A Phase 1, partially randomized, open-label, two-way, two-period crossover study to investigate the pharmacokinetic interaction between etravirine or darunavir/ritonavir and artemether/lumefantrine at steady-state in healthy HIV-negative subjects

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Background

- Artemether (ART)/Lumefantrine (LUM) is a fixed dose combination used to treat malaria caused by *Plasmodium falciparum*
  - ART/LUM 20/120-mg tablets
  - 6 dose treatment: initial dose followed by a second dose 8 hours later, then twice daily; adult dose is 80/480 mg (4 tablets)
  - Higher ART and dihydroartemisinin (DHA) AUC is significantly associated with initial parasite clearance but not long-term cure
  - Higher LUM AUC is significantly associated with cure but not parasite clearance
    - LUM$_{168h}$ > 175 or 280 ng/mL associated with cure
- Anti-malarial failure rates are higher in HIV-infected patients due to increased parasitic burden and reduced host immunity
Potential for drug interaction

- Artemether (ART) is metabolized by CYP3A to its active metabolite dihydroartemisinin (DHA)
  - Metabolized to a lesser extent by CYP2B6, 2C9 and 2C19
  - DHA is further glucuronidated
  - Artemisinin derivatives induce CYP3A, 2B6 and 2C19
    - Lower ART/DHA exposure after 3 days relative to single dose due to auto-induction

- Lumefantrine (LUM) is metabolized by CYP3A to desbutyl-lumefantrine
Potential for drug interaction continued

- Darunavir/ritonavir (DRV/rtv)
  - CYP3A and P-gp inhibitor; CYP2B6, 2C9, 2C19 and glucuronidation inducer
  - LPV/rtv decreases ART/DHA and significantly increases LUM (2 to 3-fold) in healthy volunteers and HIV-infected patients

- Etravirine (ETR)
  - CYP3A inducer; CYP2C9, 2C19 and P-gp inhibitor
  - NVP decreases ART/DHA and increases LUM in HIV-infected patients
    - AAC 2011;55:5616-5623; CROI 2012, abstract 612
### Study design: Panel 1 (ETR) and Panel 2 (DRV/rtv)

#### Panel 1, Treatment A
- Artemether/lumefantrine 80/480 mg for 3 days
  - (6 doses of 4 tablets [20/120 mg] at 0, 8, 24, 36, 48 and 60 hours)

#### Panel 1, Treatment B
- Day 1 – Day 21: 200 mg ETR b.i.d.
- Day 22: single dose of 200 mg ETR in the morning
- Day 8 – Day 11: artemether/lumefantrine 80/480 mg
  - (6 doses of 4 tablets [20/120 mg] at 0, 8, 24, 36, 48, and 60 hours)

#### Panel 2, Treatment A
- Artemether/lumefantrine 80/480 mg for 3 days
  - (6 doses of 4 tablets [20/120 mg] at 0, 8, 24, 36, 48 and 60 hours)

#### Panel 2, Treatment B
- Day 1 – Day 21: 600/100 mg DRV/rtv b.i.d.
- Day 22: single dose of 600/100 mg DRV/rtv in the morning
- Day 8 – Day 11: artemether/lumefantrine 80/480 mg
  - (6 doses of 4 tablets [20/120 mg] at 0, 8, 24, 36, 48, and 60 hours)

*Partial randomization*
Methods

- Serial PK sampling
  - ART/DHA over 8 hours after first intake; 72 hours after last intake
  - LUM over 264 hours after last intake
  - ETR, DRV/rtv over 12 hours after last intake

- PK analysis
  - Noncompartmental analysis (WinNonlin Professional 4.1)
Subject disposition and safety

- N=33 subjects: all White, male, and non-smoking.

- 5 subjects discontinued – 3 for adverse events and 2 withdrew consent.

- Panel 1 AEs:
  - 10/15 (67%) on ART/LUM,
  - 11/17 (68%) on ETR,
  - 12 (80%) on ART/LUM/ETR
  - Mostly (82%) Grade 1 or 2

- Panel 2 AEs:
  - 8/15 (53%) on ART/LUM
  - 11/15 (69%) on DRV/rtv
  - 11/15 (69%) ART/LUM/DRV/rtv
  - Mostly (81%) Grade 1 or 2

- Panels 1 and 2: Median changes in ECG and vital signs were generally minor and not clinically relevant
Mean (SD) plasma artemether concentration alone or with etravirine

Panel 1 (single dose)

Mean $\text{AUC}_{\text{8h}}$ ART/LUM + ETR: 60.4 ng.h/mL
ART/LUM: 126.9 ng.h/mL
LSM (90% CI): 0.48 (0.39-0.58)

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Mean (SD) plasma DHA concentration alone or with etravirine

Panel 1 (single dose)

Mean $\text{AUC}_{\text{last}}$ ART/LUM + ETR: 38.1 ng.h/mL
ART/LUM: 61.4 ng.h/mL

LSM (90% CI): 0.62 (0.48-0.80)
Mean (SD) plasma artemether concentration alone or with etravirine

Panel 1 (multiple dose)

- 80/480 mg artemether/lumefantrine (n=15)
- 200 mg ETR b.i.d. + 80/480 mg artemether/lumefantrine (n=14)

Mean AUC\text{last} \ ART/LUM + ETR: 38.1 ng.h/mL
ART/LUM: 61.4 ng.h/mL

LSM (90% CI) 0.62 (0.48-0.80)
Mean (SD) plasma DHA concentration alone or with etravirine

Panel 1 (multiple dose)

- 80/480 mg artemether/lumefantrine (n=15)
- 200 mg ETR b.i.d. + 80/480 mg artemether/lumefantrine (n=14)

Mean $AUC_{last}$ ART/LUM + ETR: 206.9 ng.h/mL
ART/LUM: 242.4 ng.h/mL

LSM (90% CI) 0.85 (0.75-0.97)
Mean (SD) plasma lumefantrine concentration alone or with etravirine: multiple dose

Panel 1

80/480 mg artemether/lumefantrine (n=15)

200 mg ETR b.i.d. + 80/480 mg artemether/ lumefantrine (n=14)

Mean $AUC_{264h}$ ART/LUM + ETR: 319.2 $\mu$g.h/mL
ART/LUM: 367.4 $\mu$g.h/mL

LSM (90% CI) 0.87 (0.77-0.98)
Mean (SD) plasma etravirine concentration alone or with ART/LUM: multiple dose

Panel 1

200 mg ETR b.i.d. (n=15)
200 mg ETR b.i.d. + 80/480 mg artemether/lumefantrine (n=14)

Mean AUC$_{12h}$ ART/LUM + ETR: 8950 ng.h/mL
ART/LUM: 8107 ng.h/mL
LSM (90% CI) 1.10 (1.06-1.15)
Mean (SD) plasma artemether concentration alone or with DRV/rtv

Panel 2 (multiple dose)

Mean AUC_{last} ART/LUM + DRV/rtv: 60.8 ng.h/mL
ART/LUM: 72.7 ng.h/mL
LSM (90% CI) 0.84 (0.69-1.02)
Mean (SD) plasma DHA concentration alone or with DRV/rtv

Panel 2 (multiple dose)

Mean AUC_{last} ART/LUM + DRV/rtv: 176.0 ng.h/mL
ART/LUM: 214.7 ng.h/mL

LSM (90% CI) 0.82 (0.74-0.91)
Mean (SD) plasma LUM concentration alone or with DRV/rtv: multiple dose

Panel 2

80/480 mg artemether/lumefantrine (n=15)

600/100 mg DRV/rtv b.i.d. + 80/480 mg artemether/lumefantrine (n=14)

Mean $AUC_{264h}$ ART/LUM + DRV/rtv: 1131 µg.h/mL
ART/LUM: 411 µg.h/mL

LSM (90% CI) 2.75 (2.46-3.08)
Mean (SD) plasma DRV concentration alone or with ART/LUM: multiple dose

Panel 2

Mean AUC_{12h} ART/LUM + DRV/rtv: 49,420 ng.h/mL
ART/LUM: 51,330 ng.h/mL

LSM (90% CI) 0.96 (0.90-1.03)

No effects of ART/LUM on ritonavir AUC

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PK Summary (effects on AUC)

- Single-dose ETR decreases ART (-52%) and DHA (-38%)
  - Mechanism unknown
- Multiple-dose ETR decreases ART (-38%), and slightly decreases DHA (-15%) and LUM (-13%)
  - Possibly due to CYP3A induction
- Single- and multiple-dose DRV/rtv slightly decreases artemether (-13 to -16%) and DHA (-15 to -18%)
- DRV/rtv significantly increases LUM (2.75-fold)
  - Most likely due to CYP3A inhibition
- ART/LUM has no effect on ETR, DRV or ritonavir
Conclusions and dosing recommendations

- **ETR**
  - ETR and ART/LUM can be co-administered with caution
    - Potential for decreased anti-malarial activity

- **DRV/rtv**
  - DRV/rtv and ART/LUM can be co-administered without dose adjustment
    - Single-dose co-administration of ART/LUM and LPV/tvr had no effect on QTc (Chemother Res Pract 2011, 393976).

- **Safety**
  - Co-administration of ART/LUM with ETR or DRV/r was generally safe and well tolerated
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