Synopsis

Identifier: RM2006/00557/00 **Study Number:** HPR20001

Title: A Phase IIB, Randomized, Multicenter, Parallel Group Study to Evaluate the Short-Term Safety, Pharmacokinetics and Antiviral Activity of Four Blinded Dosing Regimens of GW640385/Ritonavir Therapy Compared to Open-label Current Protease Inhibitor Therapy in HIV-1 Infected, Protease Inhibitor-Experienced Adults for 2 weeks with Long-Term Evaluation (> 48 weeks) of Safety, Pharmacokinetics and Antiviral Activity of Selected GW640385/Ritonavir Dosing Regimen(s) vs. a Ritonavir-boosted, Protease Inhibitor Containing Regimen

Investigator(s): This was a multicenter study.

Study center(s): The study was conducted at 74 sites (four in Australia, one in Belgium, four in Canada, eight in France, six in Germany, seven in Italy, two in Portugal, three in Romania, two in the United Kingdom, and 37 in the United States [including two in Puerto Rico]).

Publication(s): None at the time of this report.

Study Period: The first subject was enrolled into the study 16 Aug 2005. The last subject last visit for this 16 Week analysis was 16 Jun 2006.

Phase of Development: IIB

Objectives:

Primary:

- To select the brecanavir (BCV) dose for further study from comparisons of the dosing regimens of BCV/ritonavir (r, RTV) twice daily (BID) plus continued nucleoside or nucleotide reverse transcriptase inhibitor (nRTI) background therapy to single RTV-boosted protease inhibitor (PI/r) containing regimens in protease inhibitor (PI) experienced adult subjects based on the:
    - effect on virologic markers of HIV-1 infection,
    - BCV trough concentration ($C\tau$) at Day 15,
    - safety and tolerability of the BCV/r BID containing regimens.

Secondary:

- To assess the early antiviral activity and immunologic activity of the BCV/r BID containing regimens (including the functional monotherapy assessment at Day 15 prior to anti-retroviral therapy [ART] optimization)
- to evaluate the long-term safety, antiviral activity and tolerability of the BCV/r BID containing regimen(s)

- to explore Day 1 covariates (e.g. demographics, virology, etc.) and pharmacokinetic factors that may be associated with antiviral activity and adverse events (AEs)

- to examine incidence of Day 1 genotypic and phenotypic cross-resistance to BCV in PI-experienced subjects and its impact on treatment response

- to assess on-therapy and treatment-emergent viral resistance patterns and to compare these patterns with treatment outcome.

Methodology:

Number of subjects:

	PI/r	50,150mg BCV/r	50,300mg BCV/r	50,600mg BCV/r	150mg BCV/r	300mg BCV/r	600mg BCV/r	Total
Total Randomized, N	31	9	10	9	30	28	30	147
Total Treated, N	29	9	9	9	30	28	29	143
Total Ongoing at time of analysis[1], n (%)	20 (69)[2]	6 (67)[3]	6 (67)	7 (78)	22 (73)[4]	18 (64)	21 (72)	100 (70)
Discontinued from study prematurely, n (%)	9 (31)	3 (33)	3 (33)	2 (22)	8 (27)	10 (36)	8 (28)	43 (30)
Primary Reason for Discontinuation, n (%)								
Adverse Event[5]	1 (3)	1 (11)	1 (11)	0	2 (7)	1 (4)	1 (3)	7 (5)
Lost to follow-up	1 (3)	0	0	0	0	0	0	1 (<1)
Subject decided to withdraw from study	3 (10)	0	0	0	0	0	0	3 (2)
Disease progression	0	0	0	0	1 (3)	0	0	1 (<1)
Insufficient viral load response	3 (10)	1 (11)	2 (22)	2 (22)	5 (17)	9 (32)	6 (21)	28 (20)
Non-compliance	0	0	0	0	0	0	1 (3)	1 (<1)
Other[5]	1 (3)	1 (11)	0	0	0	0	0	2 (1)

1. Number of subjects still on study as of 16Jun2006
2. 16 subjects had discontinued randomized control PI/r and 11 switched to a BCV/r regimen prior to the data cut-off. Of these, 9/11 subjects were still on study but receiving BCV/r at the time of this analysis (2 on 150mg BCV/r, 4 on 300mg BCV/r and 3 on 600mg BCV/r
3. One subject switched to 600mg BCV/r following Amendment 2 and was on study at the time of this analysis.
4. Two subjects switched to 600mg BCV/r following Amendment 2 and both remained on study at the time of this analysis.
5. [redacted]

Diagnosis and main criteria for inclusion: Subjects infected with HIV-1 who were ≥18 years of age (or ≥16 years of age according to local regulations) were eligible for enrollment provided they met all other inclusion and exclusion criteria. Subjects must have been experiencing treatment failure defined as having plasma HIV-1 RNA ≥1,000 copies/mL at Screening, and must have had evidence of two or more multi-PI resistance mutations (L10I/F/V/R, V32I, M46I/L, I54V/L/M, V82A/F/T/S, I84V/A/C and L90M) at Screening or within three months of Screening. Additionally, subjects must have been currently receiving a regimen containing a single RTV-boosted PI without change for at least 8 weeks prior to Screening. In the absence of historic genotypic data confirming eligibility, subjects must have received at least one other PI (with or without RTV) for at least 8 weeks prior to Screening.

Treatment and Administration:

Randomized Phase: Day 1 to Week 48:

Subjects were randomized to one of five dosing groups on entry into this study.

- Treatment Arm 1 = BCV 50mg BID + RTV 100mg BID (50mg BCV/r)
- Treatment Arm 2 = BCV 150mg BID + RTV 100mg BID (150mg BCV/r)
- Treatment Arm 3 = BCV 300mg BID + RTV 100mg BID (300mg BCV/r)
- Treatment Arm 4 = BCV 600mg BID + RTV 100mg BID (600mg BCV/r)
- Control Arm = PI + RTV (PI/r)

Subjects randomized to a BCV/r containing regimen continued their ongoing background ART of at least two nRTIs +/-T20 from Day 1 through Day 15 and replaced their current failing PI/r with BCV/r. In contrast, subjects randomized to the Control Arm received their ongoing PI/r regimen from Day 1 through Day 15. At Day 15, all subjects optimized their background therapy based on Screening genotype/phenotype and the subject's treatment history. The investigator chose the most appropriate PI/r regimen for the control subject based on treatment history as well as genotypic and phenotypic resistance data. Additionally, subjects randomized to Treatment Arm 1 were re-randomized at Day 15 to one of the three higher BCV/r dosing regimens. These dosing arms are designated as follows: 50,150mg BCV/r, 50,300mg BCV/r, and 50,600mg BCV/r.

Optimized background therapy was to consist of at least two nRTIs. Subjects were also permitted to introduce T20 in their background ART at the Day 15 study visit provided the investigator indicated they would do so at randomization (Day 1). Subjects with prior T20 usage could also include T20 in their optimized background if appropriate. Concomitant use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) or dual Pis was not allowed in any treatment arm.

Control subjects who met subject management criteria (See Subject Management Criteria Based on Virologic Response below) with confirmation after Week 12 and who choose to

discontinue use of their current RTV-boosted PI and switch to a BCV/r regimen *prior to* implementation of Amendment 2 at their site were re-randomized to receive either 150/100mg, 300/100mg, or 600/100mg BCV/r BID. Following site approval of Amendment 2, subjects who were re-randomized to the 150/100mg BID BCV/r arm were identified to the investigator and were permitted to increase their BCV/r dose to 600/100mg BID or to discontinue from the study. These subjects received their BCV/r dose in an unblinded fashion and entered the Non-Randomized Phase of the study.

No substitutions in background ART for lack of antiviral activity were allowed during the Randomized Phase for any subject. Subjects were permitted to change one or more of their background ARTs on one occasion for reasons of safety or intolerability during the Randomized Phase.

Upon completion of the Week 16 study visit of the last subject enrolled, this interim data analysis was to be conducted to select the final BCV/r dose for use in the Non-Randomized Phase and in future studies. This dose was to be confirmed based on an additional interim analysis conducted when the last subject completed the Week 24 study visit. The final dose was to be communicated to sites via an amendment to this protocol.

Non-Randomized Phase: Treatment Arms 3, 4, and Control C

All subjects were to enter the Non-Randomized Phase of the study at their Week 48 visit or once the final dose of BCV/r has been determined, whichever was **later** (i.e. subjects were to complete at least 48 weeks of randomized therapy). Subjects originally randomized to BCV/r (Arms 2, 3 and 4) were to receive the final selected BCV/r dose throughout the Non-Randomized Phase of the study. Subjects in Control Arm C were to continue on their RTV-boosted PI containing regimen. Subjects enrolled within Control Arm C who experienced a protocol defined subject management criterion were given the option to receive a BCV/r containing dosing regimen. There were no restrictions to the number of times an investigator could choose to optimize a subject's background therapy within the Non-Randomized Phase. However, optimization for subjects receiving BCV/r was subject to available drug-drug interaction data. Subjects were to continue within the Non-Randomized Phase until they no longer derived clinical benefit or BCV was commercially available.

Non-Randomized Phase: Previous BCV/r 150/100 mg BID recipients

Median plasma steady-state BCV exposures following BCV/r BID were lower in recent drug interaction studies when compared to data available at the time of initiation of HPR20001. In light of this, the Week 2 plasma samples from the subset of subjects who underwent intensive serial PK sampling in HPR20001 were analyzed by treatment group. The HPR20001 data showed large intersubject variability in median plasma BCV exposure with 30-40% lower median exposures for each dose group when compared with exposures observed in previous pharmacokinetic (PK) studies (e.g. HPR10003).

Based on this PK analysis and accumulating evidence of acceptable safety and tolerability of doses of at least 300/100mg BCV/r BID, Amendment 2 was introduced to allow a dose increase for subjects currently receiving 150/100mg BCV/r BID (either by original randomization or re-randomization) to a dose of 600/100mg BID. Following

approval of Amendment 2, subjects receiving 150/100mg BCV/r were identified to the investigator and permitted to either have their dose of BCV/r increased to 600/100mg BID or be discontinued from the study. These subjects received their newly assigned BCV/r dose in an unblinded fashion and entered the Non-Randomized Phase of the study.

Subjects had completed at least their Week 12 Study assessments prior to initiating this switch. Subjects impacted by Amendment 2 must either have increased their BCV/r dose or were discontinued from the study on or before their next regularly scheduled study visit.

Subject Management Criteria Based on Virologic Response:

- **Incomplete Virologic Response:** Subject did not achieve at least a 1 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA by Week 12 (relative to Day 1 value).

- **Virologic Rebound:**

  - For subjects whose nadir was ≥ 400 copies/mL: two consecutive plasma HIV-1 RNA determinations that are >0.5 $\log_{10}$ copies/mL plasma HIV-1 RNA higher than the nadir value on or after Week 12.

  - For subjects whose nadir is <400 copies/mL: two consecutive plasma HIV-1 RNA determinations that are ≥ 400 copies/mL on or after Week 12.

Once a subject was confirmed as meeting a subject management criterion, a plasma for storage sample was sent for genotypic and phenotypic resistance testing and the result made known to the investigator when available.

The subject had to be receiving full doses of investigational products for at least two weeks at the time confirmatory plasma HIV-1 RNA and resistance testing were done, if at all possible.

A subject who met any of the above subject management criteria should have been considered for immediate discontinuation from the study. Should the investigator have preferred not to discontinue the subject from the study, the investigator must have consulted the Sponsor Medical Monitor to discuss if there was a rationale for maintaining a study subject on a regimen that was not providing sufficient virologic suppression and/or control, or if other antiretroviral treatment options maybe of greater long-term benefit to the subject.

Batch Numbers of Investigation Products used in HPR20001

Drug Name		Batch Numbers
Brecanavir Tablets	50 mg	031014216, 051070442, 051083874
Brecanavir Tablets	150 mg	051075816, 051075824, R193806
Placebo Tablets		041022481, 051075891, 051095095
Ritonavir Capsules	100 mg	22406VA, 33491VA, 051098514, 247042E21, 269972E21, 281572E21, 305832E21, 331282E23

Criteria for evaluation:

Efficacy was assessed by monitoring of quantitative plasma HIV-1 RNA, lymphocyte subsets, and Centers for Disease Control and Prevention (CDC)-defined HIV-associated conditions.

Safety was assessed by monitoring of clinical AEs and serious adverse events (SAEs), clinical laboratory evaluations, investigational product accountability, concomitant medications, background antiretroviral therapy, lipodystrophy assessments, electrocardiograms (ECGs), pregnancy tests (Screening, Days 1 and 7, and as needed), body weight and vital signs.

Other evaluations included serial plasma pharmacokinetic (PK) sampling, BCV and RTV trough sampling, measurements of α-1 acid glycoprotein, plasma for storage, and genotypic and phenotypic analyses. A plasma sample was also collected at Baseline for possible pharmacogenetic research.

Statistical methods:

This is a randomized, multicenter, parallel group, partially blinded, five-arm study with a Randomized Phase and a Non-Randomized Phase designed to identify the dose of BCV/r to be progressed for further evaluation in Phase III studies.

The sample size was chosen to provide 90% power to detect a difference of 0.7 $\log_{10}$ copies/mL between each BCV/r treatment arm and the control PI/r arm with normally distributed errors and an assumed standard deviation of 0.75 $\log_{10}$ copies/mL. At least 130 subjects were required for randomization, with a minimum of 26 subjects in each treatment group. No adjustment for multiple comparisons were made in the sample size calculation as a closed testing procedure was used to test decreasing doses against placebo and protect the Type I error rate. The primary comparison between treatments adjusted for T20 use, the number of multi-PI resistant mutations and Baseline viral load using linear regression.

Antiviral efficacy analyses were conducted on an Intent-To-Treat (Exposed) (ITT[E]) population – subjects who were randomized with evidence of receiving at least one dose of randomized investigational product. Safety analyses were conducted upon the same subjects using actual (rather than allocated) treatment groups – this was defined as the Safety population. A Per-Protocol population was defined for secondary efficacy analyses. Separate populations were also defined for PK listings (PK Concentration), PK analyses (PK Parameter), PK/PD analyses (PK/PD), analyses of viral genotype and phenotype at Baseline (Baseline Virology) and of on-treatment genotype and phenotype (On-Treatment Resistance).

The primary anti-viral response analysis was the difference in AAUCMB of $\log_{10}$ copies/mL plasma HIV-1 RNA between each BCV treatment arm and the control arm. This analysis was performed using the Last AAUCMB Carried Forward analysis strategy and excluded subjects randomized to Arm 1 (50/100mg BCV/r).

PK parameters were summarized descriptively. Dose proportionality was assessed using a power model analysis. PK/PD analysis was graphical in nature and included plots of change from Baseline HIV-RNA versus various PK parameters as well as histograms of proportions of subjects achieving a therapeutic endpoint versus quartile of inbibitory quotient (IQ). Additionally, an Emax model was used to estimate the IQ that would be required in order to achieve efficacy (viral load decrease of > 2 $\log_{10}$ copies/mL).

All subjects were assessed at Day 1 for genotype and phenotype. Subjects meeting virologic failure criteria had an HIV-1 viral genotype and phenotype assessment at the point of initial detection of virologic failure. Additional analyses of phenotype and/or genotype may have been performed at other time points.

The analysis of sequences for the protease and reverse transcriptase endocoding region (to RT codon 305) and of phenotypes for approved anti-HIV-1 antiretroviral drugs was performed at Monogram Biosciences, Inc., South San Francisco, California, and the analysis of the gag p7/p1 through p1/p6 encoding region was performed at the Department of Virology, GSK, Stevenage, UK using an in-house methodology. The lower limit for attempting analysis was set at 400 copies/mL for analysis. Analysis of T20 resistance was performed using only phenotype. Genotypes were assessed using the IAS USA resistance tables and genotype susceptibility score (GSS) and phenotypic susceptibility score (PSS) values for concomitant antiretroviral drugs were obtained using the Monogram Biosciences, Inc. algorithms. Overall resistance at Baseline and on-treatment as well as treatment-emergent resistance were assessed and the predictive value of Baseline resistance on response was examined in univariate and multivariate models.

Summary:

Demographics:

Demographic Characteristics (ITT[E] Population) for HPR20001

	PI/r N=29	50,150mg BCV/r N=9	50,300mg BCV/r N=9	50,600mg BCV/r N=9	150mg BCV/r N=30	300mg BCV/r N=28	600mg BCV/r N=29	Total N=143
Age (years)								
Mean (SD)	44.1 (8.10)	47.9 (8.61)	41.2 (4.89)	35.9 (11.17)	43.0 (9.86)	43.5 (11.18)	41.6 (9.86)	42.8 (9.69)
Median (Range)	44.0 (18-57)	49.0 (35-59)	41.0 (33-49)	38.0 (17-48)	44.0 (16-58)	42.5 (17-65)	42.0 (16-63)	43.0 (16-65)
Sex, n (%)								
Male	26 (90)	8 (89)	8 (89)	7 (78)	21 (70)	24 (86)	28 (97)	122 (85)
Female	3 (10)	1 (11)	1 (11)	2 (22)	9 (30)	4 (14)	1 (3)	21 (15)
Race, n (%)								
African American/African Heritage	6 (21)	1 (11)	2 (25)	0	4 (13)	2 (7)	8 (28)	23 (16)
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Asian	0	0	1 (13)	0	0	0	0	0
Japanese/East Asian Heritage	0	0	1 (13)	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0	0	0
White	23 (79)	8 (89)	5 (63)	9 (100)	26 (87)	26 (93)	21 (72)	118 (83)
Ethnicity, n (%)								
Hispanic or Latino	4 (14)	4 (44)	1 (11)	2 (22)	4 (13)	2 (7)	5 (17)	22 (15)
Not Hispanic or Latino	25 (86)	5 (56)	8 (89)	7 (78)	26 (87)	26 (93)	24 (83)	121 (85)

NOTE: Subject 1360 (BCV/r 50, 300mg group) entered race as “Not Applicable”. Subject is a Mexican from Mexico, with brown skin – probably Indian heritage (Mayan?).

Primary Efficacy:

Statistical Results of Plasma HIV-1 RNA AAUCMBs (log_{10} copies/mL) at Week 16 in HPR20001 (ITT[E] Population – LACF Analysis)

	PI/r N=29	150mg BCV/r N=30	300mg BCV/r N=28	600mg BCV/r N=29
Adjusted mean AAUCMB (S.E.)	-0.493 (0.1776)	-1.008 (0.1700)	-1.157 (0.1708)	-1.623 (0.1665)
Difference adjusted mean AAUCMB vs. PI/r	NA[1]	-0.52	-0.66	-1.13
95% CI for treatment difference vs. PI/r	NA[1]	-0.9, -0.1	-1.1, -0.2	-1.6, -0.7
p-value for treatment difference vs. PI/r	NA[1]	.0199	.0035	<.0001

1. NA = Not Applicable

Safety:

The primary analysis of safety data in this report was the Day 1 Forward analysis (N=116), which included data collected for subjects randomized to PI/r, 150mg BCV/r, 300mg BCV/r, 600mg BCV/r from Day 1 Forward (excluding data for subjects randomized to 50mg BCV/r at Day 1).

Adverse Events (by Overall Frequency) Occurring in ≥ 4% of Subjects in HPR20001: Safety Population (Day 1 Forward)

All Adverse Events	PI/r N=29 n (%)	150mg BCV/r N=30 n (%)	300mg BCV/r N=28 n (%)	600mg BCV/r N=29 n (%)	Total N=116 n (%)
Number of Subjects Experiencing At Least One Adverse Event	24 (83)	18 (60)	23 (82)	23 (79)	88 (76)
Diarrhea	3 (10)	1 (3)	5 (18)	4 (14)	13 (11)
Fatigue	3 (10)	2 (7)	5 (18)	3 (10)	13 (11)
Upper respiratory tract infection	0	2 (7)	3 (11)	6 (21)	11 (9)
Nausea	3 (10)	3 (10)	1 (4)	3 (10)	10 (9)
Bronchitis	0	2 (7)	2 (7)	4 (14)	8 (7)
Asthenia	1 (3)	1 (3)	2 (7)	3 (10)	7 (6)
Arthralgia	0	1 (3)	3 (11)	2 (7)	6 (5)
Sinusitis	2 (7)	0	1 (4)	3 (10)	6 (5)
Blood triglycerides increased	3 (10)	0	0	2 (7)	5 (4)
Injection site reaction	0	1 (3)	2 (7)	2 (7)	5 (4)
Rash	1 (3)	1 (3)	1 (4)	2 (7)	5 (4)

Pharmacokinetic Results:

Day 15 Geometric Mean (95% CI, [CVb%]) BCV Parameters following repeat-dose (BID) administration of BCV/r (BCV serial PK Population)

BCV Parameter	50mg BCV/r (n=16)	150mg BCV/r (n=20)	300mg BCV/r (n=12)	600mg BCV/r (n=21)
AUC(0-τ) (ng.h/mL)	1039 (797, 1354) [53]	1598 (1307, 1954) [45]	1879 (1552, 2275) [31]	1946 (1351, 2804) [95]
Cmax (ng/mL)	139 (107, 180) [52]	209 (170, 256) [46]	263 (217, 319) [31]	260 (187, 362) [83]
Cτ* (ng/mL)	53.9 (38.5, 75.6) [70]	74.1 (57.2, 96.0) [60]	79.6 (59.5, 107) [48]	89.7 (54.9, 147) [148]

*Cτ=C12h post am dose

Pharmacokinetics/Pharmacodynamic Results:

Summary of Week 16 PD endpoints by quartile of BCV Average C0:Baseline IC50 ratio following repeat-dose administration of BCV/r BID

Week 16 PD Parameter	Quartile of Average C0:Baseline IC50 Ratio (IQ)			
	1 (0 to <196.1)	2 (196.1 to <532.5)	3 (532.5 to <1052)	4 (≥1052)
HIV-1 RNA change from Baseline Median (IQR)*	-0.21 (-1.83, 0.11)	-0.50 (-1.10, -0.05)	-0.92 (-2.60, -0.03)	-1.55 (-2.79, -1.30)
Proportion of subjects with >1 log_{10} copies/mL decrease in HIV-1 RNA	0.28	0.33	0.44	0.84
Proportion of subjects with <400 copies/mL in HIV-1 RNA	0.22	0.17	0.39	0.68
Proportion of subjects with <50 copies/mL in HIV-1 RNA	0.17	0.11	0.28	0.63

*Interquartile range

Viral Genotyping and Phenotyping:

The median number of Baseline PI and nRTI resistance-associated mutations, eleven and five respectively, was consistent with a highly ART-experienced population. The most prevalent major PI resistance-associated mutations (PI-RAMs) at Baseline in BCV/r treatment groups were M46I/L (total: 79/105, 75%), V82F/A/S/T/L (total: 66/105, 63%) and L90M (63/105, 60%). Additionally, the median FC to BCV (median FC: PI/r arm: 5.34-fold, IQR: 2.0 – 11 fold; combined BCV/r arms: 5.34-fold, IQR: 2.0-19 fold) was slightly higher than that to TPV (median PI/r arm: 3.23-fold, IQR: 1.0-4.5 fold; combined BCV/r arms: 3.01-fold, IQR: 1.4-7.6 fold), but lower than the other Pis tested. Also, 89% of subjects received sub-optimal background therapy at Baseline (≤1 active drug), and 72% continued to have sub-optimal background therapy after the Day 15 optimisation and introduction of T20.

There were few major PI-RAMs or gag-cleavage site mutations associated with reduced response at Week 16.

Summary of PI mutations with association with AAUCMB response after Week 16 relative to wild type (Last AAUCMB carried forward) for HPR20001: Major PI mutations

Mutation	AAUCMB (Week 16)				P value[1]
	PI/r N=26 n Mean (SE)	150mg BCV/r N=29 n Mean (SE)	300mg BCV/r N=27 n Mean (SE)	600mg BCV/r N=26 n Mean (SE)	
Total Population	26 -0.36 (0.132)	28 -0.93 (0.166)	27 -1.16 (0.186)	25 -1.63 (0.163)	N E[2]
Major PI resistance-associated mutations					
M46I	17 -0.35 (0.161)	14 -.50 (0.162)	12 -.92 (0.313)	14 -.49 (0.243)	0.017
I47V	2 -0.74 (0.576)	7 -0.47 (0.188)	5 -0.69 (0.431)	2 -1.09 (1.220)	0.043
Minor PI resistance-associated mutations					
L10F	2 0.14 (0.034)	7 -0.68 (0.296)	5 -0.82 (0.433)	8 -1.23 (0.309)	0.022
I54V	16 -0.27 (0.173)	15 -0.82 (0.204)	15 -1.06 (0.274)	17 -1.50 (0.189)	0.023
Q58E	8 -0.41 (0.269)	8 -0.27 (0.166)	7 -0.80 (0.478)	7 -1.44 (0.314)	0.022
G73T	3 0.06 (0.071)	2 -0.78 (0.188)	1 -1.21	3 -0.42 (0.216)	0.045
Other PRO mutations					
V11I	1 -0.13	2 -0.68 (0.794)	4 -0.70 (0.679)	6 -1.01 (0.348)	0.049
L19mut	6 -0.56 (0.358)	10 -1.19 (0.363)	4 -2.23 (0.316)	7 -1.63 (0.052)	0.030
K70mut	3 -0.16 (0.135)	1 0.04	3 -0.16 (0.159)	2 -0.64 (0.770)	0.010
gag cs mutations					
L449mut[3]	7 -0.58 (0.312)	1 -1.85	5 -0.41 (0.418)	3 -0.80 (0.419)	0.049

1. P-values at each mutation are from a test of the difference between all patients with the mutation and all patients with wild-type after adjusting for the effect of treatment in a linear model.
2. N.E.: not estimated.
3. mut' = non-wildtype or wildtype/mutant mixture, without a specific preferred amino acid change

In a multi-variate analysis, several factors had an effect on the primary end point, AAUCMB, relative to the PI/r arm and/or on the proportion of virologic responders (plasma HIV-1 RNA <400 copies/mL or ≥1 $\log_{10}$ copies/mL below Baseline).

Multivariate Linear Model for Plasma HIV-1 RNA AAUCMB (log_{10} copies/mL) and Plasma HIV-1 RNA <400 copies/mL or ≥ 1log_{10} copies/mL Below Baseline at Week 16 in HPR20001

Variable Level	n	Plasma HIV-1 RNA AAUCMB (log_{10} copies/mL)			Plasma HIV-1 RNA <400 copies/mL or ≥1 log_{10} copies/mL Below Baseline	
		Estimated Effect Size	95% CI Effect Size	P-value	Odds Ratio	P-value
150mg BCV/r	29	-0.75	[-1.293,-0.206]	0.007	2	0.431
300mg BCV/r	27	-0.82	[-1.351,-0.289]	0.002	1.6	0.577
600mg BCV/r	26	-1.274	[-1.814,-0.734]	<0.001	11	0.042
T20 Introduction	19	-0.316	[-0.709, 0.077]	0.115	1.6	0.455
Baseline viral load (per tenfold increase)	108	-0.062	[-0.241, 0.116]	0.494	0.6	0.085
PSS=1	30	-0.409	[-0.756,-0.063]	0.021	2.6	0.098
PSS ≥2	31	-0.356	[-0.729, 0.017]	0.062	2	0.285
FC (PI arm) per doubling	26	0.079	[-0.017, 0.174]	0.105	0.6	0.098
FC (BCV/r arm) per doubling	82	0.193	[0.117, 0.269]	<0.001	0.6	0.002

Note: treatment effects estimated simultaneously from a multivariate model for Week 16 plasma HIV-1 RNA AAUCMB.

While the number of any one individual major PI mutation selected on-therapy with BCV/r was low, most subjects receiving either 300mg BCV/r or 600mg BCV/r were found to select at least one major PI RAM. With mutations selected at eight of twelve major PI resistance-associated codons, it appears that a wide range of resistance patterns were available to the virus. This might be expected as the population was highly genotypically diverse at Baseline. The most frequent selections were found at residues 32 (5/42), 33 (5/42) and 84 (5/42). The residue at which a gag cs mutation arose the most frequently was P453L (6/35), which is situated at the p1/p6 cleavage site.

The greatest differential of median FC between Baseline and paired on-therapy phenotype was observed with the 600mg BCV/r arm (4.8 and 16.7-fold respectively), which might be expected as this dose provided the greatest selection pressure in terms of exposure to drug. However, the lower median Baseline FC in this arm compared

with the 150mg BCV/r and 300mg BCV/r arms (27 and 8.54-fold respectively) also needs to be considered. Finally, while broad cross-resistance was observed with other Pis at Baseline, there was a trend for higher proportions of subjects to have reduced susceptibility to other Pis after BCV/r therapy.

Conclusions:

At Week 16, all BCV/r doses had antiviral responses that were superior to control PI/r, and all of the tested regimens of BCV/r appeared to be generally safe and well tolerated.

While there was a trend for higher Baseline median FC in the virologic failure groups than in the response groups and in the subjects with non-response compared to those with virologic rebound, median Baseline IC50 and FC values (0.4nM and 5.34 respectively) indicated a high level of activity retained by BCV. There was a clear dose- and exposure-response of BCV/r as demonstrated by AAUCMB and IQ analyses, respectively, despite the less than proportional relationship between the dose and PK parameters (in general, there was <20% observed change in exposure for 2-fold increases in dose). However, the overall proportions of subjects achieving viral suppression were low with subjects having 2-4 multi-PI resistance-associated mutations at Baseline generally responding better than those with ≥5 mutations. This may be attributable to the amount of treatment experience of the study population, and/or to the suboptimal exposures of BCV achieved (40-50% lower in HPR20001 when compared to prior studies HPR10003 and HPR10006).

Several different PK analyses (including Monte Carlo simulations) suggest that BCV exposures would need to double for 50% of the target population to achieve IQ values ≥1000, which is the IQ level likely to be required for >80% of the population to achieve ≥1.0 $\log_{10}$ copies/mL decrease in HIV-1 RNA and for >60% of the population to achieve undetectable (either <400 or <50 copies/mL) plasma HIV-1 RNA at Week 16. Thus, many subjects with PI resistance and extensive prior antiretroviral therapy experience may not achieve optimal viral suppression with the studied doses of BCV/r, as delivered by the current formulations of BCV.

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