A Multiple Dose Study of Raltegravir Formulations

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Abstract

Background: ISENTRESS (raltegravir) is an integrase strand transfer inhibitor indicated in combination with other anti-retroviral drugs for the treatment of human immunodeficiency virus (HIV-1) infection. ISENTRESS is currently marketed as a 400 mg oral compressed tablet (OCT) formulation of raltegravir given twice daily for a total daily dose of 800 mg. This study was conducted to characterize the steady state pharmacokinetic (PK) profile of 1200 mg doses of raltegravir to support once daily administration.

Methodology: An open-label, multiple-dose, randomized, 3-period, 3-treatment, crossover study was performed in 24 healthy male and female subjects (25 to 55 years). Subjects received either 1200 mg once daily (QD) of the OCT formulation (3x400 mg tablets), 1200 mg QD of a reformulated raltegravir (rRAL) formulation (2x600 mg tablets), or 400 mg twice daily (BID) of the OCT for 5 days. Safety and tolerability were assessed. Full PK profiles in all cases were collected after administration under fasted conditions on days 1 and 5. In pursuing a model-based drug development approach, a PK/PD viral dynamics model is being utilized to assess the feasibility of these 1200 mg doses for once daily dosing and inform future study design.

Results: RAL was found to be generally well tolerated in healthy subjects. Administration of 1200 mg OCT QD in the fasted state resulted in a day 5 geometric mean (CV%) C_{trough} of 83.1 nM (53%), C_{max} of 14.2 µM (99%), and AUC_{24hr} of 49.3 µM-hr (73%). Similarly, administration of a 1200 mg rRAL tablet QD in the fasted state resulted in a day 5 geometric mean (CV%) C_{trough} of 81.2 nM (72%), C_{max} of 20.6 µM (44%), and AUC_{24hr} of 59.4 µM-hr (34%). Administration of 400 mg OCT BID in the fasted state resulted in a day 5 geometric mean (CV%) C_{trough} of 132 nM (56%), C_{max} of 3.5 µM (153%), and AUC_{24hr} (2xAUC_{12hr}) of 26.0 µM-hr (106%).

Conclusions: Data from this study, in combination with other recently completed Phase I studies and PK/PD viral dynamics modeling and simulation, will be utilized to further assess whether QD dosing with these formulations would have a high likelihood of exerting antiviral activity similar to that of the current BID regimen, and provide insights into the feasibility of these formulations for once daily-administration.

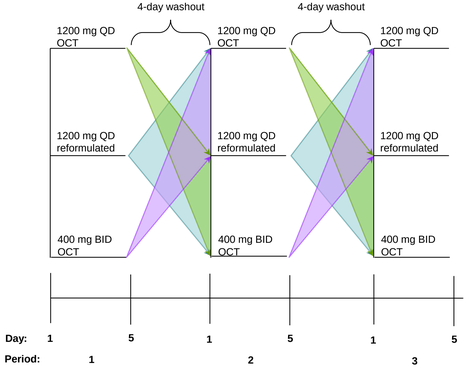
Introduction

Isentress (MK-0518, raltegravir) is an integrase strand transfer inhibitor

- Licensed in 2007
- Indicated in combination with other anitvirals for treatment of HIV-1 infection
- Marketed as a 400 mg oral compressed tablet (OCT) formulation of raltegravir (RAL) and given twice daily (BID) for a total dose of 800 mg
- Demonstrated durable efficacy and favorable safety through 5 years of follow up in clinical trials
- A Phase III trial (Protocol 071; QDMRK) studied 800 mg once daily (QD) against 400 mg BID dosing[1]
  - 318 (83%) of 382 patients in the once-daily group had virologic response compared with 343 (89%) of 386 in the twice-daily group (difference -5.7%, 95% CI -10.7 to -0.83, p=0.044)
  - Characterization of RAL exposure-response suggests that increasing the dose may result in a feasible once-daily regimen
  - C_{trough} values below 45 nM threshold were associated with a higher risk of virologic failure
  - This study and associated modeling was conducted to primarily assess the feasibility of a once-daily regimen

Methods

- Open-label, multiple-dose, randomized, 3-period, 3-treatment crossover study (Protocol 291)
- Two different formulations assessed: marketed OCT formulation and a reformulated formulation
- 24 healthy, nonsmoking, male and female subjects, from 25 to 55 years of age
- Blood samples for PK collected prior to dosing on Days 1, 3, 4, and 5 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose on Days 1 and 5. Blood samples were analyzed using a validated bioanalytical method to determine RAL concentrations in plasma[2]



- PK parameters were calculated using a noncompartmental approach
- Viral dynamics modeling was conducted based on the steady state PK data collected on Day 5 and previously presented single dose food effect data[3] using a previously described model[4]
- Model used to simulate projected efficacy for 1200 mg QD formulations versus marketed 400 mg BID regimen each in combination with 2 NRTIs, with simulations driven by observed intensive PK (including variability)
- Simulations of 10,000 subjects run to determine “true” probabilities for each treatment arm, followed by trial simulations of 1,000 trials of 345 patients per arm sampling from true distribution to obtain the probability of achieving noninferiority in a hypothetical Phase III study using a 10% noninferiority margin
- Safety was evaluated throughout the study using routine methods. Vital signs and ECGs were assessed at predose and at 2 hours postdose. Laboratory safety was assessed at predose and at 24 hours postdose

Results

Safety

- All study treatments were well tolerated. 24 subjects were enrolled in the study and 22 subjects completed. One subject was discontinued by the investigator due to fever prior to the 2nd treatment period; this event was not considered drug related. The other subject did not meet the laboratory admission criteria prior to the 2nd treatment period
- A total of 35 AEs were observed in 15 subjects. The most common AEs were somnolence (16.7%) and hypertension (16.7%). All of these AEs were mild in intensity, mostly transient, and resolved. There were no SAEs and there were no significant findings in laboratory safety tests

Pharmacokinetics

Figure 1. Mean plasma concentration profiles for RAL following administration of multiple oral doses to healthy subjects for 5 days (semi-log scale)

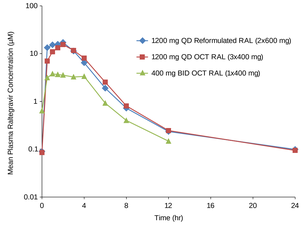


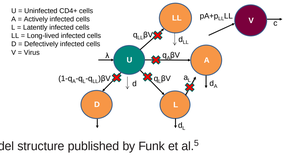
Table 1. Geometric mean (GM CV%) of pharmacokinetic parameter values for RAL following administration of multiple oral doses to healthy subjects for 5 days

Treatment	Day	N	C_{trough} (nM)	$AUC_{0\text{-}24}$ (µM-hr)	C_{max} (µM)	T_{max} (hr)[a]	% Subjects <45 nM
A: 1200 mg QD Reformulated RAL (2x600 mg) Fasted	1	23	54.7 (53.9)	59.8 (39.1)	22.6 (46.9)	1.5 (0.5-2.0)	30%
	5	23	81.2 (71.8)	59.4 (33.9)	20.6 (44.1)	2.0 (0.5-3.0)	17%
B: 1200 mg QD OCT RAL (3x400 mg) Fasted	1	22	50.4 (61.5)	42.6 (101)	12.3 (132)	2.0 (0.5-4.0)	41%
	5	22	83.1 (53.2)	49.3 (73.1)	14.2 (99.2)	2.0 (0.5-6.0)	9%
C: 400 mg BID OCT RAL (1x400 mg) Fasted	1	23	83.5 (71.2)	25.0 (142)	4.1 (172)	2.0 (0.5-4.0)	17%
	5	23	132 (56.0)	26.0 (106)	3.5 (153)	1.5 (0.5-4.0)	9%

[a]Median (Min-Max)

C_{trough} as C_{24hr} for QD treatments, C_{12hr} for BID treatments. $AUC_{0\text{-}24}$ reported for Treatment C (BID dosing) as 2 x $AUC_{0\text{-}12}$. Reformulated raltegravir administered as 2 x 600 mg tablets. Poloxamer administered QD as 3 x 400 mg tablets.

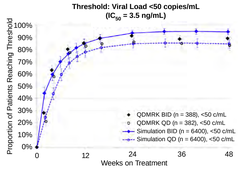
Viral Dynamics Modeling



- Based on model structure published by Funk et al.[5]
- As in the dolutegravir model presented by Zhang et al.,[6] the model was improved by inclusion of an additional effect for InSTIs on the inhibition of the conversion rate from latently infected to actively infected CD4 + cells

Viral Dynamics Modeling *(continued)*

Viral dynamics PK/PD model captures differences between 400 mg BID and 800 mg QD



Regimen	Predicted failure with resistance mutations	Observed failure with resistance mutations
400 mg BID	56%	36% (25%, 56%)
800 mg QD	70%	74% (67%, 77%)

- Short-term (10-day monotherapy) data from raltegravir and dolutegravir to refine compound-independent viral portions of model
- Long-term (48-week combo therapy) data from QDMRK (PN071)
  - Refine estimate of raltegravir potency EC_{50} (3.5 ng/mL)
  - Estimate parameters for dropout and resistance
- For both QD formulations, M&S projections indicate a high probability of achieving noninferiority to 400 mg BID OCT at either 24 or 48 weeks

Reference arm	Experimental arm (PN291)	Endpoint	Probability (90% PI) of achieving noninferiority to 400 mg BID in a Phase III study (10% NI margin; N=345/arm)
400 mg BID OCT (ISENTRESS®) fasted	1200 mg QD Reformulated (2x600 mg) fasted	W24	86% (59%-90%)
		W48	87% (61%-97%)
	1200 mg QD OCT (3x400 mg) fasted	W24	89% (58%-94%)
		W48	92% (60%-98%)

Note: Using viral dynamics model, probability of non-inferiority for 800 mg QD OCT <30%.

- Clinical significance of food effect on PK (assessed in a separate single-dose study Protocol 290) explored using viral dynamics model for scenarios in which subjects take meds consistently fasting, with low-fat meal, or high-fat meal
- A high probability of achieving noninferiority to BID ISENTRESS® is maintained across meal scenarios for reformulated raltegravir
- A drop in probability is observed for the OCT formulation in scenarios where it is consistently taken with a low-fat meal

Regimen and meal type		400 mg BID OCT (ISENTRESS®) 1st fasted 2nd fasted	1st low fat 2nd low fat	1st high fat 2nd high fat	1st fasted 2nd low fat	1st fasted 2nd high fat	1st low fat 2nd high fat
1200 mg QD reformulated (2x600 mg)	Fasted	90%	-	-	98%	85%	-
	Low fat	-	99%	-	95%	-	94%
	High fat	-	-	85%	-	94%	99%
1200 mg QD OCT (3x400 mg)	Fasted	92%	-	-	99%	88%	-
	Low fat	-	86%	-	66%	-	62%
	High fat	-	-	97%	-	99%	100%

Discussion

- RAL formulations were generally well tolerated in healthy subjects
- Multiple daily doses of 1200 mg reformulated raltegravir resulted in no accumulation at steady state, and PK parameter values observed in this study on Day 5 were similar to those observed in a previous single dose study[3] (geometric mean C_{24hr} of 59.8 nM, AUC of 58.1 µM-hr, and C_{max} of 23.1 µM)
- Multiple daily doses of 1200 mg OCT resulted in little to no accumulation at steady state. PK parameters in this study were higher than those from previous studies assessing 1200 mg doses of the OCT formulation, though these differences can be attributed to variability. The values observed in this study are in line with what would be expected for a 50% increase in dose over the 800 mg QD dose in Protocol 071 (QDMRK) in HIV-infected patients (GM C_{24hr} of 40 nM, AUC of 30.9 µM-hr, and C_{max} of 13.5 µM)
- Multiple twice-daily doses of 400 mg ISENTRESS® resulted in no accumulation at steady state. AUC and C_{max} values in this study were similar to those observed with a 400 mg BID dose in Protocol 071 in HIV-infected patients, while C_{trough} values were lower (GM C_{trough} of 257 nM, AUC of 26.3 µM-hr, and C_{max} of 3.4 µM), which again can be attributed to variability
- The probability of concluding, in a hypothetical Phase III design, noninferiority of 1200 mg given once daily in the fasted state as the OCT to 400 mg ISENTRESS® given twice daily is predicted to be 89% at Week 24 and 92% at Week 48. For reformulated raltegravir, this probability is 86% at Week 24 and 87% at Week 48
- This analysis indicates that 1200 mg of either formulation represent once daily options that are very likely to achieve noninferiority to BID ISENTRESS®
- Due to a less significant food effect on the PK of raltegravir with the reformulated raltegravir formulation, a high probability of achieving noninferiority to BID ISENTRESS® is maintained across meal scenarios for reformulated raltegravir. A drop in probability is observed for the OCT formulation in scenarios where it is consistently taken with a low-fat meal

Conclusion

- RAL formulations were generally well tolerated
- For both 1200 mg QD formulations, M&S projections indicate a high probability of achieving noninferiority to 400 mg BID ISENTRESS®
- Due to a smaller food effect on the PK of reformulated raltegravir, simulated efficacy is less dependent on meal type than for 1200 mg QD OCT
- Results of this study in combination with other data support the continued investigation of a once daily dosing regimen with reformulated raltegravir in a Phase III clinical study to be initiated in 2014

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