The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Cabotegravir

Study Number: 117010

Title: Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifampin on the pharmacokinetics of oral cabotegravir in healthy subjects

Rationale: Cabotegravir (CAB) is a 2-metal binding integrase inhibitor (INI) being developed for the treatment and prevention of human immunodeficiency virus (HIV) -1 infection by GlaxoSmithKline (GSK) on behalf of ViiV Healthcare (ViiV) as both an oral and long acting (LA) injectable nanosuspension. Rifampin (RIF) is a semi-synthetic rifamycin derivative that is highly active against mycobacteria, most gram-positive bacteria, and some gram-negative bacteria. Rifamycins serve as the cornerstone of tuberculosis (TB) therapy because of their unique sterilizing activity. In many parts of the world, HIV and TB co-infection is frequently seen and concomitant treatment of both conditions is often necessary.

No data are currently available on the effect of rifampicin (RIF) on the pharmacokinetics (PK) of CAB. Rifampicin (RIF) induces uridine 5'-diphospho-glucuronosyltransferases (UGTs) as well as cytochrome P450 (CYPs) and thus may reduce the concentrations of CAB. Cabotegravir (CAB) is primarily metabolized by UGT1A1 with some involvement from UGT1A9. Dosing RIF with dolutegravir (DTG), a related integrase inhibitor, at 50 milligrams (mg) twice daily (BID) yielded DTG levels that were similar to those seen when DTG was dosed at 50 mg once daily. A reduction in CAB serum concentrations with RIF co-administration increases the risk of treatment failure and the emergence of resistance. Given that tuberculosis (TB)/HIV co-infection is common, an evaluation of the drug interaction between CAB and RIF will inform dosing strategies for HIV treatment and prevention in the setting of TB co-infection.

Phase: I

Study Period: 01-JUL-2015 to 11-SEP-2015

Study Design: This was a phase I, single-center, open label, fixed-sequence crossover study in healthy adults, to evaluate the effect of RIF on the PK of oral CAB 30 mg. This study consisted of a screening period (within 30 days of Day 1), three treatment periods (Period 1: Day 1 to Day 7; Period 2: Day 8 to Day 20; and Period 3: Day 21 to Day 28), and a follow-up period (Day 38 to Day 42).

Centre: Quintiles Phase One Services, Limited Liability Company, 6700 West 115th Street, Overland Park, Kansas, 66211 in the United States

Indication: Infection, Human Immunodeficiency Virus

Treatment: In Treatment Period 1 subjects received a single dose of CAB 30 mg on Day 1, in Treatment Period 2 subjects received RIF 600 mg once daily for 13 days on Days 8-20, and in Treatment Period 3 subjects received single dose of CAB 30 mg on Day 21 + RIF 600 mg once daily for 8 days on Days 21-28.

Objective: To compare the single dose pharmacokinetics (PK) of cabotegravir (CAB) oral 30 mg when co-administered with rifampin (RIF) 600 mg once daily at steady-state to those of CAB oral 30 mg administered alone.

Primary Outcome (Endpoints) : Plasma CAB maximum observed concentration (Cmax), area under the concentration-time curve over infinite time (AUC[0-inf]).

Secondary Outcome (Endpoints) :

- Plasma CAB concentration at 24 hours (C24), area under the concentration-time curve up to the last measurable concentration (AUC [0-t]), time of occurrence of Cmax (tmax), half-life (t1/2), apparent clearance (CL/F)
- Safety and tolerability parameters, including adverse events (AEs), concurrent medication, clinical laboratory screens, electrocardiogram (ECG) and vital signs assessments.

Statistical Methods:

Sample size justification

Based on a within-subject coefficient of variation (CVw) of 11.4% and a sample size of 12 evaluable subjects, it was estimated that the half width of the 90% confidence interval for the treatment difference on log-scale is within 8.3% of the point estimate for AUC(0-t)/AUC(0-∞) and Cmax. If the point estimate of the ratio of geometric means was 1, then 90% confidence interval is approximately (0.92, 1.09).

Analysis Populations

The following populations were used for the analysis and reporting of data:

Screening Population: All subjects who had signed the consent form were included in this population.

Safety Population: All subjects who enrolled into the study and received at least one dose of study drug were included in the Safety Population.

Pharmacokinetic Concentration Population: The CAB PK Concentration Population included all subjects who underwent plasma PK sampling and had evaluable PK assay results.

Pharmacokinetic Parameter Population: The CAB PK Parameter Population for this study included all subjects with CAB PK parameters estimated.

Pharmacokinetic Summary Population: The CAB PK Summary Population for this study included subjects who had CAB PK parameter estimates from both serial PK sampling time periods.

PK Analyses

Plasma CAB concentration-time data were analyzed by non-compartmental methods with WinNonlin (Phoenix) 6.3. Calculations were based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters were determined: AUC(0-∞), AUC(0-t), C24, Cmax, tmax, t1/2, and CL/F.

Statistical Analyses

Descriptive summaries were presented for PK data included n, mean, standard deviation (SD), coefficient of variation for the mean (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-subject CV for the geometric mean (%CVb).

The point estimates of the geometric least squares mean (GLSM) ratio for the selected PK parameters and the associated 90% CIs were provided for treatment comparisons (test:reference).

Safety data were presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards whereas, n and percent were used as summary statistics for categorical variables.

Study Population: Eligible subjects were healthy males and females between 18 and 65 years of age (inclusive), body weight ≥50 kilograms (kg) and body mass index (BMI) within the range 18.5 – 31.0 kg/square meter (m^2) (inclusive); and alanine aminotransferase (ALT), alkaline phosphatase and bilirubin ≤1xupper limit of normal (ULN). Subjects were excluded if they had a current or chronic history of liver disease, or known hepatic or biliary abnormalities and history of clinically significant cardiovascular disease.

Demographics	Overall
Number of subjects planned [N]	15
Number of subjects entered [N]	15
Number of subjects completed as planned [n (%)]	15 (100)
Number of subjects withdrawn (any reason) [n (%)]	0
Age in Years [Mean (SD)]	48.5 (14.11)
Sex [n (%)]	
Female:	5 (33)
Male:	10 (67)
BMI (kg/m^2) [Mean (SD)]	26.71 (3.578)
Height (cm) [Mean (SD)]	172.41 (6.979)
Weight (kg) [Mean (SD)]	79.63 (12.788)
Ethnicity [n (%)]	
Hispanic or Latino:	1 (7)
Not Hispanic or Latino:	14 (93)
Race [n (%)]	
African American/African Heritage	3 (20)
White – White/Caucasian/European Heritage	12 (80)

Pharmacokinetic Results (Primary Endpoint):

Summary of Primary Plasma CAB Pharmacokinetic Parameters (N=15)		
Treatment	AUC(0-∞)[1] (hr*μg/mL)	Cmax[1] (μg/mL)
CAB	146.313 (23.9)	3.605 (16.9)
CAB+RIF	59.733 (22.4)	3.386 (19.1)

1 Geometric mean (CV%)
CAB: Single dose CAB 30 mg (Day 1)
CAB+RIF: CAB 30 mg on Day 21 (single dose) + steady state RIF 600 mg once daily (Days 8-28)
hr=hour, μg=microgram, mL=milliliter

Summary of Primary Plasma CAB Pharmacokinetic Parameters Treatment Comparisons (N=15)	
CAB PK Parameter	Treatment Comparison CAB + RIF vs CAB (GLSM ratio, 90% CI)
AUC(0-∞)	0.41 (0.36, 0.46)
Cmax	0.94 (0.87, 1.02)

CAB: Single dose CAB 30 mg (Day 1)
CAB+RIF: CAB 30 mg on Day 21 (single dose) + steady state RIF 600 mg once daily (Days 8-28)

Pharmacokinetic Results (Secondary Endpoint):

Summary of Secondary Plasma CAB Pharmacokinetic Parameters (N=15)					
Treatment	AUC(0-t)[1] (hr*μg/mL)	C24[1] (μg/mL)	t1/2[1] (hr)	CL/F[1] (L/hr)	Tmax[2] (hr)
CAB	138.828 (23.5)	1.716 (25.5)	38.507 (13.9)	0.205 (23.9)	2.000 (1.00-6.00)
CAB+RIF	57.772 (22.1)	0.860 (25.5)	16.397 (19.5)	0.502 (22.4)	1.000 (1.00-4.00)

1 Geometric mean (CV%)
2 Median (range)
CAB: Single dose CAB 30 mg (Day 1)
CAB+RIF: CAB 30 mg on Day 21 (single dose)+ steady state RIF 600 mg once daily (Days 8-28)
L=liter

Safety Results: There were no deaths, no serious AEs, and no significant AEs reported in this study. No clinically significant changes in laboratory values over time in hematology, chemistry, or urinalysis results were observed during this study. No clinically significant changes over time were noted in any vital sign evaluations. There were no pregnancies reported in the study.

AEs and SAEs were collected from the start of Study Treatment until the follow-up contact.

Most Frequent Adverse Events	CAB 30 mg Single Dose	RIF 600 mg QD	CAB 30 mg Single Dose + RIF 600 mg QD	Overall
	n (%)	n (%)	n (%)	n (%)
Any AE	3 (20)	15 (100)	1 (7)	15 (100)
Any AE related to investigational product	1 (7)	15 (100)	0	15 (100)
Most Common AEs: (≥10% overall):				
Chromaturia	0	15 (100)	0	15 (100)
Decreased appetite	0	2 (13)	0	2 (13)
Headache	1 (7)	1 (7)	0	2 (13)

Treatment A: Single dose CAB 30 mg (Day 1)
Treatment B: RIF 600 mg QD for 13 days (Days 8 – 20)
Treatment C: CAB 30 mg on Day 21 + RIF 600 mg QD for 8 days (Days 21-28)
QD=once daily

Conclusion:

- Co-administration of CAB 30 mg as a single dose with steady-state RIF 600 mg resulted in no change in CAB Cmax but a decrease in CAB AUC(0-∞) by 59%.
- CAB administered alone or in combination with steady state RIF was tolerated in the study with no deaths, no serious or clinically meaningful AEs, no vital signs or ECG abnormalities, and no Grade 3 or Grade 4 laboratory abnormalities reported in the study.
- Co-administration of RIF with oral CAB 30 mg once daily is not recommended.