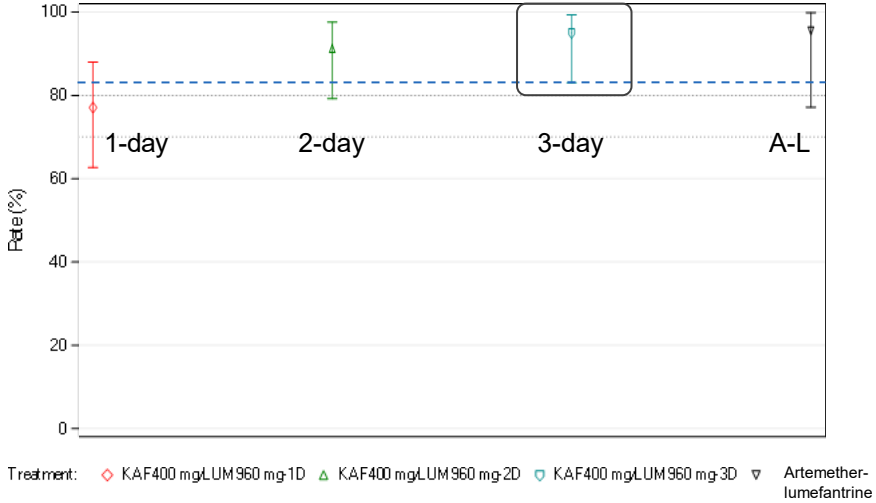
400mg ganaplacide/ 960mg LUM-SDF* effective in adults & children when given for 3 days

1° endpoint PCR-corrected adequate clinical & parasitological response (ACPR) at D29 (PP set)

Adults & adolescents ≥ 12 years



Children (2 < 12 years)



All doses/regimens effective in adults

* Given fasted

PCR: polymerase chain reaction, SDF: solid dispersion formulations

B Ogutu et al, 2023 The Lancet

Ganaplacide & LUM-SDF was well tolerated

To date:

- Overall, comparable safety to comparator (artemether-lumefantrine)
- No unexpected treatment-related safety findings
- Comparable safety profile observed between adults and children
- Most reported adverse events were related to underlying infection
- Asymptomatic QT extensions observed
- Gastro-intestinal events reported

[1]NJ White et al, N Engl J Med 2016; [2]B Ogutu et al, 2023 The Lancet

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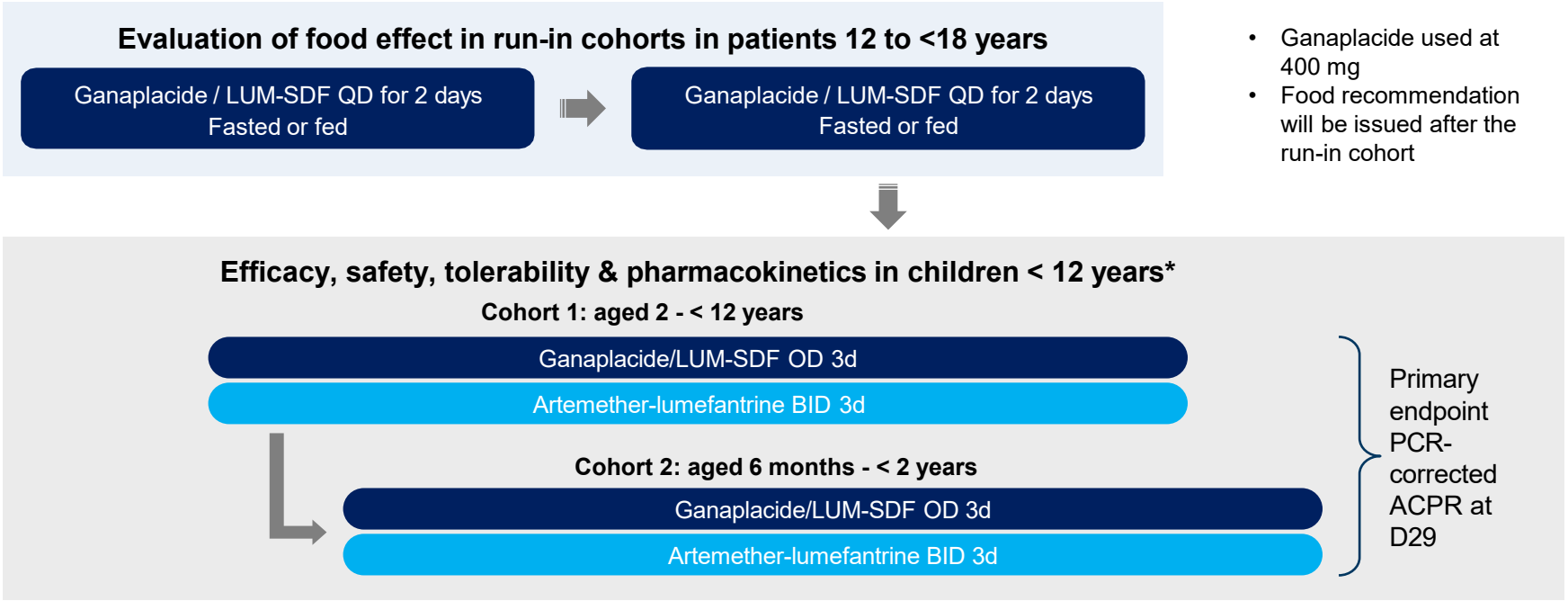
KALUMI Ph2b study design

NCT04546633



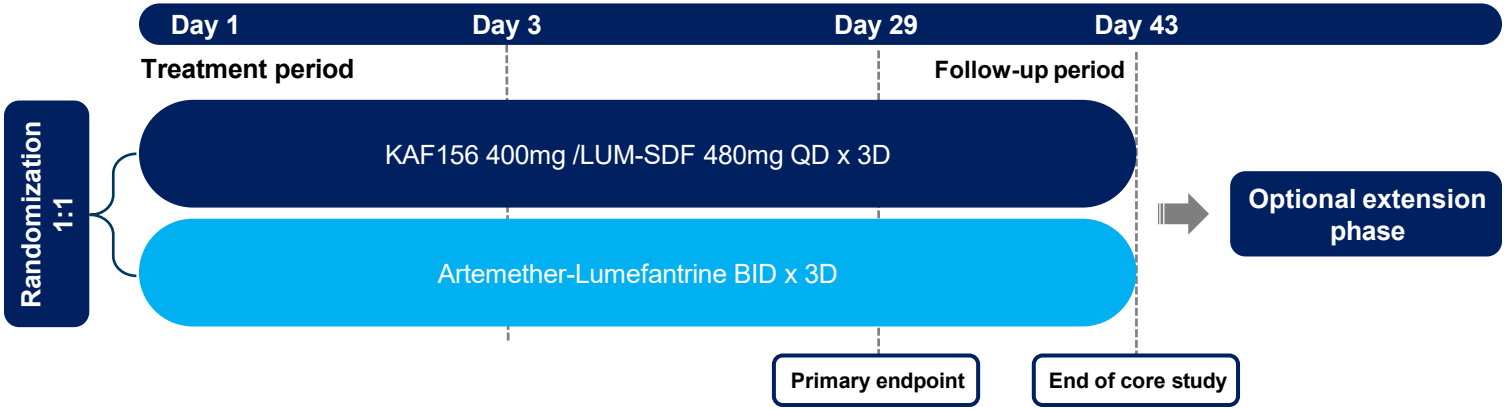
- Ganaplacide used at 400 mg
- Food recommendation will be issued after the run-in cohort

Dosed by body weight band; Total number of patients: 295

B Ogutu et al, 2023 The Lancet , https://clinicaltrials.gov/study/NCT04546633?term=NCT04546633&rank=1

KALUMA Phase 3 trial design

NCT05842954



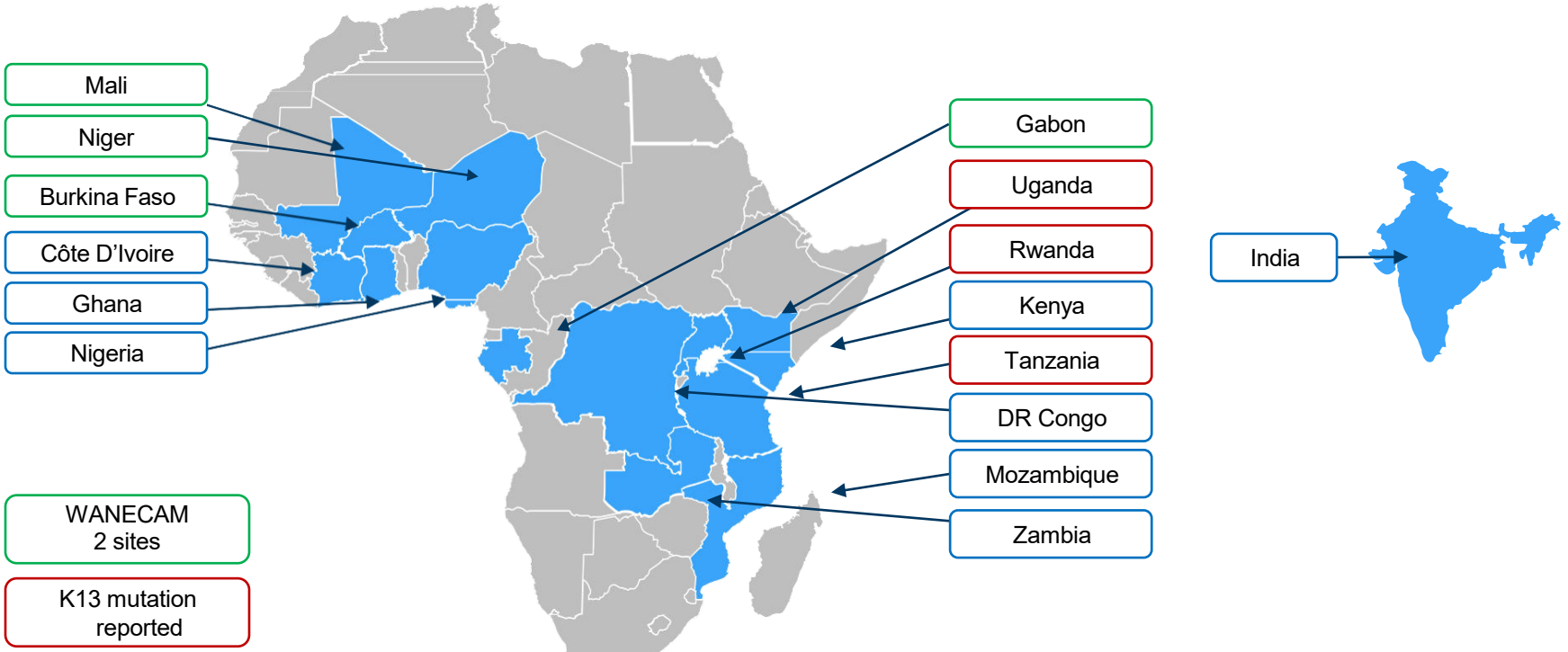
Objective	To confirm the efficacy, safety and tolerability of KLU156, a fixed dose combination of KAF156 and a solid dispersion formulation of lumefantrine, in adults and children ≥ 5 kg body weight and ≥ 2 months of age with acute uncomplicated malaria caused by *P. falciparum* (with or without other *Plasmodium sp.*) by demonstrating non-inferiority to artemether-lumefantrine
1° Endpoint	PCR-corrected ACPR at D29.
2° Endpoint	PCR-uncorrected ACPR; gametocyte carriage over time

Dose by body weight band; Total number of patients: 1500

https://clinicaltrials.gov/study/NCT05842954?term=NCT05842954&rank=1, https://pactr.samrc.ac.za/Search.aspx PACTR202303470809477

KALUMA Ph3 study footprint

NCT05842954



https://clinicaltrials.gov/study/NCT05842954?term=NCT05842954&rank=1, https://pactr.samrc.ac.za/Search.aspx PACTR202303470809477, *World Health Organization, 2023. World malaria report 2023.*

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Ganaplacide/LUM-SDF estimated timelines*

- Stringent health authority reviews and pre-qualification will follow

https://clinicaltrials.gov/study/NCT04546633?term=NCT04546633&rank=1, https://clinicaltrials.gov/study/NCT05842954?term=NCT05842954&rank=1

Our partners in clinical development of Ganaplacide

MMV
Medicines for Malaria Venture

West African Network for Clinical Trials of Antimalarial Drugs
WANECAM

BILL & MELINDA GATES foundation

EDCTP

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Thank you

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