EFFECT OF FALDAPREVIR ON RALTEGRAVIR PHARMACOKINETICS IN HEALTHY VOLUNTEERS

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BACKGROUND

- Faldaprevir (FDV) is a potent, once-daily HCV NS3/4A protease inhibitor with broad antiviral activity against HCV genotypes (GT) 1, 4, 5, and 6 in vitro[1]
- FDV is being developed for the treatment of chronic HCV GT-1 infection in mono-infected patients and patients co-infected with HIV
- In the Phase III STARTVerso4 trial, FDV in combination with pegylated interferon α-2a and ribavirin was highly efficacious and well tolerated in patients co-infected with HCV GT-1 and HIV[2]
- Raltegravir (RAL), an HIV integrase inhibitor, is an antiretroviral agent widely used to treat HIV patients[3]
- RAL is predominantly metabolized via UDP-glucuronosyltransferase 1A1 (UGT1A1) to RAL-glucuronide[3] and, therefore, co-administration with drugs that inhibit UGT1A1 may increase plasma levels of RAL
- Preclinical and clinical data indicate that FDV is an inhibitor of UGT1A1[4]
- This trial evaluated the effect of FDV on the pharmacokinetic (PK) of RAL in healthy volunteers

OBJECTIVES

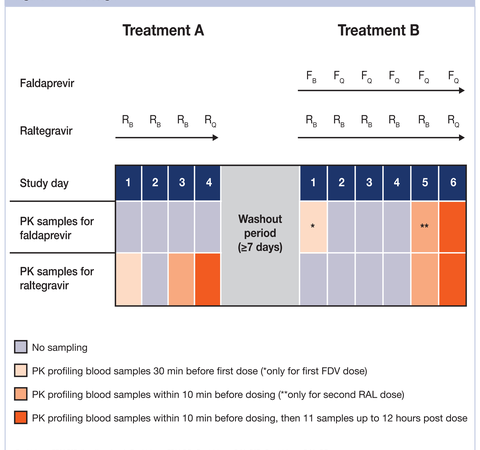
- To assess the effect of FDV on the steady-state PK of RAL
- To assess the safety and tolerability of FDV when co-administered with RAL

METHODS

TRIAL DESIGN

- Phase I, open-label, two-period, fixed-sequence study in healthy volunteers
- FDV 240 mg and RAL 400 mg were administered during two treatment sequences (**Figure 1**):
  - Treatment A: RAL 400 mg BID on Days 1–3, RAL 400 mg QD on Day 4
  - Treatment B: RAL 400 mg BID and FDV 240 mg BID (loading dose) on Day 1, RAL 400 mg BID and FDV 240 mg QD on Days 2–5, RAL 400 mg QD and FDV 240 mg QD on Day 6
- All subjects received treatments A and B in the sequence AB, separated by a washout period of at least 7 days (**Figure 1**)

Figure 1. Trial design



F_B, 240 mg FDV BID (loading dose); F_Q, 240 mg FDV QD; R_B, 400 mg RAL BID; R_Q, 400 mg RAL QD.
FDV, faldaprevir; PK, pharmacokinetic; RAL, raltegravir.

PHARMACOKINETIC EVALUATION

- Blood samples were collected at pre-determined time points for PK analyses (**Figure 1**)
- Plasma concentrations of FDV were determined by liquid chromatography–tandem mass spectrometry (LC–MS/MS, Tandem Laboratories, Salt Lake City, Utah, USA) with lower limit of quantification (LLOQ) of 10 ng/mL
- Plasma concentrations of RAL and RAL-glucuronide were determined by LC–MS/MS (PPD, Middleton, Wisconsin, USA) with LLOQ of 1.0 ng/mL

STATISTICAL ANALYSIS

- Descriptive statistics were used for safety and PK assessments
- To assess drug interaction potential, two-sided 90% confidence intervals (CIs) for the adjusted geometric mean (gMean) ratios were calculated for the primary PK parameters ($AUC_{\tau,ss}$ [area under the plasma concentration–time curve at steady state over the uniform dosing interval τ] and $C_{max,ss}$ [maximum plasma concentration at steady state]) of RAL and RAL-glucuronide using an analysis of variance (ANOVA) model
- Safety and tolerability were assessed by collection of adverse event (AE) data, physical examinations, clinical laboratory tests, vital signs, and 12-lead electrocardiogram (ECG)

RESULTS

SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

- A total of 25 subjects entered the study, of whom 24 were treated (**Table 1**)
  - One subject was unable to swallow the RAL tablet and was therefore not treated; this subject was replaced by another subject
  - One subject withdrew consent for personal reasons and discontinued from the study after Day 4 of Treatment A

TABLE 1. Demographics and baseline characteristics

	Subjects (N=24)
Gender, n (%)	
Male	12 (50.0)
Female	12 (50.0)
Race, n (%)	
White	24 (100.0)
Mean age, years (SD)	40.8 (8.8)
Mean weight, kg (SD)	78.8 (11.5)
Mean BMI, kg/m² (SD)	26.0 (3.3)

BMI, body mass index; SD, standard deviation.

PHARMACOKINETICS

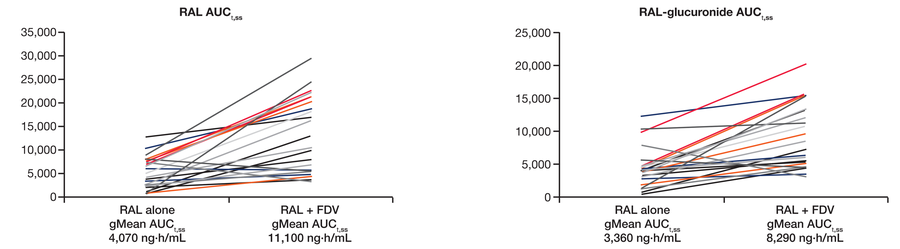
- Compared with RAL alone, co-administration of FDV with RAL resulted in an approximately 2.7-fold increase in gMean $AUC_{\tau,ss}$ and an approximately 2.5-fold increase in gMean $C_{max,ss}$ of RAL (**Table 2**, **Figures 2-4**)
- Similarly, compared with RAL alone, co-administration of FDV with RAL resulted in an approximately 2.5-fold increase in gMean $AUC_{\tau,ss}$ and an approximately 2-fold increase in gMean $C_{max,ss}$ of RAL-glucuronide (**Table 2**, **Figures 2-4**)

TABLE 2. Steady-state PK of RAL and RAL-glucuronide after administration of RAL alone or with FDV

PK parameter	RAL alone (N=24) gMean	RAL + FDV (N=23)[a] gMean	Adjusted GMR,[b] %	Two-sided 90% CI, %	Intra-individual gCV, %
RAL					
$AUC_{\tau,ss}$, ng·h/mL	4,072	11,079	272.1	199.7–370.7	67.9
$C_{max,ss}$, ng/mL	1,300	3,194	245.7	168.5–358.4	87.1
RAL-glucuronide					
$AUC_{\tau,ss}$, ng·h/mL	3,358	8,261	246.0	184.5–328.2	62.4
$C_{max,ss}$, ng/mL	764	1,488	194.8	144.7–262.4	64.7

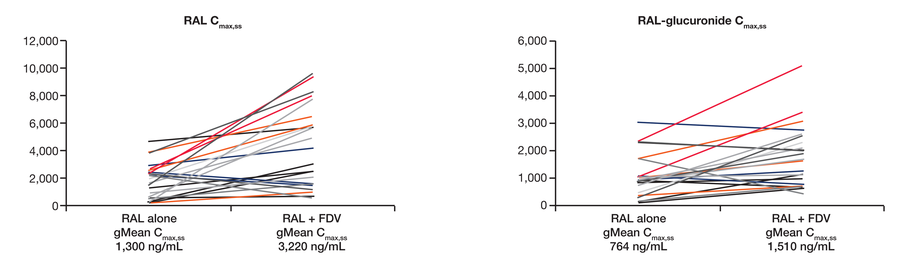
[a]One subject discontinued FDV treatment on Day 4. [b]Adjusted geometric mean ratio of (RAL + FDV/RAL alone) x 100.
$AUC_{\tau,ss}$, area under the plasma concentration–time curve at steady state over the uniform dosing interval τ; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; FDV, faldaprevir; gCV, geometric coefficient of variation; gMean, geometric mean; GMR, geometric mean ratio; PK, pharmacokinetic; RAL, raltegravir.

FIGURE 2. Individual $AUC_{\tau,ss}$ for RAL and RAL-glucuronide when RAL was administered alone or with FDV



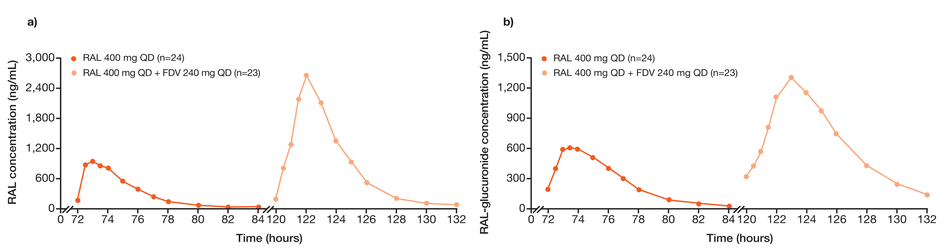
$AUC_{\tau,ss}$, area under the plasma concentration–time curve at steady state over the uniform dosing interval τ; FDV, faldaprevir; gMean, geometric mean; RAL, raltegravir.

FIGURE 3. Individual $C_{max,ss}$ for RAL and RAL-glucuronide when RAL was administered alone or with FDV



$C_{max,ss}$, maximum plasma concentration at steady state; FDV, faldaprevir; gMean, geometric mean; RAL, raltegravir.

FIGURE 4. gMean plasma concentration-time profiles for RAL (a) and RAL-glucuronide (b) when RAL was administered alone or with FDV



FDV, faldaprevir; gMean, geometric mean; RAL, raltegravir.

SAFETY

- AEs were consistent with the known safety profiles of FDV and RAL (**Table 3**)
- All AEs were of mild intensity apart from one AE rated as moderate (flatulence), which was reported during treatment with RAL + FDV
- No serious AEs, severe AEs, or AEs leading to discontinuation were reported
- A reversible increase in bilirubin was observed in nearly all subjects
  - Predominantly due to increase in indirect bilirubin
  - Bilirubin values returned to baseline during post-treatment follow-up
  - Bilirubin elevations were not accompanied by changes in markers of liver toxicity (alanine transaminase and aspartate transaminase) and not considered clinically relevant
- No other relevant changes in laboratory parameters, vital signs, or ECGs were observed

TABLE 3. Summary of AEs

	RAL alone n (%)	RAL + FDV n (%)	Total treated n (%)
Number of subjects	24 (100.0)	23 (100.0)	24 (100)
Any AE	7 (29.2)	17 (73.9)	18 (75.0)
Serious AEs	0	0	0
Severe AEs	0	0	0
AEs leading to discontinuation	0	0	0
AEs by system organ class[a]			
Gastrointestinal disorders[b]	3 (12.5)	11 (47.8)	12 (50.0)
Nervous system disorders[c]	4 (16.7)	7 (30.4)	9 (37.5)
General disorders and administration site conditions[d]	1 (4.2)	5 (21.7)	5 (20.8)
Renal and urinary disorders[e]	0	1 (4.3)	1 (4.2)

[a]More than one AE can occur in a single subject. [b]Gastrointestinal disorders: nausea, diarrhea, vomiting, flatulence, abdominal discomfort, abdominal pain upper, abdominal pain, dry mouth. [c]Nervous system disorders: headache, dizziness, syncope, tremor. [d]General disorders and administration site conditions: fatigue, feeling of relaxation. [e]Renal and urinary disorders: chromaturia.
AE, adverse event; FDV, faldaprevir; RAL, raltegravir.

SUMMARY

- Co-administration of FDV 240 mg QD (the highest dose in clinical development) with RAL 400 mg BID resulted in an approximately 2.7-fold increase in RAL overall exposure in healthy subjects
  - Exposure to both RAL and its metabolite RAL-glucuronide were almost equally increased after co-administration of FDV with RAL
  - Therefore, the observed drug–drug interaction is more likely due to interaction of FDV with transporters (i.e. P-gp) than metabolism of RAL by UGT1A1
  - Data from the STARTVerso4 study in HCV/HIV co-infected patients taking concomitant FDV and RAL demonstrated that RAL trough exposure was similar with or without concomitant administration of FDV 120 mg, and approximately 1.5-fold lower with concomitant FDV 240 mg[5]
  - The safety profiles of RAL plus FDV were similar to other regimens
  - The observed DDI is thus considered not clinically relevant
- The RAL exposures in this trial were comparable with other published data
  - Consistent with previous studies,[6] RAL exposures showed considerable variation with $AUC_{\tau,ss}$ and $C_{max,ss}$ intra-individual gCV values of 62–87%
- Both RAL alone and RAL in combination with FDV were well tolerated and no safety concerns were identified
  - Observed increases in bilirubin concentrations (predominantly indirect bilirubin) were reversible and not associated with markers of liver injury
  - Such clinically irrelevant, transient indirect bilirubin increases are a well-known effect of treatment with FDV, which is an inhibitor of UGT1A1

CONCLUSION

- Collectively, these results suggest that RAL and FDV can be safely co-administered without any dose adjustment

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DISCLOSURES

- The following authors are employees of Boehringer Ingelheim: DJ, PR, NS, JG, ME, A-MQ, and FH
- AS is an employee of CRS
- This study was carried out by Boehringer Ingelheim
- The presentation includes discussion of investigational drugs not approved for use in humans