2. SYNOPSIS

Name of Company: Bristol Myers Squibb **Name of the Finished Product:** **Name of the Active Substance:** BMS 663068	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Study title	Randomized, Open Label, Multiple Dose Study to Evaluate the Pharmacodynamics, Safety and Pharmacokinetics of BMS 663068 in HIV 1 Infected Subjects	
Principal investigator	[redacted]	
Study center	[redacted]	
Number of subjects	**Planned:**	50 subjects, i.e., 5 groups of 10 subjects
	Analyzed:	50 subjects, i.e., 5 groups of 10 subjects
Study period	**Initiation:**	23 Nov 2009
	Completion:	25 Jun 2010
Clinical phase	IIa	
Indication	HIV infection	
EudraCT Number	2009 013657 14	
Publication (reference)	Nettles et al. Pharmacodynamics, Safety, and Pharmacokinetics of BMS 663068, a Potentially First in Class Oral HIV Attachment Inhibitor. CROI 2011 Boston, abstract J 126.	

Study Design:

This was a randomized, open label, multiple dose regimens, parallel group study. Subjects were randomized into one of 5 regimen groups:

Group 1 BMS 663068 600 mg every 12 hours (Q12H) + ritonavir (RTV) 100 mg Q12H;

Group 2 BMS 663068 1200 mg every night (QHS) + RTV 100 mg QHS;

Group 3 BMS 663068 1200 mg Q12H + RTV 100 mg Q12H;

Group 4 BMS 663068 1200 mg Q12H + RTV 100 mg every day before noon (QAM);

Group 5 BMS 663068 1200 mg Q12H.

Each regimen group consisted of 10 subjects. Subjects were randomized and stratified by prior antiretroviral treatment history (antiretroviral [ARV] naïve versus ARV experienced). ARV naïve is defined as no prior ARV therapy of ≥ 1 week. Each regimen group contained approximately the same distribution of ARV naïve and ARV experienced subjects. No more than 70% of the total population was to be ARV naïve or ARV experienced. All regimen groups could initiate dosing simultaneously.

All regimens were administered under fed conditions. Subjects in Group 2 (QHS or the once daily regimen group) received study drug every 24 hours in the evening from Day 1 to Day 8. Subjects in Group 4 (RTV QAM regimen group) received BMS 663068 every 12 hours and RTV every 24 hours in the morning (with BMS 663068) from Day 1 to Day 8. Subjects in Groups 1, 3 and 5 (Q12H regimen groups) received study drug every 12 hours from Day 1 to Day 8. Plasma human immunodeficiency virus (HIV) ribonucleic acid (RNA) levels were measured before study drug administration on the mornings of Day 1 to Day 8 in Groups 1, 3, 4 and 5 and pre PM drug administration in Group 2.

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Study Design, Continued

Electrocardiogram (ECG) and vital sign assessments were done at select times during the study. Blood and urine samples for clinical laboratory evaluations were collected at specified time points throughout the study. Serial blood samples for pharmacokinetic (PK) determinations were obtained on Days 1 and 8 to 11. Blood samples for trough concentrations were obtained on Days 5 through 7 prior to morning study drug administrations (prior to evening administration for QHS regimen group) for C_{trough} and steady state assessment. In addition, blood samples for protein binding assay were collected at specified timepoints throughout the study and selected regimen groups were analyzed.

Blood for CD4+ and CD8+ lymphocyte counts and percents and activated (DR+) CD4+ and CD8+ subsets, genotyping, phenotyping, HIV co receptor usage (CCR5 versus CXCR4), exploratory resistance analysis, measurement of neutralizing antibody activity were collected at specified timepoints throughout the study. Samples for genotyping, phenotyping, HIV co receptor usage, exploratory resistance analysis, activation markers, and exploratory apoptotic markers were stored, deemed relevant, and analyzed. Neutralizing antibody activity samples may be run if deemed relevant. Screening samples for population RT/Pol genotyping to confirm that all subjects are infected with clade B HIV were analyzed in all enrolled subjects. Day 1 predose samples for envelope phenotyping were collected and analyzed for all randomized subjects.

The following table summarizes the study design.

	Regimen Group 1 (N=10)	Regimen Group 2 (N=10)	Regimen Group 3 (N=10)	Regimen Group 4 (N=10)	Regimen Group 5 (N=10)
Dose and Regimen	600 mg BMS 663068 Q12H + 100 mg RTV Q12H	1200 mg BMS 663068 QHS + 100 mg RTV QHS	1200 mg BMS 663068 Q12H + 100 mg RTV Q12H	1200 mg BMS 663068 Q12H + 100 mg RTV QAM	1200 mg BMS 663068 Q12H
Days subjects receive BMS 663068	Day 1 8				
In patient days	Day 1 to Day 11				
Furlough from clinical unit	Day 11				
Out patient visits	Day 15 and Day 50 (+/ 3 days)				
Discharge from Study	Day 50 +/ 3 days				

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Objectives:

The primary objective of this study was to assess the antiviral activity of BMS 626529 following administration of selected regimens of BMS 663068 with and without RTV administered orally to HIV infected subjects for 8 days.

The secondary objectives were:

- To assess safety and tolerability of multiple regimens of BMS 663068 with and without RTV in HIV infected subjects;
- To assess the effect of BMS 626529 following multiple regimens of BMS 663068 on CD4+ and CD8+ lymphocyte counts and percents;
- To assess the pharmacokinetics of BMS 626529 following multiple regimens of BMS 663068 with and without RTV in HIV infected subjects;
- To assess the diurnal variation in the PK exposures of BMS 626529 following multiple regimens of BMS 663068 with and without RTV in HIV infected subjects;
- To assess the plasma protein binding for BMS 626529;
- To assess the relationships between change from baseline in $\log_{10}$ HIV RNA versus Inhibitory Quotient (IQ) and PK exposures for BMS 626529 following multiple regimens of BMS 663068 with and without RTV;
- To assess the PK of RTV when coadministered with various regimens of BMS 663068.

Main selection criteria:

HIV 1 infected subjects ≥ 18 years of age and a body mass index (BMI) of 18 35kg/m^2, with CD4+ lymphocyte count ≥ 200 cells/μL and with plasma HIV RNA ≥ 5000 copies/mL who had not been on ARV therapy for ≥ 8 weeks and who were either ARV experienced or ARV naïve (naïve defined as: no prior ARV therapy of ≥ 1 week), and who were otherwise medically stable as determined by medical history, physical examination, 12 lead ECG, and clinical laboratory evaluations were eligible to participate in the study. Females had to have a negative pregnancy test within 24 hours prior to start of study medication. Women of childbearing potential were not to be nursing or pregnant and had to be using an acceptable method of contraception.

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Test product, dose, mode of administration, batch numbers:

In 5 regimen groups (BMS 663068 600 mg Q12H + RTV 100 mg Q12H, BMS 663068 1200 mg QHS + RTV 100 mg QHS, BMS 663068 1200 mg Q12H + RTV 100 mg Q12H, BMS 663068 1200 mg Q12H + RTV 100 mg QAM, BMS 663068 1200 mg Q12H), each subject was administered RTV capsules and/or BMS 663068 extended release tablets orally on Days 1 8.

Batch numbers:

- BMS 663068: 9H42122
- RTV: 9G52898

Duration of treatment:

Subjects were in the study approximately 88 days. Study participation included a 35 day screening period and follow up visits. Subjects remained in the clinical facility from Day 1 through Day 11 receiving treatment on Days 1 8.

Criteria for evaluation:

Safety Outcome Measures:
Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed AEs was tabulated and reviewed for potential significance and clinical importance.

Pharmacokinetic Measures:
For each dosing regimen, PK parameters for BMS 626529 and RTV (C_{max}, C_{trough}, T_{max}, $C_{ss,avg}$, $AUC_{(TAU)}$, $AUC_{(0-24)}$, T Half, CLT/F, V_{ss}/F, and AI) were derived from plasma concentration versus time data. IQ for BMS 626529 was calculated. Plasma protein binding (%) for BMS 626529 was determined.

Pharmacodynamic Measures:
Pharmacodynamic (PD) assessment was based on change in HIV RNA. Additionally, CD4+ and CD8+ lymphocyte counts and percentages were assessed.

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Statistical Methods:

Sample Size Determination**:**

The sample size evaluation was based on the primary objective of the study, to assess the antiviral activity of BMS 626529 following administration of selected regimens of BMS 663068 with and without RTV administered orally to HIV infected subjects for 8 days. A mean decrease from baseline in HIV RNA of at least 1 $\log_{10}$ at Day 9 within any regimen group could suggest that that dose of BMS 663068 was sufficiently active against HIV to proceed with further development of the drug. If the BMS 663068 containing regimen had no effect, then administration of the regimen to 10 subjects (ARV naïve or experienced) could provide a ≤ 1% probability to observe a mean $\log_{10}$ drop of ≥ 1. If the true population mean decrease from baseline in HIV RNA was ≥ 1.5 $\log_{10}$, then there could be a 99% probability that the observed mean decline from baseline was ≥ 1 $\log_{10}$. In addition, 10 subjects within each group could also provide > 99% power to conclude the mean decreases in $\log_{10}$ HIV RNA from baseline > 0 if the true population decrease from that group was 1 $\log_{10}$. Meanwhile, 10 subjects in each group could also provide 82% power to conclude the mean decreases in $\log_{10}$ HIV RNA from 2 groups were different if the true difference in population mean decreases from these 2 groups were 0.6 $\log_{10}$.

In addition, administration of the BMS 663068 containing regimens to 10 subjects per group provided an 80% probability of observing at least one occurrence in that regimen group of any AE that would occur with 15% incidence in the population from which the sample was drawn.

For these calculations, it was assumed that the $\log_{10}$ decrease in HIV RNA from baseline to Day 9 was normally distributed, with a standard deviation of 0.5, as estimated from AI430003.

Statistical Analysis:

Although the final decision on the further evaluation of BMS 663068 was a broader scientific assessment of its benefit/risk profile, including consideration of safety and other endpoints as previously outlined, plus relevant information external to this trial, a mean decrease from baseline in HIV RNA of at least 1 $\log_{10}$ on Day 9 within any regimen group could suggest that that dose of BMS 663068 was sufficiently active against HIV.

The magnitude of the change in $\log_{10}$ HIV RNA levels was assessed by summarizing changes from baseline, including 90% confidence intervals, by study day, regimen group, antiretroviral treatment history (ARV naïve, ARV experienced, and combined [ARV naïve + ARV experienced]). The primary assessment of the antiviral activity of BMS 663068 containing regimens was based on the $\log_{10}$ change from baseline in HIV RNA to Day 9. To assess the dependency on dose, scatter plots of $\log_{10}$ change from baseline in HIV RNA at Day 9 versus dose was provided. An ANCOVA model correcting for baseline HIV viral load and treatment group was used to test the differences in mean $\log_{10}$ decrease in HIV RNA at Day 9 between 2 regimen groups by antiretroviral treatment history (ARV naïve, ARV experienced, and combined [ARV naïve + ARV experienced]). For the combined group (ARV naïve + ARV experienced) an additional ANCOVA was used correcting also for treatment history as an additional covariate. Each individual's maximum $\log_{10}$ decrease from baseline in HIV RNA was summarized by regimen group, antiretroviral treatment history (ARV naïve, ARV experienced, and combined [ARV naïve + ARV experienced]), and frequency distributions for maximum $\log_{10}$ decrease from baseline in HIV RNA was provided by regimen group, antiretroviral treatment history (ARV naïve, ARV experienced, and combined [ARV naïve + ARV experienced]).

All recorded AEs were listed and tabulated by system organ class, Medical Dictionary for Regulatory Activities (MedDRA) preferred term and summarized by regimen group. Vital signs and results from routine laboratory tests were listed and summarized by regimen group. Any significant physical exam findings and clinical laboratory results were listed. ECG readings were evaluated by the investigator and abnormalities, if present, were listed.

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Statistical Methods, Continued:

The multiple dose pharmacokinetics of BMS 626529 and RTV were described by summary statistics for the PK parameters by regimen group, study day, antiretroviral treatment history (ARV naïve, ARV experienced, and combined [ARV naïve + ARV experienced]). Point estimates and 90% confidence intervals were constructed for accumulation indices (ratio of day 8 vs. day 1 for $AUC_{(TAU)}$, C_{max} and C_{trough}) by regimen group. These estimates were generated using general linear models fitted to log transformed data. Similar analysis were also be used to assess the effect of RTV on PK exposure of BMS 626529 and diurnal variation for groups 1, 3, 4 and 5. To assess the dependency of BMS 626529 on dose, scatter plots of C_{max}, $AUC_{(TAU)}$, and C_{trough} versus dose was provided by day. Time to steady state was evaluated by summary statistics of C_{trough} and by plotting geometric mean C_{trough} versus study day.

Protein binding for BMS 626529 was evaluated by summary statistics and tabulated by regimen group.

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Results

Baseline characteristics – Subject disposition

	Group 1	Group 2	Group 3	Group 4	Group 5	Overall
No. of subjects entered (M/F)	9/1	9/1	9/1	10/0	10/0	47/3
Age: median (min max), years	44.5 (20 48)	38.0 (25 70)	43.0 (31 48)	40.0 (26 48)	41.5 (26 54)	42.0 (20 70)
ARV treatment naïve/experienced	7/3	7/3	7/3	6/4	7/3	34/16
log_{10}HIV 1 RNA viral load: median (min max), copies/mL	4.74 (4.034 5.173)	4.40 (3.771 4.854)	4.41 (3.297 5.317)	4.24 (3.776 6.066)	4.29 (3.540 5.324)	4.40 (3.297 6.066)
IC_{50}, median (min max), µM [a]	0.00056 (0.00006 0.10000)	0.00073 (0.00004 0.01150)	0.00026 (0.00002 0.00324)	0.00027 (0.00005 0.10000)	0.00992 (0.00002 0.10000)	0.00054 (0.00002 0.10000)
protein binding adjusted EC_{90}[b], median (min max), µg/mL	0.0126 (0.001 2.245)	0.0164 (0.001 0.258)	0.0059 (<0.001 0.073)	0.0061 (0.001 2.245)	0.2226 (<0.001 2.245)	0.0122 (<0.001 2.245)
Discontinuations reason:						
No longer met the study criteria	1	1	0	0	0	2
Analysis population:						
Safety	10	10	10	10	10	50
Pharmacodynamic	9	9	10	10	10	48
Pharmacokinetic	10	10	10	10	10	50

[a] The IC_{50} for subject's virus was > 0.1 µM for a total of 7 subjects:, 2 subjects in Group 1, 1 subject in Group 4 and 4 subjects in Group 5. In the analysis, a value of 0.1 µM was used for these subjects.

[b] : Derived from phenotypically measured individual IC_{50} values at baseline

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Pharmacodynamic results

HIV 1 Viral Load :

After an initial increase in plasma viral load (HIV RNA copies/mL) on Days 2 and 3, a mean decrease in log_{10} viral load from baseline was observed for all regimen groups during the treatment period and up to Day 15 (see Figure below).

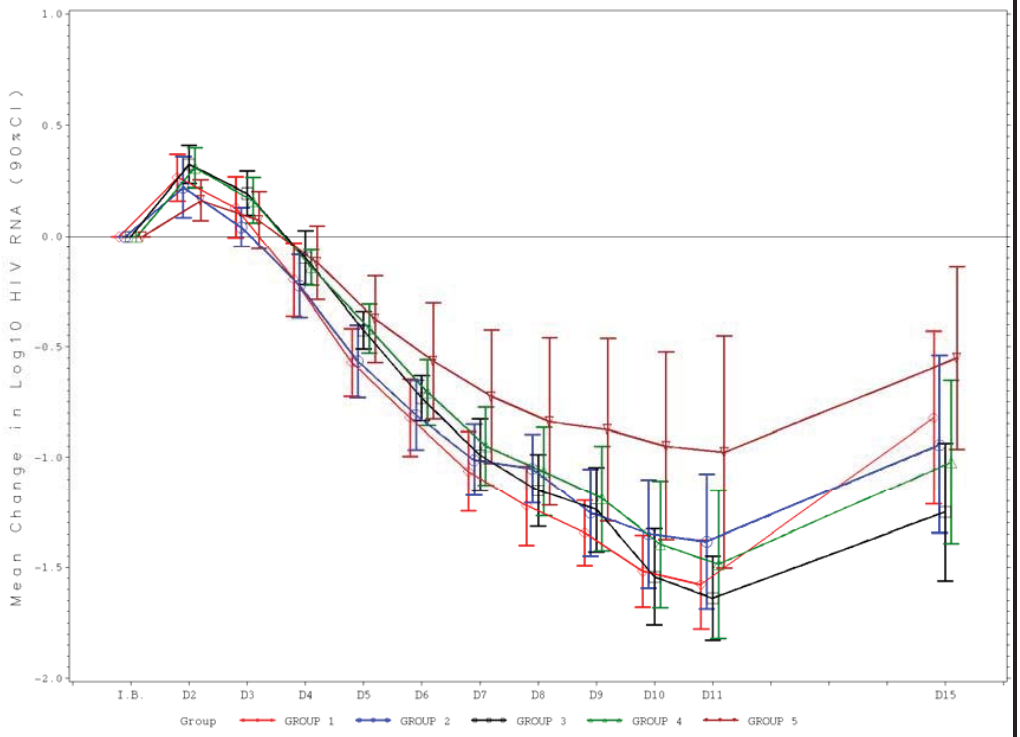

Figure: Mean Changes in Log_{10} Viral Load From Baseline

At Day 9 (the day after last intake), the mean changes from baseline in the different regimen groups were:

1.34 log_{10} copies/mL for Group 1 (BMS 663068/RTV 600/100 mg Q12H),
1.25 log_{10} copies/mL for Group 2 (BMS 663068/RTV 1200/100 mg QHS),
1.24 log_{10} copies/mL for Group 3 (BMS 663068/RTV 1200/100 mg Q12H),
1.19 log_{10} copies/mL for Group 4 (BMS 663068 1200 Q12H / RTV 100 mg QAM);
0.88 log_{10} copies/mL in Group 5 (BMS 663068 1200 mg Q12H).

These changes from baseline by Day 9 were statistically significant ($p<0.01$) for all 5 regimens. The smaller mean decrease in log_{10} copies/mL in Group 5 compared to the other regimen groups was likely due to the fact that 4 out of 10 subjects in Group 5 had a baseline IC_{50} of > 0.1µg/mL.

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The mean changes in viral load by Day 9 for the subgroup of subjects with a baseline $IC_{50} < 0.1$ µM were:

- 1.40 log_{10} copies/mL for Group 1 (BMS 663068/RTV 600/100 mg Q12H),
- 1.25 log_{10} copies/mL for Group 2 (BMS 663068/RTV 1200/100 mg QHS),
- 1.26 log_{10} copies/mL for Group 3 (BMS 663068/RTV 1200/100 mg Q12H),
- 1.29 log_{10} copies/mL for Group 4 (BMS 663068 1200 Q12H / RTV 100 mg QAM);
- 1.36 log_{10} copies/mL in Group 5 (BMS 663068 1200 mg Q12H).

For most subjects, the maximum change from baseline in plasma viral load was only observed at Day 10 to Day 15. The mean maximum change from baseline was > 1 log_{10} copies/mL in all regimen groups, including regimen Group 5.

The decrease in log_{10} HIV 1 viral load following intake of BMS 663068 with or without RTV was observed in both treatment naïve and treatment experienced subjects, with a mean change by Day 9 of > 1 log_{10} copies/mL in all regimen groups for both treatment naïve and treatment experienced subjects, except in the treatment naïve subjects in Group 5. Of the 4 subjects in Group 5 with a baseline IC_{50} of > 0.1 µM, 3 subjects were treatment naïve and 1 subject was treatment experienced.

CD4+ and CD8+ Cell Counts and Percentages:

Although some median increases from baseline in CD4+ and CD8+ cell counts were observed on Day 8. The range of median changes was +23 to +130 cells/µL for CD4+ cell counts and 33 to +388 cells/µL for CD8+ cells counts. The clinical relevance of these changes is unable to be definitively determined in this study due to the limited number of subjects and duration of treatment. There were no relevant differences between any of the regimen groups.

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PK results of BMS-626529 following multiple regimens of BMS-663068 with and without RTV

The multiple dose pharmacokinetics of BMS 626529 following administration of BMS 663068 with or without RTV showed, on Day 8, C_{max} and $AUC_{(TAU)}$ values twice higher in Groups 3 and 4 compared to Group 1, and about 30 % higher compared to Group 2 (once daily dosing) and Group 5 (BMS 663068 administrated without RTV). BMS 626529 C_{min} values were about 30 % higher in Groups 3 and 4 (respectively 0.772 and 0.613 µg/mL), compared to Groups 1 and 5 (respectively 0.411 and 0.524 µg/mL), and about 10 times higher compared to Group 2 (0.0545 µg/mL). The inter subject variability in the estimated C_{min} was relatively high (59 to 138 %).

At steady state, the same tendency was observed for C_{trough}, the highest values observed on Days 5 8 ranged from 0.743 to 0.998 µg/mL in Groups 3 and 4, compared with 0.436 to 0.628 µg/mL in Groups 1 and 5, and were 10 times higher compared to values in Group 2 (the once daily group). Steady state was achieved by study Day 5 for all regimen groups. No difference appeared between treatment naïve and treatment experienced subjects.

Summary of BMS-626529 PK Parameters

PK parameter	Group 1: BMS/RTV 600/100 mg Q12H	Group 2: BMS/RTV 1200/100 mg QHS	Group 3: BMS/RTV 1200/100 mg Q12H	Group 4: BMS/RTV 1200 mg Q12H/ 100 mg QAM	Group 5: BMS 1200 mg Q12H
Day 1					
	(N = 10)	**(N = 10)**	**(N = 10)**	**(N = 10)**	**(N = 10)**
C_{max} (µg/mL)	1.74 (59.9) [0.951 5.68]	3.85 (32.0) [2.16 6.47]	3.52 (26.6) [2.56 5.85]	4.05 (35.8) [2.40 6.32]	2.55 (27.4) [1.82 3.62]
C_{trough} (µg/mL)	0.349 (156) [0.0811 3.09]	0.699 (93.4) [0.235 2.32]	0.499 (83.4) [0.199 2.21]	0.640 (114) [0.192 3.45]	0.244 (78.3) [0.129 1.42]
$AUC_{(TAU)}$ (µg.h/mL)	9.16 (68.7) [4.15 27.8]	25.5 (38.0) [15.0 51.7]	18.3 (28.8) [12.7 27.3]	20.6 (45.0) [10.3 38.5]	13.8 (28.3) [9.37 20.7]
Day 5, 6, 7					
	(N = 9)	**(NA)**	**(N = 10)**	**(N = 10)**	**(N = 10)**
***C_{trough} Day 5 (µg/mL)**	0.473 (119) [0.0777 1.66]	0.0705 (114) [0.0174 0.280]	1.04 (72.2) [0.410 2.60]	0.760 (67.1) [0.285 1.71]	0.518 (48.2) [0.259 1.04]
***C_{trough} Day 6 (µg/mL)**	0.436 (89.5) [0.0966 1.22]	0.0743 (97.7) [0.0167 0.226]	0.839 (49.1) [0.341 1.30]	0.737 (73.2) [0.251 2.53]	0.451 (49.2) [0.177 0.860]
***C_{trough} Day 7 (µg/mL)**	0.495 (96.5) [0.181 2.07]	0.0719 (166) [0.00887 0.254]	1.08 (72.9) [0.413 3.11]	0.998 (91.8) [0.334 2.89]	0.542 (73.5) [0.232 1.41]
***C_{trough} Day 8 (µg/mL)**	0.460 (89.2) [0.175 1.56]	0.0546 (146) [0.0134 0.279]	0.743 (47.1) [0.289 1.27]	0.720 (83.5) [0.240 1.76]	0.628 (76.9) [0.218 1.87]
Day 8 (AM)					
	(N = 9)	**(NA)**	**(N = 10)**	**(N = 10)**	**(N = 10)**
C_{max} (µg/mL)	2.22 (67.1) [1.16 4.83]	NA	5.55 (37.5) [3.45 8.98]	5.10 (57.4) [2.29 11.9]	3.18 (22.0) [2.41 4.41]
C_{trough} (µg/mL)	0.422 (69.1) [0.173 0.822]	NA	0.951 (88.2) [0.277 2.70]	0.579 (71.5) [0.205 1.74]	0.469 (122) [0.113 2.14]
$AUC_{(TAU)}$ (µg h/mL)	13.1 (62.7) [6.98 26.9]	NA	29.9 (37.0) [16.1 45.0]	27.6 (48.4) [11.9 57.8]	19.5 (42.6) [31.1 55.6]
AI	1.53 (49.4) [0.707 3.82]	NA	1.63 (26.7) [1.19 3.04]	1.34 (25.4) [0.968 2.23]	1.42 (37.0) [0.947 3.11]

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Summary of BMS-626529 PK Parameters, Cont'd

Day 8 (PM)					
	(N = 9)	**(N = 9)**	**(N = 10)**	**(N = 10)**	**(N = 10)**
C_{max} (µg/mL)	2.25 (46.4) [1.04 3.80]	3.47 (31.7) [2.08 5.31]	4.60 (29.2) [2.82 6.50]	4.77 (36.2) [2.21 7.00]	3.61 (27.5) [2.11 5.33]
C_{trough} (µg/mL)	0.358 (102) [0.101 1.28]	0.0544 (156) [0.0108 0.241]	0.653 (109) [0.178 2.19]	0.553 (68.1) [0.200 1.90]	0.487 (47.5) [0.187 0.886]
$AUC_{(TAU)}$ (µg.h/mL)	13.1 (63.8) [5.04 28.0]	23.0 (48.2) [12.6 44.2]	30.6 (26.3) [18.6 44.1]	27.0 (45.2) [10.6 47.0]	22.5 (34.0) [13.8 34.6]
AI	NA	0.912 (27.1) [0.633 1.36]	NA	NA	NA
Day 8 (AM+PM)					
	(N = 9)	**(N = 9)**	**(N = 10)**	**(N = 10)**	**(N = 10)**
****C_{max} (µg/mL)**	2.24 (43.3) [1.30 4.08]	3.47 (31.7) [2.08 5.31]	5.05 (31.7) [3.12 7.30]	4.93 (40.1) [2.25 8.79]	3.39 (15.9) [2.38 4.06]
C_{min} (µg/mL)	0.411 (78.2) [0.170 1.08]	0.0545 (138) [0.0139 0.237]	0.772 (59.5) [0.386 1.69]	0.613 (65.9) [0.214 1.73]	0.524 (59.0) [0.217 1.25]
$AUC_{(0-24h)}$ (µg.h/mL)	26.8 (56.1) [12.3 54.9]	23.0 (48.2) [12.6 44.2]	60.6 (30.6) [34.7 87.2]	55.1 (44.3) [22.5 97.6]	42.6 (21.5) [31.1 55.6]

N = number of subjects
Values are geometric means (CV%) [minimum maximum]
*: prior to study drug administration on Days 5, 6, 7, 8
**: geometric mean value of AM and PM C_{max} for BID doses
C_{min}: geometric mean of predose, C12 after AM dose, and C12 after PM dose for BID doses, and geometric mean of predose and C24 for QD dose
AI: Accumulation Index; ratio of $AUC_{(TAU)}$ at steady state to $AUC_{(TAU)}$ after the first dose
NA: Not Applicable

On Day 8, the mean percent of BMS 626529 bound to plasma protein was 87.6 % at pre dose (evening dose) and 90.7 % 4 h post dose for Group 3, and 86.3 % (pre dose) and 88.9 % (4 h post dose) for Group 5. No statistically significant difference was found between the 2 groups (p value = 0.542). Therefore, the overall mean protein binding was used to calculate protein binding adjusted EC_{90} and IQ for each group, i.e., 88.4 %.

BMS 626529 accumulation was observed on Day 8 for all twice daily (Q12 h) groups, with a statistically significant increase by 30 to 60 % in plasma exposure ($AUC_{(TAU)}$) between Day 1 and Day 8 in Groups 1, 3, 4 and 5; no accumulation occurred in Group 2, the once daily regimen. A statistically significant accumulation was observed for C_{trough} on Day 8 only for Groups 1 and 5, probably because of the high variability observed for this PK parameter.

The co administration of RTV increased statistically significantly BMS 626529 C_{max} by 27 to 74 % and plasma exposure (AUCs) by 20 to 53 %, regardless the RTV dosages (Q12H or QAM). C_{min} increased by 17 (G4vsG5) to 48 % (G3vsG5).

No statistically significant diurnal PK variation (PM versus AM) was demonstrated on BMS 626529 pharmacokinetics.

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PK results of RTV when co-administered with various regimens of BMS-663068

The multiple dose pharmacokinetics of RTV when co administrated with various regimens of BMS 626529 showed, on Day 8, C_{max} values twice higher and AUCs values three times higher for BID groups (Groups 1 and 3) compared to QD doses (Groups 2 and 4). No marked difference among RTV exposure was observed between QAM and QHS administrations. The same tendency was observed for RTV C_{min} values that were four times higher in BID groups. The inter subject variability in the estimated C_{min} was relatively high (63.2 to 92.8 %).

At steady state, RTV C_{trough} values were the highest in twice daily (Q12H) groups (0.345 to 0.594 µg/mL) and about 6 times lower in QHS and QAM groups. Steady state was achieved by study Day 5 for all regimen groups. No difference appeared between treatment naïve and treatment experienced subjects.

A RTV accumulation was observed on Day 8 for all groups. The accumulation index (for $AUC_{(TAU)}$) ranged from 3.58 to 4.41 for BID doses and from 2.19 to 3.62 for QD doses.

Summary of RTV PK Parameters

PK parameter	Group 1: BMS/RTV 600/100 mg Q12H	Group 2: BMS/RTV 1200/100 mg QHS	Group 3: BMS/RTV 1200/100 mg Q12H	Group 4: BMS/RTV 1200 mg Q12H/ 100 mg QAM
Day 1				
	(N = 10)	**(N = 10)**	**(N = 10)**	**(N = 10)**
C_{max} (µg/mL)	0.330 (91.3) [0.134 1.83]	0.257 (53.8) [0.0997 0.419]	0.314 (111) [0.0531 0.883]	0.294 (59.6) [0.106 0.663]
C_{trough} (µg/mL)	0.117 (90.1) [0.0584 0.863]	0.157 (87.0) [0.0257 0.329]	0.131 (98.2) [0.0390 0.355]	NA
$AUC_{(TAU)}$ (µg.h/mL)	2.37 (99.5) [0.892 15.9]	2.91 (80.4) [0.533 5.85]	2.05 (104) [0.367 5.44]	NA
Day 5, 6, 7				
	(N = 9)	**(N =9)**	**(N = 10)**	**(N = 10)**
***C_{trough} Day 5 (µg/mL)**	0.502 (84.3) [0.264 3.13]	#0.107 (69.4) [BLOQ 0.228]	0.554 (73.9) [0.249 1.21]	0.0831 (77.8) [0.0387 0.247]
***C_{trough} Day 6 (µg/mL)**	0.526 (87.9) [0.242 3.27]	#0.0845 (67.7) [BLOQ 0.161]	0.594 (77.0) [0.215 1.21]	0.0820 (77.9) [0.0390 0.254]
***C_{trough} Day 7 (µg/mL)**	0.477 (93.5) [0.167 2.95]	#0.0844 (65.0) [BLOQ 0.158]	0.587 (76.3) [0.203 1.35]	0.0860 (79.9) [0.0357 0.248]
***C_{trough} Day 8 (µg/mL)**	0.470 (90.6) [0.240 2.71]	#0.0808 (73.2) [BLOQ 0.191]	0.503 (73.2) [0.207 1.23]	0.0891 (81.7) [0.0365 0.251]
Day 8 (AM)				
	(N = 9)	(NA)	**(N = 10)**	**(N = 10)**
C_{max} (µg/mL)	1.31 (101) [0.421 8.11]	NA	1.30 (58.3) [0.614 2.93]	0.841 (44.9) [0.410 1.50]
C_{trough} (µg/mL)	0.345 (105) [0.173 2.79]	NA	0.393 (66.3) [0.158 0.889]	0.0912 (70.5) [0.0405 0.244]
$AUC_{(TAU)}$ (µg.h/mL)	9.43 (89.1) [4.46 55.3]	NA	9.05 (62.8) [4.11 21.5]	6.76 (49.3) [3.12 13.7]
AI	3.58 (64.0) [1.16 11.5]	NA	4.41 (41.7) [3.11 11.9]	3.62 (39.8) [1.96 6.50]

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Summary of RTV PK Parameters, Cont'd

Day 8 (PM)				
	(N = 9)	**(N = 9)**	**(N = 10)**	(NA)
C_{max} (µg/mL)	1.24 (73.4) [1.04 3.80]	0.628 (56.4) [0.204 1.09]	1.48 (47.7) [0.790 3.58]	NA
C_{trough} (µg/mL)	0.453 (86.2) [0.225 2.41]	#0.0830 (71.7) [BLOQ 0.201]	0.476 (77.9) [0.142 1.10]	NA
$AUC_{(TAU)}$ (µg.h/mL)	9.23 (77.1) [3.44 42.6]	6.13 (94.3) [0.945 14.9]	10.4 (52.4) [4.70 21.9]	NA
AI	NA	2.19 (16.2) [1.75 2.76]	NA	NA
Day 8 (AM+PM)				
	(N = 9)	**(N = 9)**	**(N = 10)**	**(N = 10)**
****C_{max} (µg/mL)**	1.27 (80.0) [0.547 6.21]	0.628 (56.4) [0.204 1.09]	1.39 (50.7) [0.696 2.79]	0.841 (44.9) [0.410 1.50]
C_{min} (µg/mL)	0.419 (92.8) [0.223 2.63]	0.0790 (63.2) [0.0367 0.196]	0.455 (70.4) [0.169 1.03]	0.0902 (75.5) [0.0405 0.247]
$AUC_{(0\text{-}24h)}$ (µg.h/mL)	18.9 (80.0) [8.27 97.9]	6.13 (94.3) [0.945 14.9]	19.5 (56.6) [9.05 38.9]	6.76 (49.3) [3.12 13.7]

N = number of subjects
Values are geometric means (CV%) [minimum maximum]
#: arithmetic mean (CV%)
*: prior to study drug administration on Days 5, 6, 7, 8
**: geometric mean value of AM and PM C_{max} for BID doses
BLOQ: below the limit of quantification (< 0.01 µg/mL)
C_{min}: geometric mean of predose, C12 after AM dose, and C12 after PM dose for BID doses, and geometric mean of predose and C24 for QD dose
AI: Accumulation Index; ratio of $AUC_{(TAU)}$ at steady state to $AUC_{(TAU)}$ after the first dose
NA: Not Applicable

PK/PD Results

Groups 3 and 4 appeared to have IQ(C_{min}) and IQ($C_{ss,avg}$) values 10 times higher than the other groups (67.2 and 97.5 for IQ(C_{min}) and 252 and 327 for IQ($C_{ss,avg}$), respectively, in Groups 3 and 4). However, the difference in IQ results between groups should be interpreted with caution because not in the context of a formal PK/PD analysis, particularly since baseline susceptibility (IC_{50} values) is so variable.

No evidence of a correlation between changes in viral load from baseline (on Day 9 or the nadir) and the BMS 626529 I PK parameters was found. Log_{10} PBA EC_{90} and IQs of C_{min} and $C_{ss,avg}$ were found to correlate with antiviral activity.

Summary of BMS-626529 IQ[a] values Day 8 (AM+PM)

IQ parameter	Group 1: BMS/RTV 600/100 mg Q12H	Group 2: BMS/RTV 1200/100 mg QHS	Group 3: BMS/RTV 1200/100 mg Q12H	Group 4: BMS/RTV 1200 mg Q12H/ 100 mg QAM	Group 5: BMS 1200 mg Q12H
	(N = 9)	**(N = 9)**	**(N = 10)**	**(N = 10)**	**(N = 10)**
IQ (C_{min})	11.0 $^{N=8}$ (3510) [0.238 380]	3.86 (1070) [0.0655 47.3]	97.5 $^{N=9}$ (382) [5.43 1530]	67.2 (543) [0.519 469]	4.54 (21600) [0.151 2516]
IQ ($C_{ss,avg}$)	29.7 $^{N=8}$ (4040) [0.705 1205]	67.8 (902) [2.04 1453]	327 $^{N=9}$ (454) [19.9 6980]	252 (789) [1.27 2274]	15.4 (14900) [0.590 5433]

[a] inhibitory quotient, calculated as the ratio of BMS 626529 in vivo exposure to in vitro measured protein binding adjusted EC90

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Safety results

Adverse events:

	Group 1 N = 10	Group 2 N = 10	Group 3 N = 10	Group 4 N = 10	Group 5 N = 10	Overall N = 50
No. (%) with ≥ 1 AE(s)	8 (80.0)	5 (50.0)	9 (90.0)	8 (80.0)	9 (90.0)	39 (78.0)
No. (%) deaths	0	0	0	0	0	0
No. (%) with ≥ 1 serious AE(s)	0	0	0	0	0	0
No. (%) of treatment stopped due to AE(s)	0	0	0	0	0	0
No. (% of treatment related AEs	7 (70.0)	3 (30.0)	7 (70.0)	8 (80.0)	8 (80.0)	33 (66.0)
Incidence of AEs reported for at least 5 subjects						
Headache	4 (40.0)	3 (30.0)	4 (40.0)	3 (30.0)	4 (40.0)	18 (36.0)
Rash	2 (20.0)	1 (10.0)	2 (20.0)	1 (10.0)	2 (20.0)	8 (16.0)
Micturition urgency	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	3 (30.0)	7 (14.0)
Nasopharyngitis	1 (10.0)	0	3 (30.0)	2 (20.0)	0	6 (12.0)

The most frequent AEs (preferred terms) regardless of causality were headache, rash, micturition urgency, and nasopharyngitis. The events of nasopharyngitis were mostly reported during follow up and not considered related to the study medication by the investigator. The incidence of headache, rash and micturition urgency during the whole trial (including the treatment phase and follow up) was 36.0%, 16.0% and 14.0%, respectively. The incidence of headache, rash and micturition urgency during the treatment phase was 32.0%, 10.0% and 14.0%, respectively. Apart from the 2 subjects (4%) whose headache started during follow up, all these events of headache, rash and micturition urgency were considered related to the study treatment by the investigator. There were no relevant differences in the type or frequency of AEs in the 5 regimen groups.

Clinical laboratory parameters:

No clinically relevant trends or changes over time were apparent.

The most frequent observed treatment emergent abnormalities were below normal range neutrophils (absolute and %) and above normal range monocytes (%), C reactive protein, creatine kinase and total protein. Other abnormalities were observed in at most 10 subjects (20.0%). No relevant differences between the regimen groups were observed, although the incidence of neutrophils (absolute count) below normal range was higher in Group 5 (70.0%) than in the other regimen groups (range 20.0 to 40.0%). The overall incidence of neutrophils below normal was 38.8%.

Treatment emergent urinalysis abnormalities were rare in all regimen groups.

No AEs related to laboratory abnormalities were reported.

Other safety evaluations:

No clinically relevant effects on ECG, vital sign measurements or physical examinations were observed.

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Conclusions

- After an initial increase in plasma viral load (HIV RNA copies/mL) on Days 2 and 3, a mean decrease in $\log_{10}$ viral load from baseline was observed for all regimen groups during the treatment period and up to Day 15. These changes from baseline by Day 9 were statistically different from 0 ($p<0.01$) for all 5 regimens.
- Decreases in $\log_{10}$ HIV 1 RNA following intake of BMS 663068 was observed in both ARV treatment naïve and treatment experienced subjects.
- Exposure response analysis indicate that baseline sensitivity as measured by Env Phenotyping appears to be the most influential factor in determining the magnitude of decline in HIV RNA.
- When excluding the subjects with high baseline $IC_{50,}$ all cohorts achieved at least a ~ 1.5 $\log_{10}$ drop in mean maximal HIV RNA.
- Median increases from baseline in absolute CD4+ and CD8+ cell counts were observed on Day 8, with no relevant differences between any of the regimen groups. Although increases in absolute CD4+ and CD8+ counts were observed, the clinical relevance of these changes is unable to be definitively determined in this study due to the limited number of subjects and duration of treatment.
- None of the exploratory biomarkers have been measured at time of report writing. The analysis results of relevant biomarkers including the phenotype, tropism, activation marker, and apoptotic marker on selected time points will be reported separately.
- The BMS 663068 treatment regimens were generally safe and well tolerated with no clinically relevant differences between the regimens.
- The most frequent reported AEs were headache, rash, micturition urgency, and nasopharyngitis, with no relevant differences in incidence between the different regimen groups.
- There were no consistent, clinically relevant changes over time in laboratory, vital signs ECG parameters or physical examination. There were no relevant differences in incidence of abnormalities between regimen groups.
- Coadministration with RTV moderately increased BMS 626529 exposure; for BMS 663068 1200 mg Q12H groups, BMS 626529 C_{max}, AUCs and C_{min} were increased by 27 to 74 %, 42% and 48%, respectively, when coadministered with RTV 100 mg Q12H and 32 60%, 29% and 17% when coadministered with RTV 100 mg QHS or QAM.
- Following multiple Q12H doses, BMS 626529 accumulated to a modest extent ($AUC_{(TAU)}$ 34 to 63 %); there were no accumulation of BMS 626529 following QD doses.
- No apparent diurnal variation was observed in BMS 626529 pharmacokinetics exposures in all Q12H groups.
- No noticeable difference was apparent in BMS 626529 PK exposures between treatment naïve and treatment experienced subjects.
- Exposure response relationships indicate that baseline viral drug susceptibility (expressed as IC_{50}) appeared to be the most influential factor in determining the magnitude of decline in HIV RNA, Both IQ(C_{min}) and IQ($C_{ss,avg}$) are correlated with antiviral activity, whereas PK exposures alone were not predictive.

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