Discussion

- RAL formulations were generally well tolerated.
- For both 1200 mg QD formulas, 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 expected to be dependent on meal type.

References


M.L. Rizk, R. Krishna, V. Schulz, J. ten Bruggencate-Broeders, P. Larson, L. Wenning
Mercer & Co., Inc., Whitehouse Station, NJ

A Multiple Dose Study of Raltegravir Formulations

Introduction

Isentress (MK-0518, raltegravir) is an integrase strand transfer inhibitor indicated in combination with other antiretroviral drugs for treatment of HIV infection. The once-daily dose of raltegravir is a 400 mg oral compressed tablet (OCT). OCT formulation of raltegravir given twice daily (BID) is 400 mg and 800 mg, which is consistent with the previously shown sustained antiretroviral activity with the once-daily dose of raltegravir and provides equivalent antiretroviral activity as well as similar safety and tolerability to BID dosing. OCT formulation of raltegravir is taken with a low-fat meal to achieve steady state levels.

Viral Dynamics Modeling

- Based on model structure published by Funk et al.
- As in the dolutegravir model presented by Zhang et al. The model was improved to account for an additional effect for ISB or the induction of the concentration range from latency to actively infected CD4+ cells

Results

- PK profiles in all cases were collected after administration under fasted and fed conditions.
- This study was conducted to characterize the steady state geometric mean (CV%) C_{24}hr of 1200 mg doses of raltegravir to support the continued investigation of a once daily dosing regimen with other data support the continued investigation of a once daily dosing regimen with other data support

Materials

- Open-label, multiple-dose, randomized, 3-period, 3-treatment crossover study
- The study design included a 400 mg BID OCT (ISENTRESS®) group, a 1200 mg QD Reformulated RAL group, and a 1200 mg QD OCT (ISENTRESS®) group.

Methods

- 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.
- 3 patients in each treatment group.
- Baseline samples for PK analysis collected prior to dosing on days 1, 3, 4 and 8 at 6:00 AM and 2:00 PM
- Drug concentrations were determined using validated bioanalytical method in combination with LC-MS/MS.

Safety

- All 3 treatment groups were well tolerated.
- 24 subjects were enrolled in the study and 22 subjects completed.
- One subject was discontinued by the investigator due to be related to the treatment regimen prior to completing cycle 3.
- The other subject did not meet the laboratory admission criteria prior to the 3rd treatment period.
- A total of 36 AEs were observed in 25 subjects. The most common AEs were arthralgia (16/25) and nausea (13/25). All 36 AEs were mild to moderate in intensity, rarely described, and resolved. There were no SAEs and there were no significant safety, laboratory, or ECG changes.

Pharmacokinetics

- Multiple plasma concentration profiles for RAL following administration of multiple doses to healthy subjects for 4 days (0-24 hr):
- AUC_{24hr} (90% PI) of 400 mg BID OCT (ISENTRESS®) as 2 x AUC_{12hr} for Treatment C (BID dosing) as 2 x AUC_{0-12} for Treatment B (QD dosing). Median (Min-Max) of 39.1 (25.0, 59.4) nM, AUC of 58.1 μM-hr, and C_{max} of 25.0 μM (17%, 17% (0.5-3.0)) from latently infected to actively infected CD4+ cells
- Regimen and meal type
- High fat - -
- Low fat - -
- 2nd high fat - -
- 2nd low fat - -
- 1st low fat
- 1st high fat - -

Reference