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Pharmacokinetic (PK) Evaluation of Darunavir/Ritonavir (DRV/r) and Raltegravir (RAL) in Healthy Subjects

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Abstract

Background: Both DRV/r, a next generation PI, and RAL, an InSTI, have separately demonstrated potent clinical activity in HIV-infected patients. This study evaluated the effect of co-administration of DRV/r and RAL on PK and safety in healthy subjects.

Methods: Eighteen healthy subjects were enrolled in an open-label, sequential 2-period study. In Period 1, all subjects were administered 400 mg RAL q12hr for 4 days. In Period 2, subjects were administered 400 mg RAL + 600/100 mg DRV/r q12hr for 12 days. Period 2 immediately followed Period 1. Doses were administered with a meal.

Results: Eight subjects presented with a clinical adverse experience (AE) of rash. Seven were rated mild to moderate in intensity; one progressed to a serious adverse event of maculopapular rash. Onset occurred between Days 8 and 12 of Period 2 of concomitant dosing. Six subjects out of 18 completed the study, but constituted an insufficient data set from which to draw PK conclusions. However, based on limited data, DRV/r had only modest effect on mean RAL PK parameters. The geometric mean ratio (GMR) for RAL co-administered with DRV/r relative to RAL alone was 0.71 (90% CI: 0.38 to 1.33) for AUC_{12hr}, 0.67 (0.33 to 1.37) for C_{max}, and 1.38 (0.16 to 12.12), for C_{12hr}, respectively. Summary DRV PK parameters of AUC_{12hr}, C_{max}, C_{12hr} in the presence of RAL aligned closely to historical data reported in healthy subjects given DRV/r alone.

Conclusions: Contrary to clinical experience with the combination in HIV-infected patients, co-administration of RAL with DRV/r in healthy subjects resulted in a common adverse experience of rash. Based on limited PK data, a co-administration of DRV/r and RAL resulted in a modest effect on RAL with no clinically important changes in DRV pharmacokinetics.

Introduction

- Raltegravir (RAL) is a novel HIV-1 integrase inhibitor with potent in vitro and clinical activity against HIV-1.
- RAL is primarily metabolized by glucuronidation and has no inhibitory or inductive potential on CYP enzymes.
- Darunavir (DRV) is a novel PI with potent in vitro and clinical activity against HIV-1.
- DRV and ritonavir (RTV) are each metabolized primarily by CYP3A. DRV in combination with RTV is a net inhibitor of CYP3A.
- An evaluation for a drug interaction between RAL and DRV/r was conducted as HIV-infected patients are likely to benefit from combination administration.

Methods

Study Design

	Period 1	Period 2†	
	Days 1 through 4	Days 1 through 11	Day 12
N=18	RAL 1 x 400 mg q12h Fed	RAL 1 x 400 mg q12h + DRV 2 x 300 mg q12h + RTV 1 x 100 mg q12h Fed	RAL 1 x 400 mg (morning dose only) + DRV 2 x 300 mg (morning dose only) + RTV 1 x 100 mg (morning dose only) Fed

† Period 2 immediately followed Period I.

Safety Assessment

- Safety and tolerability were assessed by measurements of semi-recumbent heart rate and blood pressure, ECG, laboratory safety tests (CBC, chemistry panel, urinalysis), and physical examinations.
- Adverse experiences were evaluated as to their intensity, seriousness, and relationship to study drug.

Analytical and Pharmacokinetic Methods

- Plasma samples were analyzed for RAL concentrations using a validated HPLC – MS/MS assay.
- Plasma samples were analyzed for DRV and RTV concentrations using a validated HPLC – MS/MS assay.
- C_{max} and T_{max} determined by inspection.
- AUC_{12hr} calculated using linear up/log down trapezoidal method.

Statistical Analysis

- Confidence intervals for RAL and DRV C_{12hr}, AUC_{12hr} and C_{max} were constructed using the appropriate mixed-effects linear model.

Results

Subject Disposition

RANDOMIZED: Male (age range) Female (age range)	18 15 (19 to 55 yrs) 3 (20 to 22 yrs)
COMPLETED:	6
DISCONTINUED: Clinical adverse experience Laboratory adverse experience Other	12 6 0 6

Safety

RAL ± DRV/r in Healthy Subjects

Clinical Adverse Experiences - Summary

- 10 subjects reported a total of 16 clinical non-serious adverse experiences (AEs) and 1 serious adverse experience (SAE)
  - All non-serious AEs except 1 were considered to be drug-related
  - All non-serious AEs were rated mild to moderate in intensity
  - The SAE was rated as "severe"
- The most common drug-related clinical adverse experiences (reported by ≥2 subjects) were rash and headache
  - 2 non-serious AEs of headache were reported and ranged in intensity from "mild" to "moderate"
  - A total of 8 adverse experiences of rash were reported:
    - 7 subjects with non-serious AEs of rash (2 pruritic)
    - Non-serious rashes ranged in duration from 11 days to 33 days
    - 1 subject with a SAE of maculo-papular rash – subject recovered fully
  - 12 subjects were discontinued
    - 2 subjects withdrew consent
  - 6 subjects were discontinued due to a clinical AE of rash
    - All rashes had an onset during co-administration of RAL and DRV/r in Period 2 between Day 8 and Day 12; subjects were discontinued on the same or next day
  - Due to the incidence of rash, the study was not further enrolled; The PI discontinued 4 subjects

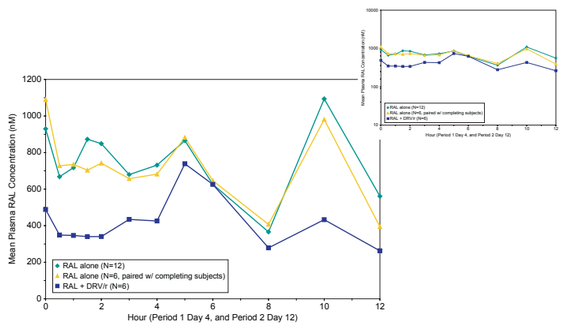
RAL ± DRV/r in HIV-Infected Subjects - Safety Summary

- In phase III studies of treatment-experienced patients with HIV infection, after at least 48 weeks of therapy, among a subset of 301 patients who received RAL (N=200) or placebo (N=101) in combination with DRV/r as part of the optimized background therapy (OBT)
  - The occurrence of rash regardless of drug relationship was higher in patients receiving RAL + DRV/r in OBT compared with Placebo + DRV/r (15.0% vs 4.0%)
  - The occurrence of rash considered drug-related was similar in the RAL + DRV/r and Placebo + DRV/r groups (3.5% vs 2.0%)
  - None of the rashes was considered serious or led to discontinuation of therapy
  - NB: mean duration of follow up was longer overall for patients randomized to raltegravir versus placebo due to higher failure rate in placebo group

Pharmacokinetics

Effect of DRV/r on RAL Pharmacokinetics

Arithmetic Mean RAL Plasma Concentration Profiles Following Multiple Oral Doses of 400-mg RAL Twice Daily With or Without Co-administration of Multiple Oral Doses of 600-mg DRV and 100-mg RTV Twice Daily to Healthy Male and Female Subjects



Pharmacokinetic Parameter	RAL Alone			RAL+ DRV + RTV			(RAL + DRV + RTV)/ (RAL Alone)	
	N	GM‡	95% CI	N	GM‡	95% CI	GMR	90% CI
C_{12hr} (nM)	6	114.49	(28.38, 461.88)	6	158.32	(39.24, 638.72)	1.38	(0.16, 12.12)
AUC_{12hr} (nM•hr)	6	6593.99	(4113.28, 10,570.80)	6	4688.17	(2924.44, 7515.59)	0.71	(0.38, 1.33)
C_{max} (nM)	6	1568.76	(934.82, 2632.63)	6	1056.37	(629.48, 1772.75)	0.67	(0.33, 1.37)
T_{max} (hr)	6	0.0§	(0.0, 10.0)	6	1.75§	(0.0, 10.0)	2.13‖	

‡ Geometric mean computed from least squares estimate from the mixed model performed on the natural-log transformed values.
§ Median (Min, Max) reported for T_{max}.
‖ Hodges Lehmann Estimate of median treatment difference. Corresponding 90% CIs is not reported for T_{max} as it is non-informative.

- Due to the incidence of rash, the study was not further enrolled. These subjects were not replaced.
- Due to an insufficient number of evaluable subjects and greater than anticipated variability, no pharmacokinetic conclusions for the effect of DRV/r on RAL can be drawn from this study.
- However, based on limited pharmacokinetic data, co-administration of DRV/r and RAL appears to result in a modest effect on RAL.

Mean DRV and RTV Plasma Pharmacokinetics Following Multiple Oral Doses of 400 mg RAL Twice Daily With or Without Co-administration of Multiple Oral Doses of 600 mg DRV and 100 mg RTV Twice Daily to Healthy Male and Female Subjects Compared to Historical Data for Co-administration of 600 mg DRV and 100 mg RTV Alone

PK Parameter (mean ± SD)	This Study N=6	Historical Data (DRV/r Alone)	This Study (N=6)	Historical Data (DRV/r Alone)
C_{12hr} (ng/mL)	2798 ± 1116	3426 ± 900[1] 2353 ± 744[2]	244.8 ± 79.20	372 ± 2821 161.5 ± 78.90[2]
C_{max} (ng/mL)	6020 ± 1659	7729 ± 1072[1] 5908 ± 916.8[2]	716.2 ± 351.6	1436 ± 682[1] 1063 ± 487.9[2]
$AUC_{0\text{-}12hr}$ (ng•hr/mL)	50,320 ± 17,080	68,830 ± 10,830[1] 44,750 ± 7773[2]	5082 ± 2248	8582 ± 4486[1] 5787 ± 2427[2]

[1] Sekar V., El Malt M., De Paepe E., Mack R., De Pauw M., Vangeneugden T., Lefebvre E., Hoetelmans R. *Effect of the HIV protease inhibitor darunavir (DRV), co-administered with low-dose ritonavir, on the pharmacokinetics of digoxin in healthy volunteers.* ASCPT, Anaheim, CA, USA, 21-24 March 2007. Abstract PII-104.

[2] Sekar V, Spinosa-Guzman S, De Paepe E, Stevens T, Tomaka F, De Pauw M, Hoetelmans RM. *Pharmacokinetic interaction trial between darunavir in combination with low-dose ritonavir and didanosine.* 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 22-25 July 2007.

These posters are available on-line at www.tibotec.com

- In the presence of RAL, mean DRV C_{12hr}, C_{max} and AUC_{12hr} aligned closely to historical data reported in healthy subjects co-administered 600 mg DRV and 100 mg ritonavir b.i.d. alone.
- These results are consistent with a report from the French expanded access program that includes an arm of 400 mg RAL b.i.d. co-administered with 600 mg DRV and 100 mg RTV b.i.d. (n=83) and which concludes that Despite a large interpatient variability, DRV/r combination had no deleterious effect on RAL C_{min}.[1]

[1] Long K., Soulié C., Schneider L., Ghosn J., Piketty C., Boué F., Reynes J., Raffi F., Calvez V., Katlama C., Peytavin G. *Therapeutic Drug Monitoring of Raltegravir (MK-0518) in Experienced HIV-infected Patients.* 11th European Aids Conference, October 24-27, 2007, Madrid, Spain.

Conclusions

- Multiple oral doses of 400-mg RAL given in combination with 600-mg DRV plus 100-mg RTV in healthy subjects resulted in a common adverse experience of rash.
- Based on limited PK data, coadministration of DRV/r and RAL resulted in a modest effect on RAL with no clinically important changes in DRV pharmacokinetics.

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