

Amprenavir (APV) 600 mg/ritonavir (RTV) 100 mg BID or APV 1200 mg/RTV 200 mg QD given in combination with abacavir (ABC) and lamivudine (3TC) maintains efficacy in ART-naive HIV-1 infected adults over 12 weeks (APV20001)

Introduction

The pharmacokinetics of most protease inhibitors, including amprenavir (APV), have been shown to be significantly enhanced when given in combination with low dose ritonavir (RTV)¹. Data in HIV-1 infected subjects has shown APV 600 mg/RTV 100 mg BID and APV 1200 mg/RTV 200 mg QD to be optimal dosing combinations². When RTV is added as an inhibitor of APV metabolism, APV plasma trough (C_{min}) concentrations increase approximately 5-fold above concentrations seen with APV alone. These increased C_{min} values provide greater drug exposure to both sensitive and resistant HIV-1 viral isolates and result in increased protein adjusted C_{min}/IC_{50} ratios. Data on the safety and efficacy of APV given in combination with RTV was obtained in Glaxo Wellcome study APV20001. This report includes a minimum of 12 weeks experience on both combinations in a cohort of subjects who chose to alter their dosing regimen to include RTV as a pharmacokinetic enhancing agent.

Methods

Subjects who completed the randomized phase of APV20001 and continued into an open label phase with APV/ABC/3TC were allowed to switch to an APV 600 mg/RTV 100 mg BID regimen or APV 1200 mg/RTV 200 mg QD regimen following a protocol amendment. Thirty-nine subjects opted to switch to either a BID or QD APV/RTV regimen in combination with ABC/3TC. Preliminary safety and efficacy results are for all subjects who have completed 12 weeks of therapy. Pharmacokinetic samples were drawn a minimum of 2 weeks after switching to an RTV-containing regimen.

Figure 1 • APV20001 study design overview

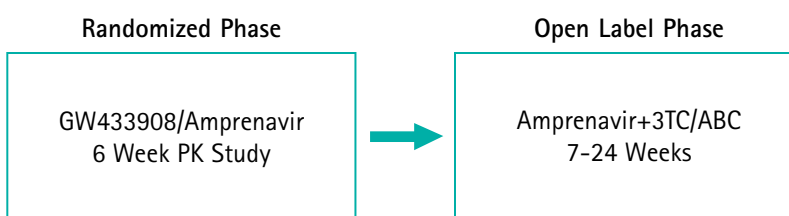
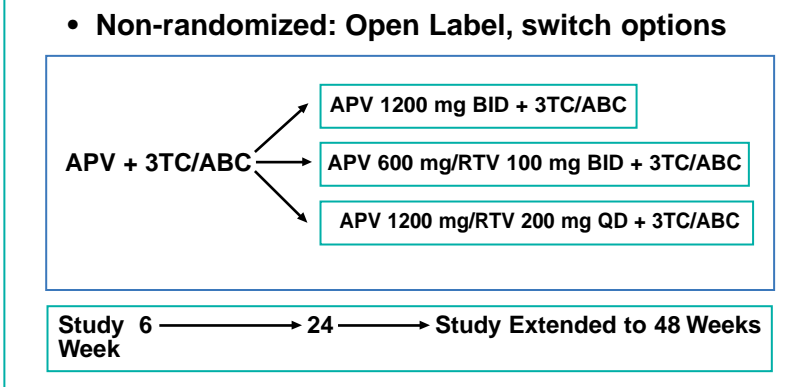


Figure 2 • APV20001 study amendment design



Accountability:

78 Subjects received study drug during the Randomized Phase, of which 61 had evaluable APV PK samples. Fifty-four subjects continued into the open label phase of the trial. Subjects were allowed to select one of the following treatment options based on preference.

Table 1 • Treatment options

Drug	Dosage	Number of Subjects
APV/RTV	600 mg/100 mg BID	21
APV/RTV	1200 mg/200 mg QD	15
APV alone	1200 mg BID	15

Note: 3 subjects who switched to an APV/RTV regimen were excluded due to non-compliance to protocol.

At the time of switch 89% of subjects had a plasma HIV-1 RNA concentration <400 copies/mL.

Results

Table 2 • Baseline characteristics of subjects opting to switch to an APV/RTV combination regimen

	APV 600 mg BID/RTV 100 mg BID (N=21)	APV 1200 mg QD/RTV 200 mg QD (N=15)
Sex		
Female	3 (14%)	10 (67%)
Male	18 (86%)	5 (33%)
Race		
White	13 (62%)	4 (27%)
Black	4 (19%)	10 (67%)
Other	4 (19%)	1 (7%)
Median baseline plasma HIV-1 RNA (log ₁₀ copies/mL) (range)	4.80 (3.43-4.88)	4.85 (3.92-4.88)
Median baseline CD4+ (cells/mm ³) (range)	348 (6-1051)	182 (9-619)

Figure 3 • APV20001 efficacy: % <400 copies/mL

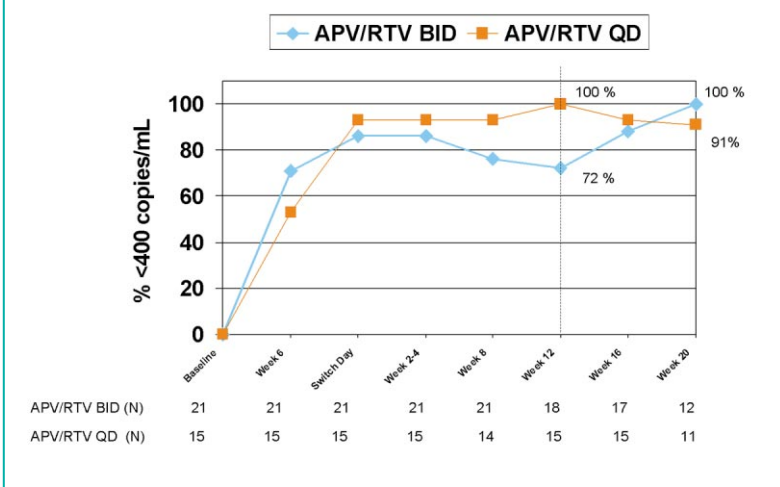


Figure 4 • APV20001 efficacy: Median change in CD4+ cells

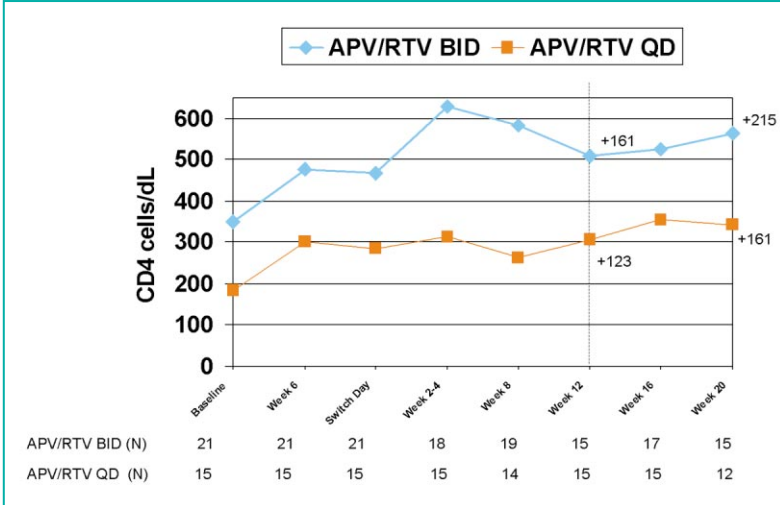


Figure 5 • APV20001 median steady-state plasma amprenavir concentration-time profiles

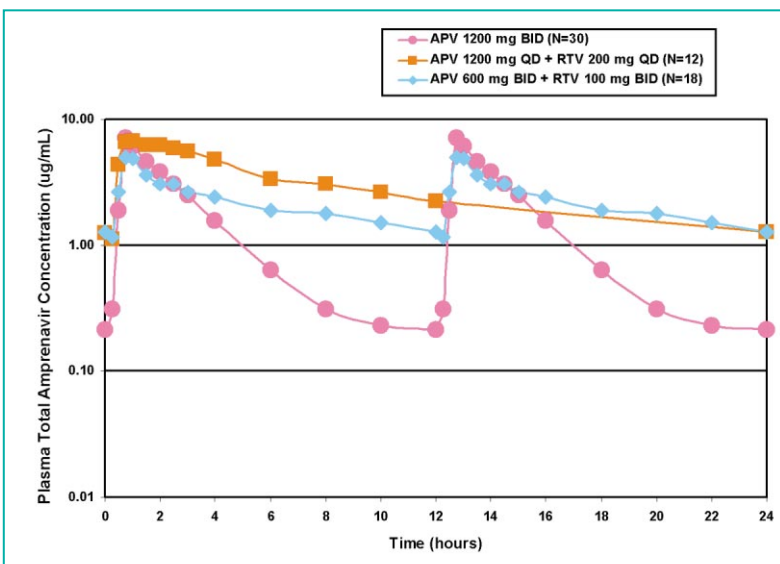


Table 3 • Steady-state plasma total amprenavir concentrations geometric mean (95% CI)

	APV 600 mg BID/RTV 100 mg BID (N=15)	APV 1200 mg QD/RTV 200 mg QD (N=12)	APV 1200 mg BID (N=27)
$C_{max,ss}$ (ug/mL)	5.39 (4.08-7.11)	7.75 (6.95-8.65)	7.34 (6.12-8.81)
AUC_{0-24} (ug-h/mL)*	28.9 (21.1-39.7)	68.2 (60.0-77.7)	18.1 (15.2-21.6)
$C_{min,ss}$ (ug/mL)	1.49 (1.06-2.08)	1.40 (1.10-1.78)	0.26 (0.19-0.34)

* The QD AUC was measured over a 24 hour period. The BID AUC was measured over a 12 hour period.

Table 4 • APV 20001: Post switch drug related adverse events

Adverse Event	APV/RTV BID (n=21)	APV/RTV QD (n=15)
Median RTV Exposure Weeks (range)	14 (2-18)	8 (8-16)
Abdominal Discomfort	1 (5%)	0
Abdominal Pain	1 (5%)	0
Constipation	0	1 (7%)
Nausea	1 (5%)	0
Vomiting	1 (5%)	1 (7%)
Diarrhea	0	1 (7%)
Oral/perioral paresthesia	0	1 (7%)
Rash	0	0
Headache	1 (5%)	0
Anorexia	2 (10%)	0

Table 5 • Selected laboratory parameters

	APV/RTV BID (n=21)	APV/RTV QD (n=15)
Median Exposure Weeks (range)	24 (12-30)	20 (16-27)
ALT		
Grade 2	1 (5%)	1 (7%)
AST		
Grade 2	0	1 (7%)
GGT		
Grade 2	2 (10%)	0
Grade 3	0	0
Grade 4	0	1 (7%)*
Cholesterol (fasting)		
Grade 2	5 (25%)	2 (13%)
Grade 3	1 (5%)	0
Triglycerides (fasting)		
Grade 2	2 (10%)	0
Grade 3	1 (5%)	0

* Patient with non-Hodgkin's lymphoma. This elevation was not felt by the investigator to be related to study drug.

Discussion

- In this group of 36 subjects, all of whom have been followed for a minimum of 12 weeks, 72% of the APV/RTV BID and 100% of the APV/RTV QD group had HIV-1 RNA <400 copies/mL. The durability of response is likely attributable to:
 - Increased APV C_{min} resulting in greater protein corrected $C_{min}:IC_{50}$ ratios
 - Prolonged $t_{1/2}$ providing improved antiviral coverage as well as greater flexibility in dosing particularly if a dose is delayed or missed.
- Immunologic reconstitution as measured by increased CD4+ T cell count continued to improve in both treatment arms over 20 weeks.
- Adverse Events were primarily gastrointestinal in origin and included nausea, vomiting, diarrhea and anorexia. These events were only mild to moderate in severity and were not treatment limiting.
- Laboratory abnormalities were limited primarily to elevations in triglycerides and cholesterol. These lipid elevations were limited to single grade increases, with only one Grade 3 elevation in cholesterol and triglyceride after switching to APV/RTV. Minimal changes in LFTs were also seen in a limited number of subjects exposed to the combination.

Conclusions

- Subjects who switched to the combination of APV/RTV in both the BID and QD regimen maintained virologic suppression and immunologic gains over a 20 week period.
- APV/RTV was well tolerated with minimal changes in laboratory parameters.
- Switching from APV 1200 mg BID to
 - APV 600 mg/RTV 100 mg BID or
 - APV 1200 mg/RTV 200 mg QD
 allows for a significant reduction of the total daily dose of APV (from 16 to 8 capsules daily) and provides the option of QD dosing of APV/RTV. This reduction in the total number of pills may improve convenience and adherence.
- These results combined with the unique resistance profile of APV support APV/RTV as an option for initial HIV therapy that includes a protease inhibitor.

References

- Sadler, et al. 7th CROI. San Francisco 2000, Abstract 77.
- Wood, et al. 5th International Congress on Drug Therapy in HIV Infection. Glasgow, UK 2000, Abstract 283.

Acknowledgments

International APV20001 Study Team