

Pharmacokinetic (PK), Safety and Efficacy Data on Cohort IIA; youth aged 6-11 from IMPAACT P1066: A Phase I/II Study to Evaluate Raltegravir (RAL) in HIV-1 Infected Youth

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Abstract

Background: RAL is a potent selective HIV-1 integrase inhibitor approved for use in adults. P1066 is a study of open label RAL in treatment experienced HIV+ youth. PK, safety and efficacy data in HIV+ youth 12-18 (cohort I) were recently reported. Here we report PK, 12 week (wk) antiretroviral activity and all available safety data through September 14, 2009 from cohort IIA, 6-11 year-old participants placed on RAL tablets.

Methods: HIV+ youth enrolled in Stage 1: dose finding with intensive PK, safety and wk 12 efficacy. Entry criteria included HIV RNA >1000 copies/mL, treatment experienced but naive to integrase inhibitors, and excluded patients with HBV or HCV. Intensive PKs were completed between days 5 and 12 for all 14 subjects enrolled. ARV were optimized after intensive PKs completed. After PK were examined, a dose for continued study was selected. Success was defined as achieving and maintaining >1-log drops from baseline or viral loads of <400 copies/ml and on-study treatment at study specified dose at wk 12. Any patients taken off-treatment prior to wk 12 were considered failures. vRNA <50 also examined. All patients were included in the safety analyses

Results: Baseline demographics: Male: 60%; Race: 90% Black/African American, Median: weight=30kgs; age=9yrs; log₁₀RNA=4.4 CD4=536. Week 12 efficacy (Intent to Treat) data is available on 8 patients. Subjects dosed at 8 mg/kg (200, 300 or 400 mg) showed a geometric mean (GM) AUC₁₂ of 14.8 µMh (2.3-111) allowing for selection of 400 mg BID of adult formulation tablets as a final dose. Subjects weighing less than 25kg were placed on alternative formulations. Repeat PKs were done on all subjects at 400 mg BID which revealed a GM AUC₁₂ of 15.8 µMh (1.6-111). At 400 mg BID the GM trough and C_{max} were 246 nM and 4.8µM. There were three grade 3 adverse events, 1 possibly related (low ANC). No treatment discontinuations were due to adverse events. At 12 wks, 75% achieved success, 95% CI [35%, 97%]; 62% achieved <50 copies/mL, 95% CI [24%, 91%]. Success was similar to previously reported data on the 12-18 year old study cohort

Conclusions: A RAL dose of 400 mg BID of the adult formulation was chosen for continued study in HIV infected youth ages 6-11 and at least 25 kg in weight. In these subjects, RAL appears generally safe and well tolerated through wk 12, and achieved efficacy rates comparable to those in treatment experienced youth aged 12-18 and adults.

Background:

- RAL is a potent inhibitor of HIV integrase, and blocks viral replication.
- Data in adults show an excellent safety profile as well as potent efficacy in experienced adults who add RAL to a new optimized regimen and when used as part of primary regimen in therapy naïve adults.^{1,2}
- Prior data from P1066 established a dose of 400 mg taken twice a day as the optimal dose for HIV+ youth aged 12-18 years of age.^{3,4,5}
- This report provides PK and updated Week 12 and Week 24 efficacy and safety data of RAL given with an optimized background regimen (OBT) in HIV+ treatment experienced youth.

Methods:

- Intensive PK performed on mini-cohort, N=4. If PK results did not meet pre-specified targets, repeat PK was performed at new dose for mini-cohort. If target criteria were met, 6 more subjects were enrolled.
- PK Targets: Geometric Mean (GM) Area-Under-The-Curve (AUC₁₂) ≥ 14 µMh and GM 12h concentration (C12h) >33 nM.
 - Analysis included subjects who received RAL 400 mg BID and had fasting intensive PKs (Group B) and 1 patient who received 400 mg BID but changed doses during study due to weight changes (Group C).
- Intent-to-Treat analysis was primary:
 - "SUCCESS" defined as having achieved and maintained at least 1-log decline in HIV RNA from baseline OR ≤400 copies/ml and still on-study treatment (raltegravir 400mg BID) at Wk 12 or 24.
 - Patients taken off treatment before Wk 12 or 24 were considered "FAILURES".
 - Analysis included subjects who received RAL 400 mg BID through Week 24 and had fasting intensive PKs (Group B).
- Safety data includes all available data as of January 4, 2010 (Group A).

Cohort IIA Population

Group	Description of Group	N
A	Total number of patients enrolled; all used in the safety analysis	14
B	RAL 400 mg BID through week 24 and had fasting intensive PKs. All included in the RNA and CD4 efficacy analyses.	10
C	Received RAL 400 mg BID but changed doses during study; including 2 who switched formulations and 1 modified dose due to wt changes	3
D	Received RAL 200-300 mg BID	1

Baseline Demographics

N=10 (Group B)
Male: 60%
Median age: 9 years (7-11)
Race: Black: 90%
Median weight: 30kg (21-46)
CD4%: 24.6% (11-42)
CD4#: 536 (202-1294)
HIV RNA log₁₀: 4.4 (3.1-5.5)

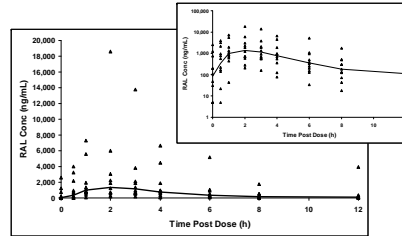
PK Results

Table 1: PK Parameters Cohort IIA, 400 mg BID Fasted

Parameter	Cohort IIA N=11*
AUC ₁₂	70 mg·h/L 15.8 µM·h
C _{min}	109 ng/ml 246 nM
CL/F %CV	49.6 L/hr 152%

* Pts in Group B plus 1 pt in Group C who had dose changes due to wt.

Figure 1: Time vs. Concentration Cohort IIA, 400 mg BID Fasted



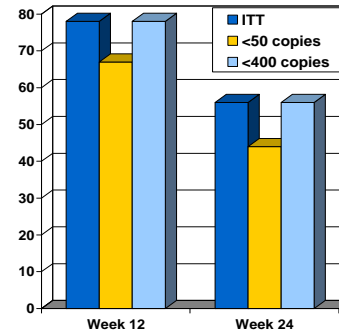
400 mg BID dose was picked based on all available data including PK at 8 mg/kg, AUC₁₂ PK data, weight bands and Cohort I results.

HIV RNA Results

Table 2: Virologic Response Week 12 and Week 24, 400 mg BID

Time point	ITT Success (95% CI)	<400 copies/mL (95% CI)	<50 copies/mL (95% CI)
Week 12	78% (40%, 97%)	78% (40%, 97%)	67% (30%, 92%)
Week 24	56% (21%, 86%)	56% (21%, 86%)	44% (14%, 79%)

Figure 2: Virologic Response Week 12 and Week 24, 400 mg BID



CD4 Results

Median CD4 Change from Baseline (pre-RAL):

Week 12: CD4 Cell Count: +86 (60, 219)
CD4 %: 2.5% (-1, 8.0%)
Week 24: CD4 Cell Count: +64 (-34, 402)
CD4 %: 2.0% (-1, 7.0%)

Safety Results

- RAL was generally well tolerated in these subjects.
- There were no RAL discontinuations due to toxicity.
- Neutropenia (Grade 3) was reported in two patients, one possibly related and one not related.
- One patient had fever and elevated bilirubin; not related
- One patient had cough; not related

Discussion

- RAL dose was established at 400 mg BID for youth ages 6-11 years and at least 25 kg in weight.
- RAL 400 mg BID was generally well tolerated in this age cohort.
- Virologic success by Intent-to-Treat analysis occurred in 78% at Week 12 and 56% at Week 24.
 - Adherence may have played a role in virologic response.

Conclusions

In HIV+ treatment-experienced youth aged 6-11 years, RAL 400 mg BID plus OBT:

- Was generally well tolerated
- At Week 24: 56% had virologic success and 44% <50 copies/mL
- Was associated with increases in CD4% and count

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