SYNOPSIS

Issue Date: 6 March 2012

Name of Sponsor/Company	Janssen EMEA Medical Affairs
Name of Finished Product	INTELENCE®; PREZISTA®
Name of Active Ingredient(s)	etravirine (ETR, also known as TMC125); darunavir (DRV, also known as TMC114)

Protocol No.: TMC125VIR1001

Title of Study: 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.

EudraCT Number: 2010-023289-13

Principal Investigator(s): Katarzyna Jarus-Dziedzic, MD - MTZ Clinical Research, [redacted] Poland

Study Center(s): Poland (1)

Study Period: 21 March 2011 – 30 July 2011. Database lock was on 20 October 2011.

Phase of Development: 1

Objectives:

The primary objectives were to determine:

- the effect of etravirine (ETR) or darunavir/ritonavir (DRV/rtv) on the pharmacokinetics of artemether, lumefantrine, and the artemether metabolite dihydroartemisinin (DHA) after single and multiple dose(s) in healthy subjects.
- the effect of artemether/lumefantrine treatment on the steady-state pharmacokinetics of ETR or DRV/rtv in healthy subjects.

The secondary objectives were to determine:

- short-term safety and tolerability of coadministration of ETR or DRV/rtv and artemether/lumefantrine in healthy subjects.
- the pharmacokinetics of ETR by cytochrome P450 (CYP)2C9 and CYP2C19 genotype.
- the pharmacokinetics of artemether and DHA after single and multiple dose(s).

Hypothesis: The hypothesis was that when ETR was coadministered with artemether/lumefantrine, a decrease of ETR, artemether, and lumefantrine concentrations, and an increase in DHA concentrations was anticipated. Secondly, when DRV/rtv was coadministered, an increase in both artemether and lumefantrine concentrations was expected with no relevant changes in DRV or rtv plasma concentrations. This was expected because ETR is a substrate and inducer of CYP3A and a substrate and inhibitor of CYP2C9 and CYP2C19. DRV/rtv is a substrate and inhibitor of CYP3A. Artemether is primarily metabolized by CYP3A and to a lesser extent by CYP2B6, CYP2C9 and CYP2C19 to the active metabolite DHA.

Methodology: This was a Phase 1, partially randomized, open-label, single-center, two-way, two-period cross-over study to investigate the pharmacokinetic interaction between ETR or DRV/rtv and the antimalarial drugs artemether/lumefantrine at steady-state. A total of 33 healthy men, between the ages of 18 and 55 years with a normal body weight (body mass index [BMI] 18.5-30.0 kg/m^2), participated in this study. Subjects were divided over 2 panels (17 subjects in Panel 1 and 16 subjects in Panel 2). Subjects in Panel 1 were treated with ETR and artemether/lumefantrine, subjects in Panel 2 were treated with DRV/rtv and artemether/lumefantrine.

In Panel 1, subjects received Treatment A (3 days of treatment with artemether/lumefantrine) and Treatment B (ETR 200 mg twice daily [b.i.d.] from Day 1 to Day 21 with a single dose of ETR 200 mg in the morning on Day 22, and from Day 8, 3 days of treatment with artemether/lumefantrine). Nine subjects were randomized to sequence AB and 8 subjects were randomized to sequence BA. There was a washout period of at least 4 weeks between Treatments A and B. Serial pharmacokinetic assessments were determined in Treatments A and B for artemether and its metabolite DHA after the first intake of artemether/lumefantrine over 8 hours and after the last intake of artemether/lumefantrine over 72 hours (3 days), and for lumefantrine after the last intake of artemether/lumefantrine over 264 hours (11 days). Serial pharmacokinetic assessments were determined over the 12-hour dosing interval for ETR on Day 8 (after the morning intake) and Day 11 of Treatment B (after the last dose of artemether/lumefantrine). In the first treatment session, a blood sample for pharmacogenomic research (ie, the genetic status for CYP2C9 and CYP2C19) was collected.

In Panel 2, DRV/rtv 600/100 mg b.i.d. was used instead of ETR 200 mg b.i.d. The dosing and sampling schedules (DRV and rtv) were identical as was done for Panel 1, with the exception of pharmacogenomic blood sampling which was not collected in subjects from Panel 2. In a first stage of treatment in Panel 2, only 4 subjects were allowed to start Treatment B. Based on the electrocardiogram (ECG) results of the first 4 subjects with evaluable ECG data after assessments on Day 11 (66 hours after the combined intake of DRV/rtv and artemether/lumefantrine), the sponsor decided whether additional subjects could be allowed to start Treatment B. Therefore, randomization in Panel 2 occurred in 2 steps. In Step 1, 4 subjects were allocated to sequence BA and evaluated for QTc prolongation. If the sponsor decided additional subjects could be allowed to start Treatment B, the remainder of the subjects was randomized in Step 2, ie, 4 subjects to BA and 8 subjects to AB (1:2 randomization).

All ETR, DRV/rtv, and artemether/lumefantrine treatments were administered under fed conditions and were taken within 10 minutes after completion of a meal.

Safety and tolerability evaluations were recorded on an ongoing basis.

Number of Subjects (planned and analyzed): It was planned that 32 healthy subjects were randomized and treated. In practice 17 subjects were randomized to Panel 1 and 16 subjects were randomized to Panel 2.

All analyses were performed on the intent-to-treat (ITT) population, unless otherwise specified.

Data Sets Analyzed: All Subjects Analysis Set

	Panel 1		Panel 2		Total
	Treatment Sequence AB	Treatment Sequence BA	Treatment Sequence AB	Treatment Sequence BA	
Planned	8	8	8	8	32
Screened	-	-	-	-	76
Randomized	9	8	8	8	33
Intent-to-treat population	9	8	8	8	33
Pharmacokinetic population	8	7	8	7	30

Intent-to-treat population includes all randomized subjects receiving at least one dose of the study medication.
Pharmacokinetic population includes all randomized subjects excluding subjects without any valid PK measurement for ETR or DRV per treatment.
Treatment A (Panel 1 and 2): artemether/lumefantrine for 3 days.
Treatment B (Panel 1): ETR 200 mg b.i.d. from Day 1 to Day 21 with a single dose of ETR 200 mg in the morning on Day 22, and from Day 8, 3 days of treatment with artemether/lumefantrine.
Treatment B (Panel 2): DRV/rtv 600/100 mg b.i.d. from Day 1 to Day 21 with a single dose of DRV/rtv 600/100 mg in the morning on Day 22, and from Day 8, 3 days of treatment with artemether/lumefantrine.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria included, but were not limited to:

- Man or woman between 18 and 55 years of age, extremes included.
- Able to comply with protocol requirements.
- A BMI (weight in kg divided by the square of height in meters) of 18.5 to 30.0 kg/m^2, extremes included.
- Non-smoking for at least 3 months prior to selection.

Exclusion criteria included, but were not limited to:

- Having participated in more than 1 study (single or multiple dose) with ETR (TMC125), DRV (TMC114), dapivirine (TMC120) and/or rilpivirine (TMC278, formerly known as R278474), or having developed a rash, erythema or urticaria while participating in a study with the aforementioned compounds.
- A positive pregnancy test or breast feeding at screening or on Day 1.
- Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia), grade 1 or greater, within 21 days prior to intake of the study medication. In case of abnormalities, screening assessments could be repeated once.
- Clinically relevant heart rhythm disturbances, known or suggested by history, or on 12-lead ECG at screening or on Day 1 (predose) of the first treatment session.
- Subjects had 1 or more of the following risk factors for QTc prolongation:
    - a confirmed prolongation of QT/QTc interval, eg, repeated demonstration of QTcF interval > 450 ms in the screening ECG (retesting to reassess eligibility was allowed once using an unscheduled visit during the screening period) or on Day 1 (predose) of the first treatment session;
    - pathological Q-waves (defined as Q-wave > 40 ms or depth > 0.4-0.5 mV);
    - evidence of ventricular pre-excitation;

- electrocardiographic evidence of complete or incomplete left bundle branch block or right bundle branch block;
- evidence of second or third degree heart block;
- intraventricular conduction delay with QRS duration > 120 ms;
- bradycardia as defined by sinus rate < 50 beats per minute;
- personal of family history of long QT syndrome;
- personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia;
- sudden unexplained death at a young age (≤ 40 years) in a first-degree relative (ie, biological parent, sibling or offspring);
- syncopal episodes;
- risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, hypomagnesemia).

- A positive HIV-1 or HIV-2 antibody test at screening.
- Malaria blood smear test positive at screening.
- Hepatitis A infection (acute, confirmed by hepatitis A antibody IgM), or hepatitis B infection (confirmed by hepatitis B surface antigen, or hepatitis C infection (confirmed by hepatitis C virus antibody at screening.
- Treatment with artemether/lumefantrine or halofantrine within 1 month before dosing.
- Planning to travel to a malaria-endemic area during participation of the study and up to 30 days after the last intake of study medication.

Test Product, Dose and Mode of Administration, Batch No.:

ETR (INTELENCE®), 200 mg b.i.d., administered as 2 tablets of 100-mg each (F060), for oral administration following a meal (batch number: 8KL2900).

DRV (PREZISTA®), 600 mg b.i.d., administered as 1 tablet of 600-mg (F032), for oral administration following a meal (batch number: ADZ0500).

Ritonavir (Norvir®), 100 mg b.i.d., administered as 1 tablet of 100-mg, for oral administration following a meal (batch number: 900438D).

Artemether/lumefantrine (Riamet®), 80/480 mg for 3 days (6 doses of 4 tablets [20/120-mg] at 0, 8, 24, 36, 48 and 60 hours), for oral administration following a meal (batch number: X0109).

Duration of Treatment: The study included a 3-week (maximum) screening period, an 8- (sequence AB) or 7-week (sequence BA) treatment period (including a washout period of at least 4 weeks), followed by a 30 to 32 days follow-up period.

Criteria for Evaluation:

Safety Evaluations

Adverse Events (AEs): AEs were reported by the subject for the duration of the study. Special attention was paid to those subjects who discontinued the study for an AE, or who experienced a severe AE (at least grade 3), or a serious AE (SAE). Serious AEs were reported to the sponsor immediately.

Laboratory Evaluations: blood samples for serum chemistry and hematology and a midstream urine sample for urinalysis were collected. A serum pregnancy test for female participants of child-bearing potential was done at screening, at Day 1 of both treatment sessions, and at follow-up. Hepatitis and HIV serology were tested at screening. A blood smear test for malaria parasites was performed at screening.

Cardiovascular Safety: Twelve-lead ECGs were recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes were available so that the different ECG intervals (RR if available, PR, QRS, and QT) and heart rate were measured. ECGs (supine after at least 5 minutes rest) were recorded in triplicate. The QT intervals were corrected for heart rate according to Bazett's (QTcB) and Fridericia's (QTcF) QT correction. During the coadministration of DRV/rtv and artemether/lumefantrine (Panel 2, Treatment B), subjects were monitored closely for QTc prolongation.

Systolic and diastolic blood pressure and pulse rate (supine after at least 5 minutes rest; and standing after at least 1 minute standing) were recorded.

Pharmacokinetic Evaluations

Serial pharmacokinetic assessments were determined for Panels 1 and 2 in Treatments A and B for artemether and its metabolite DHA after the first intake of artemether/lumefantrine over 8 hours and after the last intake of artemether/lumefantrine over 72 hours (3 days), and for lumefantrine after the last intake of artemether/lumefantrine over 264 hours (11 days). Serial pharmacokinetic assessments were determined for ETR (Panel 1) or DRV and rtv (Panel 2) over the 12-hour dosing interval on Day 8 (after the morning intake) and Day 11 (after the last dose of artemether/lumefantrine) of Treatment B.

The primary pharmacokinetic parameters were (on the logarithmic scale):

- C_{min}, C_{max}, and AUC_{12h} for ETR, DRV and rtv (Day 11 of Treatment B versus Day 8 of Treatment B) and for artemether and DHA (Day 11 of Treatment B versus Day 4 of Treatment A),
- C_{max} and AUC_{8h} for artemether and DHA (Days 8 to 9 of Treatment B versus Days 1 to 2 of Treatment A),
- C_{min}, C_{max}, and AUC_{last} for artemether and DHA (Days 11 to 14 of Treatment B versus Days 4 to 7 of Treatment A), and
- C_{min}, C_{max}, and AUC_{264h} for lumefantrine (Days 11 to 22 of Treatment B versus Days 4 to 15 of Treatment A).

Pharmacogenomic Evaluations

On Day 1 of the first treatment session, a blood sample was taken for pharmacogenomic assessment for subjects in Panel 1. The genetic status for CYP2C9 (alleles *2, *3, *4, *5, *6 and *11) and CYP2C19 (alleles *2, *3, *4, *5, *6, *8, *9 and *17) was determined in Panel 1. Genotyping of these genes was performed on identifiable samples.

Statistical Methods:

Sample size: Based on previous studies (TMC125-C168, TMC125-C178), the intra-subject variability of ETR on the log scale was estimated to be less than 0.2 (standard deviation [SD]). With this intra-subject variability and a sample size of 14 subjects who completed the study, the point estimate of pharmacokinetic parameters of ETR with and without coadministration of artemether/lumefantrine was anticipated to fall within 87% and 114% of the true ratio with 90% of confidence. Based on previous studies, the intra-subject variability of DRV on the log scale was estimated to be 0.15. With this intra-subject variability of 0.15 and a sample size of 14 subjects, the point estimate of pharmacokinetic parameters of DRV was anticipated to fall within 90% and 111% of the true ratio with 90% of confidence. No formal sample size calculation was performed for artemether/lumefantrine as an estimate of the intra-subject variability could not be retrieved from the literature.

Analysis: Descriptive statistics were calculated for the plasma concentrations of ETR, DRV, rtv, artemether, DHA and lumefantrine, and for the derived pharmacokinetic parameters. Statistics included sample size (n), mean, SD, coefficient of variation (%CV), geometric mean, median, minimum, and maximum. For each subject, plasma concentration-time data were graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and graphs with combined individual plasma concentration-time profiles were produced. Pharmacokinetic parameters were subjected to an exploratory graphical analysis including various transformations in order to get a general overview. Special attention was paid to the plasma concentrations and pharmacokinetic parameters of those subjects who had discontinued the study for an AE, or who experienced a severe AE (at least grade 3), or an SAE.

Statistical analyses were performed comparing:

- Day 11 of Treatment B (test) versus Day 8 of Treatment B (reference) for ETR (Panel 1),
- Day 11 of Treatment B (test) versus Day 8 of Treatment B (reference) for DRV and rtv (Panel 2),
- Days 8 to 9 of Treatment B (test) versus Days 1 to 2 of Treatment A (reference) for artemether and DHA (single-dose),
- Days 11 to 14 of Treatment B (test) versus Days 4 to 7 of Treatment A (reference) for artemether and DHA (multiple-dose), and
- Days 11 to 22 of Treatment B (test) versus Days 4 to 15 of Treatment A (reference) for lumefantrine.

The least square (LS) means of the primary parameters derived from the log-transformed parameters for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence and period, if applicable, as fixed effects, and subject as a random effect. A 90% CI was constructed around the difference between the LS means of test and reference. Both the difference between the LS means and the 90% CIs were transformed back to the original scale. Period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level.

The effect of CYP2C9 and CYP2C19 genotypes on the pharmacokinetics of ETR was evaluated by means of exploratory graphical analysis and descriptive statistics. The parameters C_{max} and AUC_{12h} of Treatment B, Day 8 of Panel 1 (intake ETR alone) were compared. As the study was not powered to detect differences across such subgroups, the results from these analyses should be for descriptive and not for inferential purposes.

RESULTS:

STUDY POPULATION:

In total, 76 subjects were screened. Seventeen subjects were randomly assigned to Panel 1 and 16 subjects to Panel 2. In Panel 1, 9 subjects received treatment according to sequence A/B, and 8 subjects received treatment according to sequence B/A. In Panel 2, 8 subjects received treatment according to sequence A/B, and 8 subjects received treatment according to sequence B/A.

Overall, 28 out of 33 subjects (84.8%) completed the study. Five subjects (15.2%) receiving study drug discontinued the study: 3 subjects in Panel 1 and 2 subjects in Panel 2. The reasons for discontinuation were AEs (3 subjects) and withdrawal of consent (2 subjects).

In both panels, all subjects were Caucasian males. The median age was 27.0 years (range: 21-53 years) in Panel 1, and 26.0 years (range: 21-54 years) in Panel 2. The median BMI was 23.5 kg/m^2 (19-29 kg/m^2) in Panel 1, and 24.7 kg/m^2 (21-28 kg/m^2) in Panel 2. No relevant differences among the randomization groups were observed in any of the panels.

In Panel 1, major protocol deviations were reported in 2 subjects: Subject [redacted] (A/B) entered the study while meeting exclusion criterion 7 at screening (phosphorus levels were grade 2 decreased), and Subject [redacted] (A/B) had no second ECG recording on Day 11 of Treatment B.

In Panel 2, major protocol deviations were reported in 2 subjects: Subject [redacted] (A/B) experienced grade 3 increased LDL levels on Day 5 of Treatment A and on Day 12 of Treatment B but was not withdrawn from the study, and Subject [redacted] (B/A) experienced grade 3 lipase and pancreatic amylase levels on Day 11 of Treatment B but was not withdrawn from the study.

PHARMACOKINETIC RESULTS:

Pharmacokinetics in Panel 1

Pharmacokinetics of artemether (Panel 1) (mean ± SD, t_{max}: median [range])	**artemether/lumefantrine (reference)**	**artemether/lumefantrine + ETR 200 mg b.i.d. (test)**
n	15	15[a]
Day 1/Day 8		
$C_{6h\ 1st\ intake}$, ng/mL	5.48 ± 2.55	1.85 ± 1.75
C_{max}, ng/mL	50.0 ± 32.2	31.1 ± 20.5
t_{max}, h	1.00 (0.50 - 4.00)	0.98 (0.48 - 3.98)
AUC_{8h}, ng.h/mL	139 ± 81.1	73.4 ± 45.2
Day 4/Day 11		
C_{0h}, ng/mL	0 ± -	0 ± -
$C_{6h\ 6th\ intake}$, ng/mL	3.08 ± 2.16	1.96 ± 1.05
C_{min}, ng/mL	0 ± -	0 ± -
C_{max}, ng/mL	22.9 ± 15.1	17.8 ± 13.3
t_{max}, h	2.00 (0.50 - 4.00)	1.98 (0.48 - 3.98)
C_{avg}, ng/mL	6.13 ± 3.96	4.19 ± 2.74
FI, %	385 ± 139	418 ± 137
AUC_{last}, ng.h/mL	79.3 ± 57.4	48.6 ± 33.1
	LS mean ratio (90% CI)[b]	
		Test vs reference
Day 1/Day 8		15 vs 15
C_{max}		0.56 (0.43 - 0.74)
AUC_{8h}		0.48 (0.39 - 0.58)
Day 4/Day 11		14 vs 15
C_{min}		0.82 (0.67 - 1.01)
C_{max}		0.72 (0.55 - 0.94)
AUC_{last}		0.62 (0.48 - 0.80)

0 = NQ = Not Quantifiable (< 1.00 ng/mL)
[a] n=14 for Day 11
[b] C_{min} LS mean ratio is based on n=4, AUC and C_{max} LS mean ratios are based on n=14 (Reference = Treatment A, Day 4 and Test = Treatment B, Day 11)

Pharmacokinetics of DHA (Panel 1) (mean ± SD, t_{max}: median [range])	**artemether/lumefantrine (reference)**	**artemether/lumefantrine + ETR 200 mg b.i.d. (test)**
n	15	15[a]
Day 1/Day 8		
$C_{6h\ 1st\ intake}$, ng/mL	9.17 ± 3.95	6.32 ± 4.69
C_{max}, ng/mL	49.8 ± 24.3	53.7 ± 27.6
t_{max}, h	2.00 (1.00 - 4.00)	1.98 (0.98 - 3.98)
AUC_{8h}, ng.h/mL	165 ± 69.4	144 ± 42.3
Day 4/Day 11		
C_{0h}, ng/mL	1.45 ± 1.27	0 ± -
$C_{6h\ 6th\ intake}$, ng/mL	11.7 ± 7.81	9.89 ± 4.64
C_{min}, ng/mL	1.21 ± 0.885	0 ± -
C_{max}, ng/mL	76.7 ± 31.7	64.8 ± 27.9
t_{max}, h	2.00 (0.50 - 4.00)	1.98 (0.48 - 3.98)
C_{avg}, ng/mL	21.3 ± 7.52	18.0 ± 5.60
FI, %	353 ± 83.7	349 ± 70.4
AUC_{last}, ng.h/mL	256 ± 90.7	214 ± 66.7
	LS mean ratio (90% CI)[b]	
		Test vs reference
Day 1/Day 8		15 vs 15
C_{max}		1.05 (0.86 - 1.27)
AUC_{8h}		0.87 (0.77 - 0.99)
Day 4/Day 11		14 vs 15
C_{min}		0.83 (0.71 - 0.97)
C_{max}		0.84 (0.71 - 0.99)
AUC_{last}		0.85 (0.75 - 0.97)

0 = NQ = Not Quantifiable (< 1.00 ng/mL)
[a] n=14 for Day 11
[b] C_{min} LS mean ratio is based on n=10, AUC and C_{max} LS mean ratios are based on n=14 (Reference = Treatment A, Day 4 and Test = Treatment B, Day 11)

Pharmacokinetics of lumefantrine (Panel 1) (mean ± SD, t_{max}: median [range])	**artemether/lumefantrine (reference)**	**artemether/lumefantrine + ETR 200 mg b.i.d. (test)**
n	15	15[a]
Day 4/Day 11		
C_{0h}, µg/mL	6.77 ± 2.40	6.75 ± 2.14
$C_{6h\ 6th\ intake}$, µg/mL	10.7 ± 3.29	11.9 ± 4.19
C_{min}, µg/mL	6.11 ± 2.11	6.10 ± 2.23
C_{max}, µg/mL	10.8 ± 3.37	12.0 ± 4.10
t_{max}, h	6.00 (4.00 - 8.00)	5.98 (3.98 - 5.98)
C_{avg}, µg/mL	8.31 ± 2.55	8.90 ± 2.91
FI, %	57.2 ± 16.6	65.9 ± 25.7
AUC_{264h}, µg.h/mL	396 ± 152	343 ± 114
	LS mean ratio (90% CI)	
		Test vs reference
n		14 vs 15
C_{min}		0.97 (0.83 - 1.15)
C_{max}		1.07 (0.94 - 1.23)
AUC_{264h}		0.87 (0.77 - 0.98)

[a] n=14 for Day 11

Pharmacokinetics of ETR (Panel 1) (mean ± SD, t_{max}: median [range])	**ETR 200 mg b.i.d. (reference)**	**ETR 200 mg b.i.d. + artemether/lumefantrine (test)**
n	15	14
Day 8/Day 11		
C_{0h}, ng/mL	516 ± 217	585 ± 203
C_{min}, ng/mL	488 ± 190	547 ± 193
C_{max}, ng/mL	939 ± 263	1053 ± 248
t_{max}, h	4.00 (1.00-6.00)	4.00 (2.00-6.00)
C_{avg}, ng/mL	715 ± 231	802 ± 215
FI, %	66.2 ± 19.1	65.4 ± 16.9
AUC_{12h}, ng.h/mL	8492 ± 2746	9522 ± 2557
	LS mean ratio (90% CI)	
		Test vs reference
n		14 vs 15
C_{min}		1.08 (1.04 - 1.14)
C_{max}		1.11 (1.06 - 1.17)
AUC_{12h}		1.10 (1.06 - 1.15)

Pharmacokinetics in Panel 2

Pharmacokinetics of artemether (Panel 2) (mean ± SD, t_{max}: median [range])	**artemether/lumefantrine (reference)**	**artemether/lumefantrine + DRV/rtv 600/100 mg b.i.d. (test)**
n	15	14
Day 1/Day 8		
$C_{6h\ 1st\ intake}$, ng/mL	7.14 ± 6.71	8.03 ± 8.15
C_{max}, ng/mL	63.4 ± 25.2	56.0 ± 32.1
t_{max}, h	1.00 (0.50 - 4.00)	1.47 (0.47 - 5.97)
AUC_{8h}, ng.h/mL	172 ± 82.5	146 ± 66.6
Day 4/Day 11		
C_{0h}, ng/mL	0 ± -	0 ± -
$C_{6h\ 6th\ intake}$, ng/mL	3.79 ± 2.77	3.43 ± 2.11
C_{min}, ng/mL	0 ± -	0 ± -
C_{max}, ng/mL	25.3 ± 19.2	17.9 ± 8.01
t_{max}, h	1.00 (0.50 - 4.00)	1.47 (0.47 - 3.97)
C_{avg}, ng/mL	6.95 ± 4.17	5.33 ± 2.29
FI, %	354 ± 119	339 ± 114
AUC_{last}, ng.h/mL	92.2 ± 66.7	65.7 ± 33.4
	LS mean ratio (90% CI)[b]	
		Test vs reference
Day 1/Day 8		14 vs 15
C_{max}	-	0.85 (0.68 - 1.05)
AUC_{8h}	-	0.91 (0.78 - 1.06)
Day 4/Day 11		14 vs 15
C_{min}	-	0.97 (0.90 - 1.05)
C_{max}	-	0.82 (0.61 - 1.11)
AUC_{last}	-	0.84 (0.69 - 1.02)

0 = NQ = Not Quantifiable (< 1.00 ng/mL)

[b] C_{min} LS mean ratio is based on n=4, AUC and C_{max} LS mean ratios are based on n=14 (Reference = Treatment A, Day 4 and Test = Treatment B, Day 11)

Pharmacokinetics of DHA (Panel 2) (mean ± SD, t_{max}: median [range])	**artemether/lumefantrine (reference)**	**artemether/lumefantrine + DRV/rtv 600/100 mg b.i.d. (test)**
n	15	14
Day 1/Day 8		
$C_{6h\ 1st\ intake}$, ng/mL	8.45 ± 6.84	9.81 ± 5.66
C_{max}, ng/mL	55.3 ± 18.4	62.6 ± 29.5
t_{max}, h	2.00 (1.00 - 4.00)	1.47 (0.97 - 5.97)
AUC_{8h}, ng.h/mL	164 ± 47.9	184 ± 57.0
Day 4/Day 11		
C_{0h}, ng/mL	1.19 ± 1.16	1.08 ± 1.07
$C_{6h\ 6th\ intake}$, ng/mL	11.4 ± 5.91	8.67 ± 3.48
C_{min}, ng/mL	1.14 ± 1.15	1.01 ± 1.04
C_{max}, ng/mL	65.1 ± 26.1	52.5 ± 25.9
t_{max}, h	2.00 (1.00 - 4.00)	1.97 (0.47 - 3.97)
C_{avg}, ng/mL	18.8 ± 5.86	15.0 ± 3.92
FI, %	335 ± 76.4	331 ± 95.2
AUC_{last}, ng.h/mL	227 ± 74.9	177 ± 46.9
	LS mean ratio (90% CI)[a]	
		Test vs reference
Day 1/Day 8		14 vs 15
C_{max}		1.06 (0.82 - 1.39)
AUC_{8h}		1.12 (0.96 - 1.30)
Day 4/Day 11		14 vs 15
C_{min}		1.00 (0.82 - 1.22)
C_{max}		0.82 (0.66 - 1.01)
AUC_{last}		0.82 (0.74 - 0.91)

[a] C_{min} LS mean ratio is based on n=9, AUC and C_{max} LS mean ratios are based on n=14 (Reference = Treatment A, Day 4 and Test = Treatment B, Day 11)

Pharmacokinetics of lumefantrine (Panel 2) (mean ± SD, t_{max}: median [range])	**artemether/lumefantrine (reference)**	**artemether/lumefantrine + DRV/rtv 600/100 mg b.i.d. (test)**
n	15	14[a]
Day 4/Day 11		
C_{0h}, µg/mL	7.39 ± 3.88	16.3 ± 6.59
$C_{6h\ 6th\ intake}$, µg/mL	12.6 ± 5.06	19.6 ± 7.00
C_{min}, µg/mL	7.05 ± 3.56	14.5 ± 5.49
C_{max}, µg/mL	12.8 ± 5.05	20.4 ± 7.39
t_{max}, h	6.00 (4.00 - 8.00)	5.97 (1.97 - 11.85)
C_{avg}, µg/mL	9.99 ± 4.30	17.6 ± 6.66
FI, %	61.8 ± 27.0	33.7 ± 9.23
AUC_{264h}, µg.h/mL	467 ± 275	1174 ± 628
	LS mean ratio (90% CI)	
		Test vs reference
n		14 vs 15
C_{min}		2.26 (1.92 - 2.67)
C_{max}		1.65 (1.49 - 1.83)
AUC_{264h}		2.75 (2.46 - 3.08)

[a] n=13 for AUC_{264h}

Pharmacokinetics of DRV (Panel 2) (mean ± SD, t_{max}: median [range])	**DRV/rtv 600/100 mg b.i.d. (reference)**	**DRV/rtv 600/100 mg b.i.d. + artemether/lumefantrine (test)**
n	14	14
Day 8/Day 11		
C_{0h}, ng/mL	3930 ± 1222	3451 ± 1213
C_{min}, ng/mL	2886 ± 697	2629 ± 1057
C_{max}, ng/mL	6294 ± 1428	6305 ± 1493
t_{max}, h	4.00 (0.50 - 4.00)	4.00 (1.00 - 4.00)
C_{avg}, ng/mL	4421 ± 977	4316 ± 1243
FI, %	77.3 ± 13.0	89.1 ± 21.9
AUC_{12h}, ng.h/mL	52526 ± 11606	51271 ± 14768
	LS mean ratio (90% CI)	
		Test vs reference
n		14 vs 14
C_{min}		0.87 (0.77 - 0.98)
C_{max}		1.00 (0.93 - 1.07)
AUC_{12h}		0.96 (0.90 - 1.03)

Pharmacokinetics of ritonavir (Panel 2) (mean ± SD, t_{max}: median [range])	**DRV/rtv 600/100 mg b.i.d. (reference)**	**DRV/rtv 600/100 mg b.i.d. + artemether/lumefantrine (test)**
n	14	14
Day 8/Day 11		
C_{0h}, ng/mL	331 ± 147	289 ± 93.7
C_{min}, ng/mL	194 ± 87.0	187 ± 54.9
C_{max}, ng/mL	945 ± 392	783 ± 253
t_{max}, h	4.00 (2.00 - 6.00)	4.00 (1.00 - 6.00)
C_{avg}, ng/mL	523 ± 205	463 ± 148
FI, %	143 ± 27.8	129 ± 19.5
AUC_{12h}, ng.h/mL	6218 ± 2431	5498 ± 1757
	LS mean ratio (90% CI)	
		Test vs reference
n		14 vs 14
C_{min}		1.01 (0.88 - 1.16)
C_{max}		0.85 (0.73 - 0.99)
AUC_{12h}		0.90 (0.80 - 1.01)

SAFETY RESULTS:

Safety in Panel 1

No deaths were reported in this study. Except for 1 subject (5.9%) with an SAE (grade 3 tendon rupture, not related to ETR or artemether/lumefantrine) during the follow-up period, no SAEs were reported during this study. Two subjects permanently discontinued study medication because of an AE (1 subject due to grade 2 enterocolitis during treatment with artemether/lumefantrine, and 1 subject due to grade 1 rash during coadministration of artemether/lumefantrine and ETR).

Overall, 17 subjects (100.0%) had at least one AE during the study. Ten subjects (66.7%) had at least 1 AE during treatment with artemether/lumefantrine, 11 subjects (68.8%) while on ETR alone, and 12 subjects (80.0%) during coadministration of artemether/lumefantrine and ETR. Except for injection site reaction (due to blood draws) and rash which were observed in 3 subjects (20.0%) during coadministration of artemether/lumefantrine and ETR, all AEs occurred in at most 2 subjects during each of the treatment sessions.

The majority of AEs were grade 1 or 2 (14 subjects [82.4%]). No grade 4 AEs were reported. Overall, worst case grade 3 AEs were observed in 3 subjects (17.6%): in 1 subject (6.7%) during administration of artemether/lumefantrine (hypophosphatemia), in 1 subject (6.3%) during administration of ETR alone (hypophosphatemia), and in 1 subject (6.3%) during follow-up (tendon rupture).

Out of 17 subjects with an AE, 10 subjects (58.8%) had an AE considered at least possibly related to ETR as judged by the investigator. Six subjects (37.5%) had at least 1 AE at least possibly related to ETR during treatment with ETR alone, and 5 subjects (33.3%) during coadministration of artemether/lumefantrine and ETR. Except for rash which was observed in 3 subjects (20.0%) during coadministration of artemether/lumefantrine and ETR, all AEs at least possibly related to ETR occurred in at most 2 subjects during each of the treatment sessions.

No relevant differences in the incidence of AEs were observed when artemether/lumefantrine and ETR were coadministered compared to when artemether/lumefantrine or ETR were administered alone.

Summary of Adverse Events During the Study in Panel 1
(Study TMC125VIR1001: ITT Population)

Incidence, n (%)	Artemether/ Lumefantrine N = 15	ETR N = 16	ETR + Artemether/ Lumefantrine N = 15	Whole Study[a] N = 17
Any AE	10 (66.7)	11 (68.8)	12 (80.0)	17 (100.0)
Any SAE	0	0	0	1 (5.9)
Any death	0	0	0	0
Any AE leading to permanent discontinuation	1 (6.7)	0	1 (6.7)	2 (11.8)
Any grade 3 AE (worst grade)	1 (6.7)	1 (6.3)	0	3 (17.6)
Any grade 4 AE (worst grade)	0	0	0	0
Any AE at least possibly related to ETR	0	6 (37.5)	5 (33.3)	10 (58.8)

[a] Whole study includes screening, the treatment periods, and follow-up.
N = number of subjects with data; n = number of subjects with observation

Incidence of Adverse Events Reported in > 1 Subject During the Whole Study by System Organ Class and Preferred Term (Regardless of Severity and Drug Relatedness) for Panel 1
(Study TMC125VIR1001: ITT Population)

System Organ Class Preferred Term, n (%)	Artemether/ Lumefantrine N = 15	ETR N = 16	ETR + Artemether/ Lumefantrine N = 15	Whole Study[a] N = 17
Any AE	***10 (66.7)***	***11 (68.8)***	***12 (80.0)***	***17 (100.0)***
Gastrointestinal disorders	**4 (26.7)**	**3 (18.8)**	**0**	**7 (41.2)**
Abdominal pain	1 (6.7)	1 (6.3)	0	2 (11.8)
Nausea	2 (13.3)	0	0	2 (11.8)
General disorders and administration site conditions	**2 (13.3)**	**0**	**3 (20.0)**	**5 (29.4)**
Injection site reaction	2 (13.3)	0	3 (20.0)	5 (29.4)
Hepatobiliary disorders	**1 (6.7)**	**2 (12.5)**	**0**	**3 (17.6)**
Hyperbilirubinemia	1 (6.7)	2 (12.5)	0	3 (17.6)
Infections and infestations	**2 (13.3)**	**0**	**0**	**4 (23.5)**
Injury, poisoning and procedural complications	**0**	**0**	**1 (6.7)**	**2 (11.8)**
Investigations	**1 (6.7)**	**1 (6.3)**	**1 (6.7)**	**4 (23.5)**
ALT increased	1 (6.7)	1 (6.3)	1 (6.7)	3 (17.6)
AST increased	0	0	1 (6.7)	2 (11.8)
Metabolism and nutrition disorders	**3 (20.0)**	**4 (25.0)**	**4 (26.7)**	**12 (70.6)**
Hypercalcemia	0	0	0	2 (11.8)
Hypercholesterolemia	1 (6.7)	2 (12.5)	0	5 (29.4)
Hyperuricemia	0	1 (6.3)	2 (13.3)	4 (23.5)
Hypophosphatemia	2 (13.3)	2 (12.5)	1 (6.7)	5 (29.4)
Nervous system disorders	**2 (13.3)**	**2 (12.5)**	**0**	**4 (23.5)**
Headache	0	2 (12.5)	0	2 (11.8)
Respiratory, thoracic and mediastinal disorders	**1 (6.7)**	**0**	**1 (6.7)**	**2 (11.8)**
Skin and subcutaneous tissue disorders	**1 (6.7)**	**0**	**4 (26.7)**	**5 (29.4)**
Rash	1 (6.7)	0	3 (20.0)	4 (23.5)
Vascular disorders	**2 (13.3)**	**1 (6.3)**	**2 (13.3)**	**4 (23.5)**
Hypertension	1 (6.7)	1 (6.3)	2 (13.3)	3 (17.6)

[a] Whole study includes screening, the treatment periods, and follow-up.
N = number of subjects with data; n = number of subjects with observation

Median laboratory values were visually inspected for trends over time. No clinically relevant trends or changes were apparent from these analyses. Most of the treatment-emergent graded laboratory

abnormalities were grade 1. No treatment-emergent grade 4 laboratory abnormalities were observed. Grade 3 laboratory abnormalities (hypophosphatemia) were observed during administration of artemether/lumefantrine (1 subject [6.7%]) and during administration of ETR alone (1 subject [6.3%]). The most frequently observed treatment-emergent nongraded laboratory abnormalities (ie, observed in more than 2 subjects per treatment session) were α_1-acid glycoprotein, mean corpuscular volume, and high density lipoprotein (HDL) below normal, and chloride, mean corpuscular hemoglobin concentration, and LDH above normal. Except for chloride above normal which was more frequently observed during coadministration of artemether/lumefantrine and ETR compared to when artemether/lumefantrine or ETR were administered alone (46.7% versus 20.0% and 18.8%), no relevant differences in the incidence of these abnormalities were observed between the treatment sessions. Adverse events related to laboratory abnormalities were observed in at most 2 subjects per treatment session. No relevant differences in the incidence of these AEs were observed between the treatment sessions.

Median changes in ECG and vital signs parameters were generally minor and not considered clinically relevant. None of the subjects had a QTc interval > 450 ms during the course of the study. No QTc changes from baseline larger than 60 ms were observed. No ECG abnormalities were reported as an AE during the course of the study. Vital signs-related AEs were observed in 4 subjects: 3 subjects (17.6%) experienced hypertension (1 subject during coadministration of artemether/lumefantrine and ETR, 1 subject during administration of artemether/lumefantrine alone and during coadministration of artemether/lumefantrine and ETR, and 1 subject during administration of ETR alone), and 1 subject (5.9%) experienced hypotension during administration of artemether/lumefantrine alone. No other vital signs-related AEs were observed.

Safety in Panel 2

No deaths or other SAEs were reported. One subject permanently discontinued study medication because of an AE during administration of DRV/rtv alone (grade 4 AST increased).

Overall, 15 subjects (93.8%) had at least one AE during the study. Eight subjects (53.3%) had at least 1 AE during treatment with artemether/lumefantrine, 11 subjects (68.8%) while on DRV/rtv alone, and 11 subjects (78.6%) during coadministration of artemether/lumefantrine and DRV/rtv. Except for AST increased which was observed in 4 subjects (26.7%) during administration of artemether/lumefantrine, lipase increased observed in 3 subjects (20.0%) during administration of artemether/lumefantrine and in 4 subjects (28.6%) during coadministration of artemether/lumefantrine and DRV/rtv, hypercholesterolemia observed in 4 subjects (28.6%) during coadministration of artemether/lumefantrine and DRV/rtv, hyperuricemia observed in 3 subjects (21.4%) during coadministration of artemether/lumefantrine and DRV/rtv, and headache observed in 3 subjects (18.8%) during administration of DRV/rtv alone, all AEs occurred in at most 2 subjects during each of the treatment sessions.

The majority of AEs were grade 1 or 2 (13 subjects [81.3%]). One subject (6.3%) had a worst case grade 4 AE during administration of DRV/rtv alone (AST increased). For this subject, ALT levels were at most grade 2 increased, reported as AE, and except for total bilirubin below normal at a single time point, total bilirubin was within normal limits throughout the study. One subject (7.1%) had a worst case grade 3 AE during coadministration of artemether/lumefantrine and DRV/rtv (blood amylase increased and lipase increased). Both subjects were asymptomatic.

Most AEs were considered not or doubtfully related to DRV/rtv. Adverse events considered at least possibly related to DRV/rtv by the investigator were reported in 7 subjects (43.8%) during the study. Six subjects (37.5%) had at least 1 AE at least possibly related to DRV/rtv during treatment with DRV/rtv alone, and 6 subjects (42.9%) during coadministration of artemether/lumefantrine and DRV/rtv. Except for lipase increased which was observed in 4 subjects (28.6%) during coadministration of artemether/lumefantrine and DRV/rtv, and AST increased observed in 2 subjects (12.5%) during administration of DRV/rtv alone, all AEs at least possibly related to DRV/rtv occurred in at most 1 subject during each of the treatment sessions.

No relevant differences in the incidence of AEs were observed when artemether/lumefantrine and DRV/rtv were coadministered compared to when artemether/lumefantrine or DRV/rtv were administered alone.

Summary of Adverse Events During the Study in Panel 2
(Study TMC125VIR1001: ITT Population)

Incidence, n (%)	Artemether/ Lumefantrine N = 15	DRV/rtv N = 16	DRV/rtv + Artemether/ Lumefantrine N = 14	Whole Study[a] N = 16
Any AE	8 (53.3)	11 (68.8)	11 (78.6)	15 (93.8)
Any SAE	0	0	0	0
Any death	0	0	0	0
Any AE leading to permanent discontinuation	0	1 (6.3)	0	1 (6.3)
Any grade 3 AE (worst grade)	0	0	1 (7.1)	1 (6.3)
Any grade 4 AE (worst grade)	0	1 (6.3)	0	1 (6.3)
Any AE at least possibly related to DRV/rtv	0	6 (37.5)	6 (42.9)	7 (43.8)

[a] Whole study includes screening, the treatment periods, and follow-up.
N = number of subjects with data; n = number of subjects with observation

Incidence of Adverse Events Reported in > 1 Subject During the Whole Study by System Organ Class and Preferred Term (Regardless of Severity and Drug Relatedness) for Panel 2
(Study TMC125VIR1001: ITT Population)

System Organ Class Preferred Term, n (%)	Artemether/ Lumefantrine N = 15	DRV/rtv N = 16	DRV/rtv + Artemether/ Lumefantrine N = 14	Whole Study[a] N = 16
Any AE	***8 (53.3)***	***11 (68.8)***	***11 (78.6)***	***15 (93.8)***
Eye disorders	**1 (6.7)**	**1 (6.3)**	**0**	**2 (12.5)**
Gastrointestinal disorders	**1 (6.7)**	**0**	**2 (14.3)**	**3 (18.8)**
Abdominal pain	1 (6.7)	0	1 (7.1)	2 (12.5)
General disorders and administration site conditions	**0**	**1 (6.3)**	**3 (21.4)**	**4 (25.0)**
Asthenia	0	1 (6.3)	1 (7.1)	2 (12.5)
Injection site reaction	0	0	2 (14.3)	2 (12.5)
Infections and infestations	**0**	**2 (12.5)**	**1 (7.1)**	**4 (25.0)**
Nasopharyngitis	0	1 (6.3)	1 (7.1)	2 (12.5)
Investigations	**6 (40.0)**	**5 (31.3)**	**5 (35.7)**	**9 (56.3)**
ALT increased	1 (6.7)	1 (6.3)	1 (7.1)	3 (18.8)
AST increased	4 (26.7)	2 (12.5)	0	5 (31.3)
Lipase increased	3 (20.0)	2 (12.5)	4 (28.6)	5 (31.3)
Metabolism and nutrition disorders	**3 (20.0)**	**3 (18.8)**	**6 (42.9)**	**12 (75.0)**
Hypercalcemia	1 (6.7)	0	1 (7.1)	6 (37.5)
Hypercholesterolemia	0	1 (6.3)	4 (28.6)	6 (37.5)
Hyperglycemia	0	0	0	2 (12.5)
Hyperuricemia	2 (13.3)	0	3 (21.4)	5 (31.3)
Hypophosphatemia	0	2 (12.5)	0	2 (12.5)
Nervous system disorders	**2 (13.3)**	**4 (25.0)**	**2 (14.3)**	**6 (37.5)**
Headache	0	3 (18.8)	2 (14.3)	3 (18.8)
Renal and urinary disorders	**0**	**2 (12.5)**	**1 (7.1)**	**3 (18.8)**
Proteinuria	0	2 (12.5)	0	2 (12.5)

[a] Whole study includes screening, the treatment periods, and follow-up.
N = number of subjects with data; n = number of subjects with observation

Median laboratory values were visually inspected for trends over time. No clinically relevant trends or changes were apparent from these analyses. Most of the treatment-emergent graded laboratory abnormalities were grade 1. A treatment-emergent grade 4 laboratory abnormality was observed in 1 subject (6.3%) during administration of DRV/rtv alone (AST increased). Grade 3 laboratory abnormalities were observed during administration of artemether/lumefantrine (increased LDL in 1 subject [6.7%]) and during coadministration of artemether/lumefantrine and DRV/rtv (increased lipase, amylase, and LDL, each in 1 subject [7.1%]). The most frequently observed treatment-emergent nongraded laboratory abnormalities (ie, observed in more than 2 subjects per treatment session) were hematocrit, HDL, and insulin below normal, and chloride, direct bilirubin, and lactate dehydrogenase above normal. Except for HDL below normal and chloride above normal which were more frequently observed during coadministration of artemether/lumefantrine and DRV/rtv compared to when artemether/lumefantrine or DRV/rtv were administered alone (HDL below normal: 50.0% versus 20.0% and 25.0%; chloride above normal: 50.0% versus 26.7% and 0%), no relevant differences in the incidence of these abnormalities were observed between the treatment sessions.

Adverse events related to laboratory abnormalities were observed in at most 2 subjects per treatment session, except for AST increased which was observed in 4 subjects (26.7%) during administration of artemether/lumefantrine, lipase increased observed in 3 subjects (20.0%) during administration of artemether/lumefantrine and in 4 subjects (28.6%) during coadministration of artemether/lumefantrine and DRV/rtv, and hyperuricemia observed in 3 subjects (21.4%) during coadministration of artemether/lumefantrine and DRV/rtv. No relevant differences in the incidence of these AEs were observed between the treatment sessions.

Median changes in ECG and vital signs parameters were generally minor and not considered clinically relevant. One subject had a QTc interval > 450 ms during coadministration of artemether/lumefantrine and DRV/rtv. No QTc changes from baseline larger than 60 ms were observed. Overall, 1 subject experienced grade 1 tachycardia during administration of DRV/rtv alone. No other ECG abnormalities were reported as an AE during the course of the study. Vital signs-related AEs were observed in 1 subject (hypertension) during coadministration of artemether/lumefantrine and DRV/rtv. No other vital signs-related AEs were observed.

CONCLUSION(S):

In conclusion, after single-dose intake of artemether/lumefantrine in the presence of ETR, C_{max} and AUC_{8h} of artemether were decreased, respectively, 44% and 52% compared to after single-dose administration of artemether/lumefantrine alone, while after multiple-dose intakes of artemether/lumefantrine in the presence of ETR, C_{min}, C_{max}, and AUC_{last} of artemether were decreased, respectively, 18%, 28%, and 38% compared to after multiple-dose administration of artemether/lumefantrine alone, based on the ratios of the LS means.

After single-dose intake of artemether/lumefantrine in the presence of ETR, C_{max} and AUC_{8h} of DHA were, respectively, increased 1.05-fold and 13% decreased compared to single-dose administration of artemether/lumefantrine alone, while after multiple-dose intakes of artemether/lumefantrine in the presence of ETR, C_{min}, C_{max}, and AUC_{last} of DHA were, respectively, 17%, 16%, and 15% decreased compared to multiple-dose administration of artemether/lumefantrine alone, based on the ratios of the LS means.

After multiple-dose intake of artemether/lumefantrine alone or in the presence of ETR, C_{min} and C_{max} of lumefantrine were comparable, however, AUC_{264h} of lumefantrine was 13% lower after the combined intake of artemether/lumefantrine and ETR compared to multiple-dose intake of artemether/lumefantrine alone, based on the ratios of the LS means.

After intake of ETR alone or in the presence of artemether/lumefantrine, C_{min}, $C_{max,}$ and AUC_{12h} of ETR were comparable, based on the ratios of the LS means.

After single-dose intake of artemether/lumefantrine in the presence of DRV/rtv, C_{max} and AUC_{8h} of artemether were, respectively, 15% and 9% lower compared to single-dose administration of artemether/lumefantrine alone, while after multiple-dose intakes of artemether/lumefantrine in the presence of DRV/rtv, C_{max} and AUC_{last} of artemether were, respectively, 18% and 16% lower compared to multiple-dose administration of artemether/lumefantrine alone, based on the ratios of the LS means. C_{min} of artemether was comparable for both treatments.

After single-dose intake of artemether/lumefantrine in the presence of DRV/rtv, C_{max} and AUC_{8h} of DHA were, respectively, increased 1.06- and 1.12-fold compared to single-dose administration of artemether/lumefantrine alone, while after multiple-dose intakes of artemether/lumefantrine in the presence of DRV/rtv, C_{max} and AUC_{last} of DHA were both 18% lower compared to multiple-dose administration of artemether/lumefantrine alone, based on the ratios of the LS means. C_{min} of DHA was comparable for both treatments.

After multiple-dose intake of artemether/lumefantrine in the presence of DRV/rtv, C_{min}, C_{max}, and AUC_{264h} of lumefantrine were, respectively, 2.26-, 1.65-, and 2.75-fold higher compared to multiple-dose administration of artemether/lumefantrine alone, based on the ratios of the LS means.

After multiple-dose intake of DRV/rtv alone or in the presence of artemether/lumefantrine, C_{max} and AUC_{12h} of DRV were comparable, while C_{min} of DRV was 13% lower after the combined intake of DRV/rtv and artemether/lumefantrine compared to multiple-dose intake of DRV/rtv alone, based on the ratios of the LS means.

ETR 200 mg b.i.d. and DRV/rtv 600/100 mg b.i.d., each administered alone or each in combination with artemether/lumefantrine was generally safe and well tolerated in healthy subjects.