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# Clinical Protocol AI438006

Randomized, Open label, Multiple-Dose Study to Evaluate the Pharmacodynamics, Safety and Pharmacokinetics of BMS-663068 in HIV-1 Infected Subjects

**Revised Protocol Number: 03**

**Incorporates Amendment 04**

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

# DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Original Protocol | 22-Jun-2009 | Not applicable |
| Amendment 02 | 15-Oct-2009 | Incorporated Germany Competent Authority (BfArM) request the change the inclusion criteria of CD4+ counts from ≥100 cells/μL to ≥200 cells/μL.<br><br>This amendment also incorporates the Ethics Committee (EC) request to remove 'legally acceptable representative' from the standard protocol wordings in the Informed consent section; this exception to Global Standards has been granted. Also incorporated the EC request to include study stopping rules and clarify that subjects who are unwilling to practice adequate infection protection will be excluded from this study.<br><br>This amendment also clarifies the following: SAE reporting procedure and procedures to be performed for subjects who are prematurely discontinued from the study. Also, laboratory information regarding Troponin and creatinine clearance is updated. Updated statistician information. Removed requirement from synopsis section for WOCBP to be using acceptable method of contraception for at least 8 weeks before dosing. |
| Revised Protocol 01 | 15-Oct-2009 | Incorporates amendment 02 |
| Administrative Letter 01 | 01-Dec-2009 | Updated international emergency number |
| Amendment 03 | 25-Jan-2010 | Modify inclusion/exclusion criteria and clarify operational issues. Incorporate a secondary objective to characterize the pharmacokinetics of ritonavir. |
| Revised Protocol 02 | 25-Jan-2010 | Incorporates amendment 03 and administrative letter dated 01-Dec-2009 |
| Amendment 04 | 08-Mar-2010 | This amendment clarifies that interim analyses will be conducted. |
| Revised Protocol 03 | 08-Mar-2010 | Incorporates amendment 04 |

# SYNOPSIS

## Clinical Protocol AI438006

**Title of Study:** Protocol AI438006: Randomized, Open label, Multiple-Dose Study to Evaluate the Pharmacodynamics, Safety and Pharmacokinetics of BMS-663068 in HIV-1 Infected Subjects

**Indication:** HIV

**Estimated Number of Study Centers and Countries/Regions:** Approximately 6 centers in approximately 3 countries

**Study Phase:** IIA

**Research Hypothesis:** Administration of BMS-663068, a prodrug for BMS-626529, will result in a mean decrease of at least 1 $\log_{10}$ in HIV RNA at Day 9 following 8 days of therapy in at least one dosing regimen that is safe and well tolerated in Clade B HIV-1 infected subjects.

**Primary Objective:** To assess the antiviral activity of BMS-626529 following administration of selected regimens of BMS-663068 with and without Ritonavir (RTV) administered orally to HIV infected subjects for 8 days.

**Secondary Objective(s):**

- 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 PK of BMS-626529 following multiple regimens of BMS-663068 with and without RTV in HIV infected subjects
- To asses 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

**Exploratory Objective(s):**

- To explore the effect of BMS-626529 following multiple regimens of BMS-663068 with and without RTV on activated (DR+) CD4+ and CD8+ subsets
- To explore the effect of BMS-626529 following multiple regimens of BMS-663068 with and without RTV on neutralizing antibody activity

- To explore the effect of BMS-626529 following multiple regimens of BMS-663068 with and without RTV on HIV co-receptor usage (CCR5 versus CXCR4) and to explore the relationship between HIV co-receptor usage and antiviral activity
- To explore the difference in antiviral activity of BMS-626529 following multiple regimens of BMS-663068 with and without RTV by prior antiretroviral (ARV) treatment history (ARV naive versus ARV experienced)
- To explore the change in viral susceptibility measured by envelope genotype and phenotype

**Study Design:** This is a randomized, open label, multiple-dose regimens, parallel group study. Subjects will be randomized into one of 5 regimen groups:

- Group 1- BMS-663068 600 mg Q12H + RTV 100 mg Q12H;
- Group 2 - BMS-663068 1200 mg 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 QAM;
- Group 5 - BMS-663068 1200 mg Q12H.

Each regimen group will consist of 10 subjects. Subjects in each regimen will be randomized and stratified by prior antiretroviral treatment history (ARV naive versus ARV experienced). ARV naive is defined as no prior ARV therapy of ≥ 1 week. Each regimen group will contain approximately the same distribution of ARV naive and ARV experienced subjects. No more than 70% of the total population will be ARV naive or ARV experienced. All regimen groups may initiate dosing simultaneously.

All regimens will be administered under fed conditions. Subjects in Group 2 (QHS regimen group) will receive study drug every 24 hours in the evening from Day 1 to Day 8. Subjects in Group 4 (RTV QAM regimen group) will receive 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 group) will receive study drug every 12 hours from Day 1 to Day 8. Plasma HIV RNA levels will be 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.

ECG and vital sign assessments will be done at select times during the study. Blood and urine samples for clinical laboratory evaluations will be collected at specified time points throughout the study. Serial blood samples for pharmacokinetic determinations will be obtained on Days 1 and 8 to 11. Blood samples for trough concentrations will be obtained on Days 5 through 7 prior to morning study drug administrations (prior to evening administration for QHS regimen group) for Ctrough and steady-state assessment. In addition, blood samples for protein binding assay will be collected at specified timepoints throughout the study and selected regimen groups will be 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 will be collected at specified timepoints throughout the study. Samples for genotyping, phenotyping, HIV co-receptor usage, exploratory resistance analysis, activation markers, exploratory apoptotic markers and neutralizing antibody activity will generally be stored and analyzed if deemed relevant. Screening samples for population RT/Pol genotyping to confirm that all subjects are infected with clade B HIV will be analyzed in all enrolled subjects. Day 1 predose samples for envelope phenotyping will be collected and analyzed for all randomized subjects.

The following table summarizes the study design and study parameters.

| Study Design Table | | | | | |
|---|---|---|---|---|---|
| | 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 | | | | |

**Duration of Study:** Subjects will be in the study approximately 88 days. Study participation includes a 35-day screening period and follow-up visits. Subjects will remain in the clinical facility from Day -1 through Day 11.

**Number of Subjects:** 50

**Study Population:** HIV-1infected subjects ≥ 18 years of age and a BMI of 18 - 35kg/m2, with CD4+ lymphocyte count ≥ 200 cells/μL and with plasma HIV RNA ≥ 5000 copies/mL who have not been on ARV therapy for ≥ 8 weeks and who are either ARV experienced or ARV naive (naive defined as: no prior ARV therapy of ≥ 1 week), and who are otherwise medically stable as determined by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluations will be eligible to participate in the study. Females must have a negative pregnancy test within 24 hours prior to start of study medication. Women of childbearing potential must not be nursing or pregnant and must be using an acceptable method of contraception.

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):** 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 will be administered RTV capsules and/or BMS-663068 extended release tablets orally on Days 1-8.

**Study Assessments and Endpoints:**

- Safety Outcome Measures: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.
- Pharmacokinetic Measures: For each dosing regimen, pharmacokinetic parameters for BMS-626529 and RTV (Cmax, Ctrough, Tmax, Css,avg, AUC(TAU), AUC(0-24), T-HALF, CLT/F, Vss/F, and AI) will be derived from plasma concentration versus time data. IQ for BMS-626529 will be calculated. Plasma protein binding (%) for BMS-626529 will be determined.
- Pharmacodynamic Measures: Pharmacodynamic assessment will be based on change in HIV RNA. Additionally, CD4+ and CD8+ lymphocyte counts and percents will be assessed.
- Exploratory Measures: Activated (DR+) CD4+ and CD8+ subsets, changes in envelope genotypes and phenotypes, HIV co-receptor usage (CCR5 versus CXCR4), and measurement of neutralizing antibody activity will be assessed, if deemed relevant.

**Statistical Methods:**

**Sample Size Determination:** The sample size evaluation is 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 log10 at Day 9 within any one regimen group may suggest that that dose of BMS-663068 is sufficiently active against HIV to proceed with further development of the drug. If the BMS-663068 containing regimen has no effect, then administration of the regimen to 10 subjects (ARV naive or experienced) would provide a ≤1% probability to observe a mean log10 drop of ≥1. If the true population mean decrease from baseline in HIV RNA is ≥1.5 log10, then there would be a 99% probability that the observed mean decline from baseline would be ≥1 log10. In addition, 10 subjects within each group can also provide >99% power to conclude the mean decreases in log10 HIV RNA from baseline > 0 if the true population decrease from that group is 1 log10. Meanwhile, 10 subjects in each group can also provide 82% power to conclude the mean decreases in log10 HIV RNA from two groups are different if the true difference in population mean decreases from these two groups is 0.6 log10.

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

For these calculations, it is assumed that the $\log_{10}$ decrease in HIV RNA from baseline to Day 9 is 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 will be 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 log10 on Day 9 within any one regimen group may suggest that that dose of BMS-663068 is sufficiently active against HIV.

The magnitude of the change in log10 HIV RNA levels will be assessed by summarizing changes from baseline, including 90% confidence intervals, by study day, regimen group, antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]). The primary assessment of the antiviral activity of BMS-663068 containing regimens will be based on the log10 change from baseline in HIV RNA to Day 9. To assess the dependency on dose, scatter plots of log10 change from

baseline in HIV RNA at Day 9 versus dose will be provided. Two groups t-test will be used to test the differences in mean log10 decrease in HIV RNA at Day 9 between two regimen groups by antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]). Each individual's maximum log10 decrease from baseline in HIV RNA will be summarized by regimen group, antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]), and frequency distributions for maximum log10 decrease from baseline in HIV RNA will be provided by regimen group, antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]).

All recorded adverse events will be listed and tabulated by system organ class, MedDRA preferred term and summarized by regimen group. Vital signs and results from routine laboratory tests will be listed and summarized by regimen group. Any significant physical exam findings and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

The multiple-dose pharmacokinetics of BMS-626529 and RTV will be described by summary statistics for the pharmacokinetic parameters by regimen group, study day, antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]). Point estimates and 90% confidence intervals will be constructed for accumulation indices (ratio of day 8 vs. day 1 for AUC(TAU), Cmax and Ctrough) by regimen group. These estimates will be generated using general linear models fitted to log-transformed data. Similar analysis will also be used to access 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 Cmax, AUC(TAU), and Ctrough versus dose will be provided by day. Time to steady-state will be evaluated by summary statistics of Ctrough and by plotting geometric mean Ctrough versus study day.

Protein binding for BMS-626529 will be evaluated by summary statistics and tabulated by regimen group.

The effect of BMS-626529 following multiple regimens of BMS-663068 with and without RTV on PD measures (i.e., CD4+ and CD8+ T lymphocyte counts and percents and the corresponding changes in these parameters from baseline) will be assessed by summary statistics. Scatter plots will be used to assess the relationship between the changes from baseline in plasma HIV RNA and BMS-626529 protein biding adjusted EC90, a threshold of protein binding adjusted EC90 will be determined based on this scatter plot and summary statistics will be provided for the changes from baseline in plasma HIV RNA by regimen group, excluding subjects with protein binding adjusted EC90 above this threshold.

Scatter plots will also be used to assess the relationship between the changes from baseline in plasma HIV RNA and BMS-626529 IQs and to assess the correlation between $\log_{10}$ changes from baseline in HIV RNA and IQs. Summary statistics for exploratory biomarkers and corresponding changes from baseline, or percent changes from baseline as appropriate, will be tabulated by regimen group, study day and time point. Possible associations between changes in exploratory biomarkers of interest and BMS-6603068 dose or exposure will be explored graphically and by suitable statistical models, if appropriate. Some nonlinear models, such as but not limited to generalized least squares, will also be explored. Ad-hoc statistical analysis would be considered.

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# 1 INTRODUCTION AND STUDY RATIONALE

## 1.1 Research Hypothesis

Administration of BMS-663068, a prodrug for BMS-626529, will result in a mean decrease of at least 1 $\log_{10}$ in HIV RNA at Day 9 following 8 days of therapy in at least one dosing regimen that is safe and well tolerated in Clade B HIV-1 infected subjects.

## 1.2 Investigational Product Development Rationale

Infection with HIV-1 is recognized as being of pandemic proportions, with death from acquired immunodeficiency syndrome (AIDS) continuing to be a leading cause of death in adults between the ages of 25 and 44 in developed countries, and still more devastating in the developing world. Despite the availability of a number of different classes of antiretroviral agents providing a variety of treatment options, treatment failure continues to occur as a result of viral heterogeneity, drug-associated toxicity, and poor adherence with the emergence of drug-resistant strains. Transmission of antiretroviral resistant viruses in newly diagnosed HIV infections has been documented[1,2] and is expected to continue. New classes of antiretroviral drugs that are safe, tolerable and able to provide potent, durable antiviral activity with different mechanisms of action are needed.

BMS-663068 is a methyl phosphate prodrug of BMS-626529,[3,4] and represents one of a novel class of antiretroviral agents that blocks the first step of viral entry, namely the attachment of viral gp120 envelope to the cellular CD4 receptor. BMS-626529, the active moiety of BMS-663068, is efficacious against macrophage-, T-cell-, and dual tropic laboratory HIV-1 strains. By virtue of its novel mechanism of action, BMS-663068 is expected to have inhibitory activity against viral strains that exhibit resistance to other antiretroviral agents. Additionally, given its mechanistic and intrinsic properties, BMS-663068 will fill an unmet medical need and will be an important addition to the available antiretroviral armamentarium.

## 1.3 Summary of Results of Investigational Program

### 1.3.1 Virology

#### *1.3.1.1 BMS-663068*

In vitro data show that BMS-663068 itself has significantly less antiviral activity than BMS-626529, and that hydrolysis to the parent is required for potent fusion inhibition. Further information is provided in the Investigator Brochure for BMS-663068.[5]

#### *1.3.1.2 BMS-626529*

BMS-626529 is an attachment inhibitor that binds to the HIV-1 envelope glycoprotein gp120 and selectively inhibit the interaction between the virus and its host receptor CD4, thereby preventing the fusion of viral and cellular membranes.

In cell culture assays, BMS-626529 blocked the infection of eight of nine macrophage-, T-, and dual tropic laboratory strains of B subtype HIV-1 with $EC_{50}$ values ranging from 0.41 to 58 nM (the ninth strain had an $EC_{50}$ value of >2000 nM). It also exhibited potent antiviral activity against non-subtype B clinical isolates, with a median $EC_{50}$ of 2.8 nM. BMS-626529 was inactive against HIV-2 strain 287 and other RNA viruses. It did not affect the major HIV-1 enzymes, reverse transcriptase, protease, or integrase, and its activity was minimally affected (1.5 to 2.1 fold increase in $EC_{50}$) by the presence of 40% human serum. Cytotoxicity in cell culture was low, with $EC_{50}$ values ranging from 105 to > 200 μM in 13 cell lines examined. Finally, in a two-drug combination study in cell culture, BMS-626529 showed additive to synergistic interactions with 19 approved anti-HIV drugs. No antagonism of antiviral efficacy, or enhancement of cytotoxicity was seen with any of the two-drug combinations. Thus, BMS-626529 is a potent attachment inhibitor which merits further investigation for possible use in anti-HIV combination therapy.

### 1.3.2 Toxicology

Nonclinical toxicology studies in rats and dogs were conducted with both BMS-626529 (active moiety) and BMS-663068 (prodrug). *In vivo* exposures to BMS-626529 were generally higher following oral administration to rats and dogs of BMS-663068. There was no target organ toxicity following oral administration of BMS-626529 for 2 weeks in either rats or dogs. In a 2-week oral toxicity study of BMS-663068 in rats, the no-observed-adverse-effect-level (NOAEL) was ≤ 300 mg/kg/day (mean BMS-626529 AUC ≤ 1822 μg•h/mL) with only minimal clinical pathology perturbations and organ weight changes that lacked correlation with other parameters. In a 1-month oral toxicity study in rats at doses of 0, 100, 300 and 1000 mg/kg/day, drug-related effects at 300 and/or 1000 mg/kg/day (AUC ≥ 1860 μg•h/mL) included the following: increased kidney weights (5 to 23%); minimal glomerulopathy, that generally (although not directly in individual animals) correlated with an increased urine total protein output (1.35 to 1.48x); increased incidence of mammary gland hyperplasia in females and a shift in estrous cyclicity that correlated with decreased uterine weight (~30%) and an increased incidence of minimal to slight degeneration of seminiferous tubular epithelium. The NOAEL for the 1-month study was 100 mg/kg/day (Day 30 mean AUC ≤ 1510 μg•h/mL).

In a 2-week dog study of BMS-663068, mortality and severe toxicity occurred in dogs at the high dose of 300/200 mg/kg/day (mean BMS-626529 AUC ≥ 851 μg•hr/mL) and was characterized by persistent decreased physical activity, emesis, joint pain, anemia, increased fibrinogen, necrosis and inflammation of the adrenal gland, lymphoid depletion, and inflammatory lesions of the joints, heart, and meninges. BMS-663068 at 100 mg/kg/day (mean BMS- 626529 AUC 307 - 593 μg•hr/mL) was associated with transient decreases in physical activity, emesis and joint pain, but there were no microscopic correlates. BMS-663068 at 30 mg/kg/day (mean AUC ≤ 130 μg•h/mL) produced transient decreases in physical activity only, and was considered the NOAEL. A 1-month oral toxicity study in dogs was conducted at doses of 0, 50, 100, 150 and 200 mg/kg/day. Dogs that received ≥ 100 mg/kg/day (mean Day 29 AUC ≥ 477 μg•hr/mL) had prominent effects that included neurologic signs of toxicity, body-weight loss, increases in bilirubin, and cortical hemorrhage and coagulative necrosis of the adrenal gland. BMS-663068 was not tolerated at 200 mg/kg/day (mean Day 19/18 AUC ≥ 853 μg•h/mL) resulting in euthanasia of 1 dog on Day 15 and early termination of this dose

level on Days 19/20. BMS-663068 was not genotoxic in standard genetic toxicity assays. Administration of either BMS-663068 or BMS-626529 prolonged (~8 to 18 msec) the QT interval of telemetered dogs at plasma BMS-626529 concentrations ≥ 3.6 μg/mL but there was no drug-related effect on QT interval at plasma BMS-626529 concentrations ≤ 2.5 μg/mL.

BMS-663068 and BMS-626529 absorbed light in the 290 to 700 nm range. The definitive in vitro phototoxicity assay in Balb/C3Tc mouse fibroblasts indicated that BMS-626529 had no phototoxic potential (preliminary data from study DS09011).

BMS-663068 was administered to pregnant rats during the period of organogenesis at doses of 0, 100, 300, 600 and 1000 mg/kg/day.[6] BMS-663068 was well-tolerated at 100 mg/kg/day (AUC 1430 μg●h/mL). At ≥ 300 mg/kg/day, however, maternal toxicities were evident; and at 1000 mg/kg/day, developmental toxicities were also observed. Maternal toxicity included reductions in food consumption and group mean body weights, thinning hair or alopecia, and red perivaginal substance. Developmental toxicities consisted of fetal malformations (including cleft palate, microstomia and oral cleft) and variations as well as a reduction in mean fetal body weights. The definitive embryo-fetal development study in rats has not been performed and will be completed prior to the start of Phase 2B.

Further information is provided in the Investigator Brochure for BMS-663068.[5]

### 1.3.3 Preclinical Metabolism and Pharmacokinetics

BMS-663068 is the methyl phosphate prodrug of the active HIV attachment inhibitor, BMS-626529. A series of exploratory and definitive (GLP) *in vitro* and *in vivo* PK and metabolism studies were conducted in rats, dogs, and monkeys to provide a preliminary assessment of the absorption, distribution, metabolism, and elimination (ADME) of BMS-663068.[7]

BMS-663068 was hydrolyzed to form the active parent BMS-626529 in the presence of sera, hepatocytes, and human placental alkaline phosphatase (ALP). The conversion of BMS-663068 to BMS-626529 was near stoichiometric in the hepatocyte incubations, suggesting that non-hydrolytic metabolic pathways play minor roles for BMS-663068 in

the liver. BMS-626529 was rapidly formed following IV administration of BMS-663068 in rats, dogs and monkeys. The absolute oral bioavailability of BMS-626529 following oral administration of BMS-663068 was 80% in rats and essentially 100% in dogs and monkeys, with very little or no BMS-663068 detected in the plasma.

The results of two-week toxicokinetic studies in rats and dogs show that, following daily oral doses of BMS-663068, systemic exposure to BMS-663068 is minimal and that systemic exposure to BMS-626529 increases with dose in a less than dose-proportional manner, remains unchanged with repeated dosing, and is not substantially different for males and female.

#### *1.3.3.1 Absorption*

BMS-663068 exhibited low permeability in Caco-2 cells (Pc = 14-18 nm/sec) whereas BMS-626529 showed good Caco-2 permeability (Pc = 111 nm/sec).[8] No or very low levels of BMS-663068 were detected in rat, dog and monkey plasma after oral administration of BMS-663068. The absolute bioavailability of BMS-626529 following oral administration of BMS-663068 was greater than 80% in rats, dogs and monkeys. It is likely that following oral administration of BMS-663068, BMS-663068 was hydrolyzed to form BMS-626529 by ALP at the brush border membranes of the intestinal lumen, and BMS-626529 was readily absorbed due to its high permeability.

#### *1.3.3.2 Distribution*

The steady-state volume of distribution of BMS-663068 ranged from 0.21 to 0.51 L/kg in rats, dogs, and monkeys, indicating limited extravascular (tissue) distribution.[7] The percent of BMS-663068 bound to plasma protein was not determined due to instability of BMS-663068 in serum.[7] For BMS-626529, protein binding was 95.1% and 84.0% in rat and human sera, respectively.[8]

#### *1.3.3.3 Metabolism*

The prodrug BMS-663068 is hydrolyzed to BMS-626529, the active compound. The reaction appears to be catalyzed by hydrolytic enzymes, particularly ALP. The *in vitro* hydrolysis of BMS-663068 to BMS-626529 was evaluated in a variety of species using

liver microsomes and hepatocyte preparations. In mouse, rat, dog, monkey and human liver microsomes, the metabolic clearance of BMS-663068 was low, suggesting relatively low ALP activities in these microsomal preparations and an absence of oxidative metabolism of BMS-663068.

During comparative *in vitro* metabolism studies of BMS-626529 conducted in human, rat and chimpanzee liver microsomes, human, monkey and dog hepatocytes, and aroclor and non-aroclor-induced rat liver S9, 6 metabolites were identified as follows: a monooxygenated metabolite on the piperazine ring of BMS-626529 (M1), an *O*-demethylated and dehydrogenated metabolite of BMS-626529 (M2), debenzoylated BMS-626529 (M3), a dehydrogenated metabolite on the piperazine ring of BMS-626529 (M4), a monooxygenated metabolite on the azaindole ring system of BMS-626529 (M6) and a piperazine ring-opened metabolite of BMS-626529 (M7).[8] The extents of these pathways are unknown.

No direct *in vivo* metabolism studies of BMS-663068 were conducted, but *in vivo* biotransformation studies with BMS-626529 were conducted in rats, dogs, cynomolgus monkeys and chimpanzees.[8] In a bile duct-cannulated rat study, BMS-626529 was the predominant drug-related component in rat plasma with only trace amounts of M1, M4 and M7. In rat bile, metabolites M1, M6, M7 and M5 (mono-oxygenated metabolite on the azaindole ring system of BMS-626529) were identified, but BMS-626529 appeared to be the major drug-related component. No metabolites or BMS-626529 were identified in rat urine. In plasma from monkeys and dogs, BMS-626529 appeared to be the major drug-related component but M7 was also identified. In chimpanzee plasma, M1, M3, M4, M7 and BMS-626529 were identified. In chimpanzee urine, M1, M3, M7 and BMS-626529 were all identified. Preliminary data suggest the debenzoylated pathway (M3 metabolite) may be an important pathway in humans (preliminary data - subject to change).

#### *1.3.3.4 Elimination*

In dogs, mean recoveries of administered radiolabeled BMS-663068 through 168 h postdose were 64.44% in feces and 21.73% in urine.[9] Elimination $t_{1/2}$ in rats, dogs, and monkeys were all less than 0.5 hours for BMS-663068 and 3.2, 4.2, and 3.2 hours for

BMS-626529, respectively.[7] Based on the rapid appearance of BMS-626529 and lack of BMS-663068 in plasma following administration of BMS-663068, hydrolysis to BMS-626529 appears to be the major elimination pathway for BMS-663068 *in vivo*. Renal excretion is a minor pathway for BMS-626529 in chimpanzee.[8] In bile duct-cannulated (BDC) dogs, mean recoveries of the administered dose through 48 h postdose were 27.34% in bile, 22.71% in urine and 21.27% in feces. Preliminary data in BDC rats indicate that ~35% of the administered radioactivity was recovered in bile (collected up to 24 h) following an oral administration of $^{14}$C-BMS-663068.

### 1.3.4 Phase I Clinical Studies

The safety, tolerability, and PK of BMS-663068 were evaluated in a single ascending dose (SAD) study in healthy volunteers (AI438001), a GI site of absorption study (AI438002), a relative bioavailabilty study of 3 ER formulations (AI438003), a multiple ascending dose (MAD) study in healthy volunteers (AI438004) and an absorption, distribution, metabolism and elimination (ADME) study (AI438005). The results of AI438004 and AI438005 are preliminary and not yet reported in a clinical study report. Additionally, a previous study (AI434001) evaluated the clinical safety, tolerability, and PK of BMS-626529, the active moiety of BMS-663068. The development of BMS-626529 was suspended due to poor PK profiles. The safety and tolerability profiles from the above studies are summarized below.

PK results from the SAD study (AI438001) and preliminary results from the MAD study (AI438004) indicate that after oral doses the prodrug BMS-663068 was below the assay limit of quantitation (1 ng/mL) in the majority of subjects. In contrast, BMS-626529 was readily absorbed after an oral dose of BMS-663068 IR formulation and reached maximum concentration (Cmax) within 1 hour post dose in most subjects. When dosed with the slow-release ER tablet and under fed condition, Cmax can be reached within 4 hours post dose; administration with a standard meal had no effect on Cmax and AUC but increased C12 by about 148%. After a single dose, the increase in exposure to BMS-626529 was more than dose proportional over the range of 20 to 1000 mg of BMS-663068. Following multiple doses, steady state appears to have been achieved within 24 hours of dosing. Accumulation was modest; the average accumulation ratios based on AUC ranged from approximately 1.3 to 1.5 after 600 mg Q12h and 1200 mg Q12h +/-

RTV. Coadministration of 100 mg RTV with BMS-663068 1200 mg ER tablet Q12h significantly increased BMS-626529 Cmax, AUC and C12 by 64%, 2.1-fold and 4.1-fold, respectively; the apparent terminal half life was increased from 7 to 15 hours. Diurnal effect on BMS-626529 PK was observed after multiple doses. Compared to morning administration, evening dose of 1200 mg BMS-663068 ER resulted in approximately 43%, 46% and 99% higher BMS-626529 Cmax, AUC and Cmin, respectively. In the SAD study, less than ~5% of administered dose was eliminated as BMS-626529 in the urine, suggesting that renal excretion is not an important elimination pathway for unchanged BMS-626529.

For more information regarding clinical study results, please refer to the Investigator's Brochure.[5]

#### *1.3.4.1 BMS-663068 Single Ascending Dose Study in Healthy Subjects (AI438001)*

Eighty-eight (88) healthy subjects were enrolled, randomized, and dosed in Protocol AI438001. Single, oral doses of 20 to 1000 mg BMS-663068, including 200 mg BMS-663068 dosed with 100 mg ritonavir (RTV) were administered. There were no deaths or discontinuations due to adverse events (AEs). One (1) serious adverse event (SAE) was reported for a subject who received BMS-663068 20 mg. The subject was diagnosed with viral meningitis on Day 7. Overall, a total of 33 treatment-emergent AEs occurred in 20 of the 66 subjects (30.3%) who received BMS-663068 at any dose. A similar percentage of subjects who received placebo had treatment-emergent AEs (11 AEs, 7 of 22 subjects [31.8%]). The most frequently reported treatment-emergent AEs in subjects treated with BMS-663068 at any dose were nausea (7 subjects, 10.6%) and headache (6 subjects, 9.1%). No dose-related laboratory marked abnormalities (MA) trends were observed. There was no evidence that BMS-663068 had any clinically relevant effects on ECG parameters, systolic and diastolic blood pressures, heart rate, respiration, or body temperature. Although, the overall ECG data suggests no clinically relevant ECG effect, individual ΔQTcF values at Tmax versus the corresponding BMS-626529 Cmax suggests an increasing trend towards greater ΔQTcF with higher BMS-626529 concentration. Despite this trend, no subject had a QT interval ≥ 500 msec or had a QTcF ≥ 450 msec. Except for 1 subject that received 200 mg BMS-663068, no subject on any dose of BMS-663068 had a QTcF change from baseline > 60 msec. The finding of

QTcF > 60 msec was felt to be an artifact related to low T-wave amplitude after consultation with a BMS cardiologist.

#### *1.3.4.2 BMS-663068 Site of Absorption Study in Healthy Subjects (AI438002)*

The site-specific GI absorption and clinical safety of BMS-663068 and the active moiety BMS-626529 was evaluated in Protocol AI438002, an open-label, randomized, 4-period, 4-treatment crossover study. A total of 8 healthy males received 100 mg BMS-663068 in a clinical capsule or in an InteliSite® capsule for release of 100 mg BMS-663068 to the designated region of the GI tract (proximal small intestine, distal small intestine, and ileocecal/ascending colon) under fasted conditions. There were no deaths, no dose-limiting toxicities and no discontinuations due to AEs. Nine (9) AEs were reported in a total of 3 of 8 (38%) subjects. The most common AE was sore throat for which there were 3 events experienced by 2 subjects (25%, 2 of 8). All events of sore throat were considered unrelated to study drug. All other AEs were reported by 1 subject each (13%, 1 of 8). The data suggest that single doses of BMS-663068 had no clinically relevant effects on laboratory assessments, ECG, vital sign measurements or physical examinations.

#### *1.3.4.3 Bioavailability Study Assessing 3 Extending Release Formulations of BMS-663068 (AI438003)*

Protocol AI438003 was a 2-part study. Part I was an open-label, 4- or 3-way crossover study designed to assess the PK of BMS-663068 when administered in each of 3 ER formulations, relative to the immediate release (IR) formulation all under fasted conditions or each of the 3 ER formulations under fed conditions. Twenty-eight (28) subjects were enrolled, randomized, and received at least 1 dose of study drug in Part I. In addition, there was a second part to the study where subjects received either the slow or intermediate ER formulations at single doses of 1200 mg, 1800 mg, and 600 mg plus RTV with a standard meal. Twenty-eight (28) subjects were enrolled in Part 2 and received at least 1 dose of the study drug. There were no deaths or dose-limiting toxicities. There was 1 SAE reported (Mobitz type I second degree atrioventricular (AV) block) following administration of Slow ER 1800 mg BMS-663068 fed considered by the Investigator to be possibly related to study treatment. A total of 55 treatment-emergent

AEs occurred in 29 of the 56 subjects (51.8%) who received BMS-663068 at any dose. The most frequently reported treatment-emergent AEs in subjects treated with BMS 663068 were headache (18 events in 16 subjects, 28.6%) and nausea (5 events in 5 subjects, 8.9%). There were no clinically relevant trends in changes in laboratory parameters or vital signs and no trends in physical examination findings. Though the study was not designed to assess time matched changes in ECG parameters, the overall ECG data suggests no clinically relevant effect including no trend in individual ΔQTcF values at Tmax versus the corresponding BMS-626529 Cmax. Overall, BMS-663068 ER formulations were generally safe and well tolerated when given as single oral doses to healthy subjects.

#### *1.3.4.4 BMS-663068 Multiple Ascending Dose Study in Healthy Subjects (AI438004)*

Forty (40) healthy subjects were enrolled in Protocol AI438004. Ten days of oral doses of 100 and 200 mg IR Q8H and 600 mg + RTV, 1200 mg, and 1200 mg +RTV Q12H were to be administered to 30 subjects and 10 subjects received placebo. The results of this study are preliminary and have not been reported in a CSR. There were no deaths. One subject discontinued dosing due to an AE of rash. Rash and pruritis were common AEs when coadministered with RTV, generally occurring in a similar percentage of BMS-663068 + RTV versus placebo + RTV-recipients. A complete list of AEs is provided in the IB[5]. All laboratory abnormalities were considered not clinically relevant. The data suggest that multiple doses of BMS-663068 had no clinically relevant effects on laboratory assessments, ECG, vital sign measurements or physical examinations. Overall, 10 days of dosing with BMS-663068 IR and ER formulations with and without RTV were generally safe and well tolerated when given to healthy subjects.

#### *1.3.4.5 BMS-663068 ADME study in Healthy Subjects (AI438005)*

This is a non-randomized, open-label, single dose study in healthy male subjects to assess the pharmacokinetic and metabolism of [$^{14}$C]-labeled BMS-663068 administered with and without RTV. A total of 18 healthy male subjects were enrolled into the study. Subjects received a single oral dose of 300 mg of [$^{14}$C] BMS-663068 containing 100 μCi of total radioactivity administered without or with a RTV lead-in period. The results of this study are preliminary and have not been reported in a CSR. Adverse events reported

in greater than 10% of subjects were flatulence (7 of 18 subjects, 39%) and headache (2 of 18, 11%). No other AE occurred in more than 1 subject. The data suggest that single doses of [$^{14}$C]-labeled BMS-663068 had no clinically relevant effects on laboratory assessments, ECG, vital sign measurements or physical examinations. Overall, single doses of [$^{14}$C]-labeled BMS-663068 administered with and without RTV were generally safe and well tolerated when given to healthy subjects.

#### *1.3.4.6 BMS-626529 Single Ascending Dose Study in Healthy Subjects (AI434001)*

The active moiety, BMS-626529, was also evaluated in a Phase 1 SAD study in healthy subjects. Eighty-eight (88) healthy subjects were enrolled in Protocol AI434001. Single, oral doses of 25 to 1800 mg of BMS-626529 were administered to 66 subjects and 22 subjects received placebo. There were no SAEs, deaths, or discontinuations due to AEs. Overall, 16 AEs were reported for 11 of 88 (13%) subjects: 7 (11%) BMS-626529 and 4 (18%) placebo. The most frequent AEs were CK elevation and myalgia (2 subjects each). The CK elevations were severe and very severe and were reported by 1 subject who received placebo (unresolved at study closure) and 1 who received BMS-626529 50-mg capsule (resolved 8 days later). Similarly, the AEs of myalgia (both mild) were reported by 1 placebo recipient and 1 subject who received BMS-626529 50-mg capsule; neither had CK elevations. All other AEs were reported by 1 (1%) subject each. The incidence of AEs did not appear dose related. Data suggest that BMS-626529 had no clinically relevant effect on laboratory measures, vital sign measurements, physical examinations, or ECGs. Overall, BMS-626529 appeared to be safe and well tolerated when given as single oral doses to healthy subjects.

### 1.3.5 Ritonavir (Norvir®)

Ritonavir (RTV) is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor which leads to production of non-infectious immature HIV particles. The PK of RTV have been studied in healthy subjects and HIV-infected patients. After a 600 mg dose of oral solution, peak concentrations of RTV were achieved approximately 2 hours and 4 hours after dosing under fasting and non-fasting conditions, respectively. *In vitro* studies utilizing human liver microsomes have demonstrated that

CYP3A is the major isoform involved in RTV metabolism, although CYP2D6 also contributes. Ritonavir inhibits CYP3A *in vitro* and *in vivo*. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (>3-fold) when co-administered with RTV. RTV also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with RTV could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. RTV also appears to induce CYP3A as well as other enzymes, including glucuronosyl transferase, CYP1A2, and possibly CYP2C9. RTV is rarely used at the original therapeutic dose of 600 mg administered b.i.d. because of the high incidence of a variety of side effects. The fact that RTV is a potent inhibitor of cytochrome P450-based metabolism has been employed to increase the exposure of other co-administered HIV protease inhibitors which are better tolerated.[10,11] Ritonavir achieves its metabolic inhibition at doses, which are much lower than therapeutic, for example 100 mg QD when combined with atazanavir will boost the AUCs of atazanavir.[12] The most frequent clinical and laboratory AEs reported in subjects receiving RTV as monotherapy or in combination with nucleoside analogues include asthenia, nausea, vomiting, abdominal pain, diarrhea, anorexia, taste perversion, circumoral paresthesia, peripheral neuropathy, dizziness and insomnia. Laboratory abnormalities reported with the use of RTV are elevations in hepatic transaminase levels, nonfasting triglyceride, cholesterol, creatine phosphokinase, and uric acid. It has been reported, in rare cases, post marketing, hepatic dysfunction including some fatalities generally occurred in subjects taking RTV 600 mg BID and multiple concomitant medication in patients suffering from advanced HIV disease. The frequency of adverse events following administration of low-dose RTV is not well known, as it would not be administered alone, in such low doses. However, it is expected that the incidence of AEs would be reduced at low doses. Additional information on Norvir® can be found in the package insert.[13]

## 1.4 Study Rationale

This study is being conducted to assess the antiviral activity, safety, tolerability and PK of selected regimens of BMS-663068 with and without RTV in HIV-1 infected subjects. BMS-663068 is a methyl phosphate prodrug of BMS-626529,[3,4] and represents one of a

novel class of antiretroviral agents that blocks the first step of viral entry, namely the attachment of viral gp120 envelope to the cellular CD4 receptor. Proof of concept was achieved with a prior HIV attachment inhibitor, BMS-488043, in Protocol AI430003.[14] BMS-488043 at doses of 800 and 1800 mg produced viral load decline of greater than 0.7 log10 copies/mL from baseline on Day 8, thereby providing confidence that the compound has antiviral activity in HIV infected subjects. BMS-488043 was safe and well tolerated; however, a high fat meal were required to achieve adequate exposure. Therefore, development of BMS-488043 was halted. The current formulation of BMS-663068 has improved PK properties and BMS-626529 has an ~ 16 fold slower off rate; thus, BMS-663068 should produce antiviral effects at least as good as BMS-448043 without the undesirable dosing requirements.

BMS-626529, the active moiety of BMS-663068, is efficacious against macrophage-, T-cell-, and dual tropic laboratory HIV-1 strains. Given the in vitro sensitivity of BMS-626529, it is anticipated that BMS-663068 will be most effective at inhibiting entry of clade B HIV-1; therefore, this study will restrict enrollment to subjects infected by HIV-1 clade B. Clade B HIV is a frequent encountered clade in many parts of the world, including North /Central/South America and Europe.

In study AI430003, antiviral effect of BMS-488043 was greater in treatment naive patients compared to treatment experienced patients. Viral susceptibility and exposure to the study drug, especially Cmin values, were lower in treatment experienced patients compared to treatment naive patients. This was an unexpected finding without a clear explanation; therefore, the current study will be stratified to assess the antiviral activity of BMS-626529 in antiretroviral naive versus experienced subjects to reassess the prior finding.

The current study will employ an 8 day dosing duration which is fairly standard for novel HIV therapeutics, is the same dosing duration used in the AI430003 study and generally allows adequate assessment of antiviral activity without an unreasonable amount of risk that viral resistance to BMS-663068 will occur. The 8 day dosing duration is also supported by a completed 10 day study in healthy volunteers, AI438004.

The twice daily doses of BMS-663068 in the current study were selected because they are anticipated to provide Cmin BMS-626529 concentrations above the majority of HIV

protein binding adjusted $EC_{90}$. Most groups will coadminister RTV, which has been shown to improve BMS-626529 exposures in humans. A once daily regimen group has been selected to better define the PK parameter (Cmin versus AUC) most important to antiviral effect.

Pharmacodynamic parameters and endpoints (HIV RNA, CD4+ and CD8+ lymphocyte counts and percents, viral susceptibility measured by phenotype) have been selected to optimize the doses of BMS-663068 which will move into later phase development. Exploratory biomarkers (activated (DR+) CD4+ and CD8+ subsets, neutralizing antibody activity and HIV co-receptor) usage have been included to fully characterize the potential for BMS-663068 as a therapeutic.

## 1.5 Overall Risk/Benefit Assessment

Since this is not a treatment study, there is no direct benefit to the subjects participating in this study other than contributing to the research of a product. The antiviral effect anticipated to be observed in this study are likely to be transient and of no clinical benefit. Resistance may develop to HIV attachment inhibitors or HIV protease inhibitors, and this resistance may result in lifelong loss in ability to use these classes of medication for treatment benefit. Subjects should not delay or defer use of HAART regimens specifically to allow participation in this trial.

### 1.5.1 BMS-663068

The preclinical and clinical safety profile of BMS-663068 and BMS-626529 are described in this protocol in section 1.3.3 and 1.3.4 and in the BMS-663068 IB. In general, BMS-663068 and BMS-626529 have been well tolerated with no clinically relevant impact on laboratory assessments, ECGs, vital signs or physical examinations. High exposures associated with the immediate formulation were associated with nausea. In most studies, the most frequent AE was headache, which generally occurred in a similar percentage of BMS-663068- versus placebo-recipients. Rash and pruritis were a common AE when coadministered with RTV, generally occurring in a similar percentage of BMS-663068 + RTV- versus placebo + RTV-recipients. Details on exposure margin relative to NOAEL from toxicology studies are also outlined in the BMS-663068 IB.[5]

There is a risk of increased Cmax and possible drug toxicity (nausea or vomiting) associated with chewing or breaking the tablets.

BMS-663068 was administered to pregnant rats during the period of organogenesis at doses of 0, 100, 300, 600 and 1000 mg/kg/day. [15] BMS-663068 was well-tolerated at 100 mg/kg/day. At ≥ 300 mg/kg/day, however, maternal toxicities were evident; and at 1000 mg/kg/day, developmental toxicities were also observed. Maternal toxicity included reductions in food consumption and group mean body weights, thinning hair or alopecia, and red perivaginal substance. Developmental toxicities consisted of fetal malformations (including cleft palate, microstomia and oral cleft) and variations as well as a reduction in mean fetal body weights. The definitive embryo-fetal development study in rats has not been performed and will be completed prior to the start of Phase 2B.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy for 8 weeks prior to dosing, throughout the study, and for 12 weeks after the study in such a manner that the risk of pregnancy is minimized. Women will undergo frequent pregnancy tests and will remain as inpatients during dosing. Women who are pregnant or breastfeeding are excluded. Sexually active fertile men not using effective birth control if their partners are WOCBP will also be excluded.

BMS-663068 is hydrolyzed to the active form (BMS-626529) through the action of intestinal alkaline phosphatase with the concomitant liberation of an equimolar amount of formaldehyde. The amount of formaldehyde estimated to be released at the highest dosage of BMS-663068 is still about 7-fold below the established NOAEL dosage of formaldehyde of 15 mg/kg/day in a 2-year bioassay.[16,17] Therefore based on the data, there is little potential for formaldehyde-related toxicities from exposure to BMS-663068, and if there were any potential toxicity due to formaldehyde exposure, it would be irritation to the gastrointestinal tract directly exposed to the tablets. Due to the potential for toxicities associated with formaldehyde exposure the following safeguards are being implemented in this protocol: subjects will be informed in the consent of the possible risk of gastrointestinal tract irritation, individuals with recent gastrointestinal conditions that would increase the likelihood of clinically relevant gastrointestinal irritation or bleeding will be excluded, concomitant use if medications associated with gastrointestinal tract irritation will be excluded, and stopping rules related to new onset of signs or symptoms

associated with severe gastrointestinal irritation or gastrointestinal tract bleeding will be defined.

### 1.5.2 Ritonavir

The most frequent clinical and laboratory adverse events reported in subjects who received RTV as monotherapy or in combination with nucleoside analogues include asthenia, nausea, vomiting, abdominal pain, and diarrhea.[13] Laboratory abnormalities reported with the use of RTV include elevations in hepatic transaminase levels, nonfasting triglyceride, cholesterol, creatine phosphokinase, and uric acid. The frequency of adverse events following administration of low dose RTV (100 mg QD) is not well known. However, it is expected that the incidence of adverse events with this low dose would be reduced. Subjects in the current study will be monitored for all adverse events and clinical laboratory abnormalities.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is 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.

## 2.2 Secondary Objectives

Secondary objective(s):

- 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 PK 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

## 2.3 Exploratory Objectives

- To explore the effect of BMS-626529 following multiple regimens of BMS-663068 with and without RTV on activated (DR+) CD4+ and CD8+ subsets
- To explore the effect of BMS-626529 following multiple regimens of BMS-663068 with and without RTV on neutralizing antibody activity
- To explore the effect of BMS-626529 following multiple regimens of BMS-663068 with and without RTV on HIV co-receptor usage (CCR5 versus CXCR4) and to explore the relationship between HIV co-receptor usage and antiviral activity
- To explore the difference in antiviral activity of BMS-626529 following multiple regimens of BMS-663068 with and without RTV by prior antiretroviral (ARV) treatment history (ARV naive versus ARV experienced)
- To explore the change in viral susceptibility measured by envelope genotype and phenotype

# 3 ETHICAL CONSIDERATIONS

## 3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

## 3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

## 3.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

Appendix 1 contains BMS procedures on obtaining informed consent from all subjects, prior to participating in a clinical study. The relevant procedures must be used whenever they are applicable (see subject selection criteria in Sections 4.2.1 and 4.2.2).

Informed consent given by legally acceptable representatives or witnesses is **not** permitted in this study.

# 4 INVESTIGATIONAL PLAN

## 4.1 Study Design and Duration

This is a randomized, open label, multiple-dose parallel study. Subjects will undergo screening evaluations to determine eligibility within 35 days prior to study enrollment. Subjects will be admitted to the clinical facility the evening prior to dosing (Day -1). Subjects will be randomized into one of 5 regimen groups: Group 1 - BMS-663068 600 mg Q12H + RTV 100 mg Q12H; Group 2 - BMS-663068 1200 mg 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 QAM; Group 5 - BMS-663068 1200 mg Q12H.

Each regimen group will consist of 10 subjects. Subjects in each regimen will be randomized and stratified by prior antiretroviral treatment history (ARV naive versus ARV experienced). ARV naive is defined as; no prior ARV therapy of ≥ 1 week. Each regimen group will contain approximately the same distribution of ARV naive and ARV experienced subjects. No more than 70% of the total population (or within each regimen group) will be ARV naive or ARV experienced. All regimen groups may initiate dosing simultaneously. Subjects will be confined to the clinical facility until Day 11. Subjects will return to the unit on Day 15 for a follow-up visit and on Day 50 for discharge procedures. Subjects may have a ± 3 day window around the discharge visit day (Day 50). Safety assessments consisting of ECGs, vital signs, physical exams and clinical laboratory tests will be conducted at screening and at selected time points throughout the study.

All doses will be administered under fed conditions. Subjects in Group 2 (QHS regimen group) will receive study drug every 24 hours in the evening (PM) from Day 1 to Day 8. Subjects in Group 4 (RTV QAM regimen group) will receive 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 group) will receive study drug every 12 hours from Day 1 to Day 8.

Plasma HIV RNA levels will be measured pre-AM 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. On days when dose is not administered, sample collection time should be maintained. Serial blood samples for pharmacokinetic determinations will be obtained on Days 1 and 8-11. Blood samples for trough concentrations will be obtained on Days 5 through 7 prior to morning study drug administrations (prior to evening administration for Group 2, QHS regimen group) for Ctrough and steady-state assessment. In addition, blood samples for protein binding assay will be collected at specified timepoints throughout the study and selected regimen groups will be 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 will be collected at specified timepoints throughout the study. These samples may be analyzed if deemed relevant. Screening samples for population RT/Pol genotyping to confirm that all subjects are infected with clade B HIV will be analyzed in all enrolled subjects. Day 1 predose samples for envelope phenotyping will be collected and analyzed for all randomized subjects.

Approximately 800 mL of blood will be drawn from each subject during the study.

The approximate duration of the study is 88 days. Study participation includes a 35-day screening period, 8-day treatment and 2 follow-up visits.

End of the study will be the date of the last visit of the last subject undergoing the study. Last visit will be the last follow-up visit of a subject.

At the end of the study, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

Table 4.1 summarizes the study design and study parameters.

**Table 4.1: AI438006 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 | | | | |

## 4.2 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1.

No exceptions will be granted.

### 4.2.1 Inclusion Criteria

**1) Signed Written Informed Consent**

a) The signed informed consent form

**2) Target Population**

a) Clade B HIV-1 infected subjects meeting the following criteria at the screening visit (within 35 days of enrollment):

i) Plasma HIV RNA level ≥ 5,000 copies/mL (may be repeated for confirmation)

ii) Antiretroviral naive or experienced (ARV naive is defined by: No prior antiretroviral therapy of ≥ 1 week)

iii) CD4+ lymphocyte measurement ≥ 200 cells/μL (may be repeated for confirmation)
iv) Off all antiretroviral therapy with HIV activity for ≥ 8 weeks
v) Have not previously received an HIV attachment inhibitor

b) Body Mass Index (BMI) of 18 to 35 kg/$m^2$, inclusive. BMI = weight (kg)/ [height (m)]$^2$
c) Not currently co-infected with HCV or HBV

**3) Age and Sex**

a) Men and women, ≥ 18 years of age

Women of childbearing potential (WOCBP) must be using an adequate method of contraception (generally defined as two separate forms of contraception, one of which must be an effective barrier method (eg, condom with spermicide), to avoid pregnancy throughout the study and for up to 12 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause or
- For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

### 4.2.2 Exclusion Criteria

**1) Sex and Reproductive Status**

a) WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy (generally defined as two effective forms of contraception) for the entire study period and for up to 12 weeks after the last dose of investigational product.

b) WOCBP using a prohibited contraceptive method including oral, injectable, or implantable hormonal contraceptive agent within 12 weeks of enrollment.

c) Women who are pregnant or breastfeeding.

d) Women with a positive pregnancy test on enrollment or prior to investigational product administration.

e) Sexually active fertile men not using effective birth control (generally defined as two effective forms of contraception) during study participation and for at least 12 weeks after the last dose of investigational product if their partners are WOCBP.

**2) Medical History and Concurrent Diseases**

a) Any significant acute or chronic medical illness which is not stable or is not controlled with medication or not consistent with HIV infection.

b) Current or recent (within 3 months) gastrointestinal disease that, in the opinion of the Investigator or Medical Monitor, may impact on drug absorption and/or put the subject at risk for GI tract irritation and/or bleeding. Exclusionary diseases include, but are not limited to gastrointestinal ulcers, esophageal or gastric varicies, or hematochezia.

c) Acute diarrhea lasting ≥ 1 day, within 3 weeks prior to randomization. Diarrhea will be defined as the passage of liquid feces and/or a stool frequency greater than three times per day.

d) Any major surgery within 4 weeks of study drug administration.

e) Any gastrointestinal surgery that could impact upon the absorption of study drug.

f) Donation of blood or plasma to a blood bank or in a clinical study (except a Screening visit or follow up visit of less than 50 mL) within 4 weeks of study drug administration.

g) Blood transfusion within 4 weeks of study drug administration.

h) Inability to tolerate oral medication.

i) Inability to be venipunctured and/or tolerate venous access.

j) A personal history of clinically relevant cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes, or additional risk factors for torsades de pointes.

k) A personal or family history of long QT syndrome.

l) Subjects who are **unwilling** to practice adequate infection protection during and after study participation to minimize potential for spread of HIV infection, including HIV which may have developed resistance to HIV attachment inhibitors. Such protections could include, but are not limited to behaviors to minimize potential for exposure to the subjects' bodily fluids or initiation of HAART therapy if indicated and recommended by a physician.

m) Recent (within 6 months) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 2).

n) Any other medical, psychiatric and/or social reason which, in the opinion of the Investigator, would make the candidate inappropriate for participation in this study.

**3) Physical and Laboratory Test Findings**

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations or not consistent with the subject's degree of HIV infection.

b) Confirmed QT value > 500 msec at screening or Day -1.

c) Confirmed QTc value > 470 msec for women and > 450 msec for men at screening or Day -1.

d) Evidence of second or third degree heart block at screening or Day -1, confirmed by repeat ECG.

e) Positive urine screen for drugs of abuse at either Screening or Day -1 without a valid prescription (subjects positive for cannabinoids and/or amphetamines will be included, unless excluded by exclusion criteria 2m in Section 4.2.2).

f) Positive blood screen for hepatitis B surface antigen.

g) Positive blood screen for hepatitis C antibody and hepatitis C RNA.

h) Any of the following screening or Day -1 laboratory results outside of the ranges specified below as defined by the central laboratory, confirmed by repeat analysis.

i) Absolute Neutrophil Count (ANC) 0.7 x lower limit of normal (LLN)

ii) Hemoglobin 0.8 x LLN

iii) ALT > 3 x upper limit of normal (ULN)

iv) Creatinine clearance (as estimated by method of Cockcroft and Gault[18]) less than 60 mL/min.

**4) Allergies and Adverse Drug Reactions**

a) History of allergy to an HIV attachment inhibitor.
b) History of allergy to HIV protease inhibitor (e.g. RTV).
c) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

**5) Prohibited Treatments and/or Therapies**

a) Prior exposure to an HIV attachment inhibitor (including BMS-488043 or BMS-663068).
b) Exposure to any investigational drug or placebo within 4 weeks of study drug administration.
c) Use of any prescription drugs within 4 weeks prior to study drug administration. However, certain drugs may be allowed if approved by the BMS medical monitor.
d) Use of any other drugs, including over-the-counter medications, vitamins and/or herbal preparations (eg. St. John's wort), within 1 week prior to study drug administration. However, certain drugs may be allowed if approved by the BMS medical monitor.
e) Use of an oral, injectable or implantable hormonal contraceptive agent within 12 weeks of study drug administration.
f) Use of any prescription drugs or OTC drugs that may cause GI tract irritation or bleeding (ie, NSAIDs, aspirin) within 2 weeks of study drug administration, unless approved by the BMS medical monitor.
g) Use of alcohol-containing beverages within 3 days prior to study drug administration.
h) Use of grapefruit or grapefruit-containing products or Seville orange-containing products within 7 days prior to study drug administration.

**6) Other Exclusion Criteria**

a) Prisoners or subjects who are involuntarily incarcerated.
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

### 4.2.3 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) (investigational or noninvestigational treatment) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (see Section 7.6.2)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Inability to comply with protocol
- Discretion of the investigator
- Clinically relevant ventricular arrhythmia including torsades de pointes
- Confirmed QTcB or QTcF value > 500 msec
- Type 2 (Mobitz II) second or third-degree heart block (confirmed by repeat ECG)
- New onset of clinically relevant gastrointestinal bleeding
- New onset of signs and symptoms of severe persistent gastrointestinal irritation (such as abdominal pain) deemed unrelated to another etiology

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

**Dosing within a regimen group will be stopped and the study halted until safety information can be reviewed in the event of the following situations:**

- Two or more subjects within a regimen group experience new onset of QTcF values >500 msec following dosing (confirmed by repeat ECG)
- Two or more subjects within a regimen group experience second-degree Mobitz II or third-degree heart block (confirmed by a repeat ECG)
- Clinically relevant ventricular arrhythmia including torsades de pointes in any subject in a given dose panel
- Two or more subjects within a regimen group experience new onset of clinically relevant gastrointestinal bleeding
- Two or more subjects within a regimen group experience new onset of signs and symptoms of severe persistent gastrointestinal irritation (such as abdominal pain) deemed unrelated to another etiology
- Two or more subjects within a regimen group experience the same drug-related severe clinical or laboratory adverse event

**The study may be terminated prematurely if**:

- The Sponsor, in consultation with the Principal Investigators, feels that the number and/or severity of AEs justifies discontinuation of the study.
- The Sponsor considers the applied doses of the study drug to be no longer relevant.
- The Sponsor decides to discontinue the study.
- Data not known before become available and raise concern about the safety of the study drug so that continuation would pose potential risks to the subjects.

Premature termination of the study must be documented and clinical study results will be reported according to the requirements outlined in this protocol as far as applicable.

# 5 TREATMENTS

## 5.1 Study Treatment

All protocol-specified investigational and noninvestigational products are considered study drug. BMS-663068 will be administered as a tablet formulation. Ritonavir will be administered as a capsule. Table 5.1A outlines the total dose and number of tablets or capsules per daily dose for each group.

**Table 5.1A: Treatment Administration**

| Group | Study Drug Tablet/Capsule Strength | Number of Tablets or Capsules per time of day | Total Daily Dose |
|---|---|---|---|
| 1 | BMS-663068 600 mg tablet | 1 in AM; 1 in PM | 1200 mg |
| | RTV 100 mg capsule | 1 in AM; 1 in PM | 200 mg |
| 2 | BMS-663068 600 mg tablet | 2 in PM | 1200 mg |
| | RTV 100 mg capsule | 1 in PM | 100 mg |
| 3 | BMS-663068 600 mg tablet | 2 in AM; 2 in PM | 2400 mg |
| | RTV 100 mg capsule | 1 in AM; 1 in PM | 200 mg |
| 4 | BMS-663068 600 mg tablet | 2 in AM; 2 in PM | 2400 mg |
| | RTV 100 mg capsule | 1 AM | 100 mg |
| 5 | BMS-663068 600 mg tablet | 2 in AM; 2 in PM | 2400 mg |

All doses will be administered under fed conditions. In the morning of Days 1 through 8 a standard breakfast meal will be administered as breakfast to subjects in Groups 1, 3, 4, and 5 prior to dosing of study drug. On Days 1 through 8 for all groups, an evening snack (approximately 300 - 350 kcal) will be administered prior to the evening dose of study drug. The meal and snack will be ingested within ~30 minutes and will be completed within ~5 minutes prior to dosing of study drug. At the time of dosing, ~240 mL of water will be administered to the subjects along with the study medication. The BMS-663068 tablet(s) must be swallowed intact and are not to be chewed. The water will be consumed within approximately 5 minutes of dosing. The time of the first dose administration will be called "0" hour (AM for groups 1, 3, 4 and 5; PM for group 2). Table 5.1B provides a description of a representative standard breakfast.

Restrictions related to food and fluid intake are described in Section 5.5.2.

**Table 5.1B: Representative Standard Breakfast**

| Food Item | Calories (kcal) | Fat (g) | Carbohydrates (g) | Protein (g) |
|---|---|---|---|---|
| 1 egg fried | 90 | 7.0 | 0.4 | 6.3 |
| 2 slices of white bread toasted | 129 | 1.8 | 24.0 | 4.0 |
| 1 tablespoon jelly | 56 | Trace | 13.8 | Trace |
| 8 fluid ounces (237 mL) of whole milk | 146 | 7.9 | 11.0 | 7.9 |
| **Total Grams (g)** | - | 16.7 | 49.3 | 18.2 |
| **Total Calories (kcal)** | 421 | 153 | 197 | 73 |
| **% of Total Calories** | 100 | 36 | 47 | 17 |

Source: US Department of Agriculture, Agricultural Research Service. 2007 USDA National Nutrient Database for Standard Reference, Release 21.[19]

### 5.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, investigational product(s) are: BMS-663068 tablets and Ritonavir capsules

### 5.1.2 Noninvestigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products.

In this protocol, noninvestigational product(s) is/are: Not applicable for this study.

### 5.1.3 Identification

For all study sites, Bristol-Myers Squibb R&D will supply the following investigational product:

**Table 5.1.3: Investigational Product Identification**

| Unit | Route | Appearance |
|---|---|---|
| BMS-663068-03 Tablet, 600 mg | Oral | Plain, white biconvex, capsule-shaped film-coated tablet |
| Ritonavir Capsule, 100 mg | Oral | White, soft capsule |

### 5.1.4 Packaging and Labeling

BMS-663068-03 tablets and ritonavir capsules will be packaged in bottles. Each bottle will be labeled as open-label with a 1-panel label which will contain at least the following information: protocol number (either as a prefix or full number), container number, batch number, product name and potency, number of tablets/capsules, dosing instructions, and storage conditions.

Bottles of BMS-663068-03 600 mg tablets will contain 35 tablets each and bottles of ritonavir 100 mg capsules will contain 84 capsules each.

### 5.1.5 Handling and Dispensing

Study drug supplied by the sponsor or sourced by the investigator should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that study drug is only dispensed to study subjects. The study drug must be dispensed only from official study sites by authorized personnel according to local regulations.

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

BMS-663068-03 tablets should be stored at 15-25ºC (59-77ºF). Ritonavir 100 mg capsules should be stored in a refrigerator, at 2-8ºC (36-46ºF) until dispensed, protected from freezing and excessive heat, and the bottles should be kept tightly closed.

Please refer to Section 9.2.2 for information on study drug record retention and 9.3 for destruction and return instructions.

## 5.2 Method of Assigning Subjects to a Treatment

Subjects in each group will be randomized and stratified by prior antiretroviral (ARV) treatment history (ARV naive versus ARV experienced). No more than 70% of the total population will be ARV naive or ARV experienced. All regimen groups may initiate dosing simultaneously.

Subjects will be randomized to a group according to a computer-generated randomization scheme. The Randomization schedule will be prepared by a Randomization Coordinator within the Drug Supply Management Department of the Bristol-Myers Squibb Research and Development or the designated CRO.

All enrolled subjects will be assigned a sequential subject number starting with PPD at the time the study specific ICF is signed. Screen failures will keep their subject number assigned at enrollment. Enrolled subjects meeting inclusion and exclusion criteria will be randomized. Randomization numbers will be assigned prior to dosing for each group.

Subjects will not be replaced.

## 5.3 Selection and Timing of Dose for Each Subject

### 5.3.1 Dose Modifications

Modification of the dosage schedule may not be made without a written amendment to the protocol.

## 5.4 Blinding/Unblinding

Not applicable.

## 5.5 Concomitant Treatments

### 5.5.1 Prohibited and/or Restricted Treatments

Restrictions on medications taken prior to enrollment in the study are described in Section 4.2.2. Medications taken within 4 weeks prior to administration of study medication must be recorded on the CRF.

No concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed by the investigator for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

### 5.5.2 Other Restrictions and Precautions

1) Subjects are not permitted to use any other drugs, including prescription medications, over-the-counter medications, and herbal preparations, for the duration of the study, including any that prolong the QT/QTc interval, alter GI motility or may cause GI bleeding and/or irritation.
2) Subjects are to refrain from strenuous exercise, contact sports, and sunbathing from Day -1 to Day 15.
3) Subjects are not permitted to consume alcohol-containing beverages from 3 days prior to the first dose until Day 15.
4) Subjects are not permitted to consume grapefruit-containing products or Seville orange-containing products from 7 days prior to the first dose until Day 15.
5) Subjects are permitted to smoke during the study. However, during the inpatient phase, subjects must abide by the policies of the clinical facility.
6) Subjects are required to remain in the clinical facility from Day -1 to Day 11, or until furloughed.
7) On study Days 1 to 8, subjects are required to fast (nothing to eat or drink except water) for at least 7 hours prior to breakfast. Subjects may not drink water one hour after study drug administration except with dosing. Water may be consumed *ad libitum* at other times.
8) On study Days 1 to 8, a standard breakfast will be served prior to the first AM dose of study drug; a standard lunch will be served approximately 4 hours post the AM dose; a standard dinner will be served approximately 8 hours post the AM dose and a standard light snack will be served in conjunction with the PM dose (approximately 12 hours post the AM dose). No other food should be consumed. Refer to Section 5.1 for details regarding study drug administration.

9) On study Days 1 to 8, subjects should maintain an upright (seated or standing) position for at least 2 hours postdose, with the exception of being supine in preparation for ECG recordings.
10) Male subjects are not permitted to donate sperm or father a child throughout the study and for 12 weeks after the last dose of investigational product.
11) Subjects are not permitted to consume food containing poppy seeds from the time of screening until Day 15.

## 5.6 Treatment Compliance

Study drug will be administered in the clinical facility. After administration of BMS-663068 and/or RTV, a mouth check will be performed to verify that the subject has swallowed the dose. When multiple tablets or capsules are administered as part of a single dose, the mouth check should be performed after the final pill has been taken. The volunteer should drink the entire aliquot of water given to swallow the pills.

# 6 STUDY ASSESSMENTS AND PROCEDURES

## 6.1 Flow Chart/Time and Events Schedule

**Table 6.1: Flow Chart for Protocol AI438006**

| Event | Screening | Study Day | | | | | | | | | | | | Follow up | Study Discharge[j] | Protocol Sections |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 35 Days of Study Day 1 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 15 | 50 ± 3 days | |
| Signed Protocol Specific Consent Form / Enrollment | x | | | | | | | | | | | | | | | 3.3, 4.2.1 |
| Medical History | x | | | | | | | | | | | | | | | 4.2, 6.3 |
| Vital Signs | x | x | x[a] | | | x[a] | | | | x[a] | | | x | x | x | 6.3 |
| Physical Measurements | x | x[b] | | | | | | | | x[b] | | | x[b] | x[b] | x[b] | 6.3 |
| Physical Examination | x | | x[i] | | | | | | | x | | | x | x | x | 6.3 |
| 12-lead ECG | x | x | x[a] | | | x[a] | | | | x[a] | | | x | | x | 6.3 |
| Clinical Laboratory Tests | x | x | | | | x | | | | x | | | x | | x | 6.3 |
| Serology | x | | | | | | | | | | | | | | | 6.3 |

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**Table 6.1: Flow Chart for Protocol AI438006**

| Event | Screening | Study Day | | | | | | | | | | | | Follow up | Study Discharge[j] | Protocol Sections |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 35 Days of Study Day 1 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 15 | 50 ± 3 days | |
| Urine Drug Screen | x | x | | | | | | | | | | | | | | 6.3 |
| Pregnancy Test | x | x | | | | x | | | | | | | x | | x | 4.2.1, 6.3, 7.6 |
| Report to Study Site | x | x | | | | | | | | | | | | x | x | 4.1 |
| Study Drug Administration | | | x | x | x | x | x | x | x | x | | | | | | 5 |
| Blood Pharmacokinetic Sampling | | | x | x[c] | | | x | x | x | x | x | x | x | | | 6.5, Tables 6.5.1A and 6.5.1B |
| Blood Sampling for HIV-1 RNA Analysis | x | | x[d] | x[d] | x[d] | x[d] | x[d] | x[d] | x[d] | x[d] | x[d] | x[d] | x[d] | x | x | 6.3 |
| Blood Sampling for Protein Binding | | | | | | | | | | x[e] | | | | | | 6.5 |
| Blood Sampling for CD4+ and CD8+ Counts | x | | x[d] | | | | | | | x[d] | | | | x | x | 6.3 |
| Plasma Collection RT/Pol genotype | x | | | | | | | | | | | | | | | 6.3 |

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**Table 6.1: Flow Chart for Protocol AI438006**

| Event | Screening | Study Day | | | | | | | | | | | | Follow up | Study Discharge[j] | Protocol Sections |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 35 Days of Study Day 1 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 15 | 50 ± 3 days | |
| Plasma Collection HIV Env genotyping & phenotyping[f] | x | | x[d] | | | x[d] | | | | x[d] | | | | x | x | 6.9.1 |
| Plasma Collection[g] | x | | x[d] | | | | | | | x[d] | | | | x | x | 6.9.1 |
| Blood (PBMC) Collection[h] | x | | x | | | x | | | | x | | | | x | x | 6.9.1 |
| Monitor for Serious Adverse Events | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. | | | | | | | | | | | | | | | 7 |
| Monitor for Non-Serious Adverse Events | | | x | x | x | x | x | x | x | x | x | x | x | x | x | 7 |

[a] 4 hours post-AM dose in groups 1, 3, 4 and 5; 4 hours post-PM dose in group 2. Vital signs will include heart rate and blood pressure measurements.

[b] Weight only

[c] Group 2 only

[d] Pre-AM dose in groups 1, 3, 4 and 5; Pre-PM dose in group 2. On days when dose is not administered, sample collection time should be maintained.

[e] Pre-PM dose and 4 hours post-PM dose

[f] Env Genotyping and phenotyping analysis: Env. phenotyping to be analyzed on Day 1 in all dosed subjects; all other samples to be stored and analyzed if deemed relevant.

[g] Neutralizing antibody activity, HIV co-receptor usage and samples for exploratory resistance analysis; to be stored and analyzed if deemed relevant

[h] Activation markers and exploratory apoptotic markers; to be stored and analyzed if deemed relevant

[i] If the screening physical exam is performed within 24 hours of dosing on Day 1, then a single examination may count as both the screening and predose evaluation

[j] Evaluations performed prior to study discharge or for subjects who are prematurely discontinued from the study.

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In the event multiple procedures are required at a single timepoint, the following is a list of procedures from highest priority to low:

1) Pharmacokinetic Sampling
2) Safety (ECG)
3) Safety (vital signs)
4) Safety (clinical labs)

## 6.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support (ACLS) cart will be immediately available on the premises. The site will have a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), investigator brochure and study drug (BMS-663068 and ritonavir). Case report forms (electronic or hard copy) will be provided by BMS. The Central Laboratory will provide labels and tubes for the collection of blood samples for PK/PD, for genotyping analysis, and for clinical lab samples being analyzed centrally.

## 6.3 Safety Assessments

### 6.3.1 Medical History

A detailed medical history will be obtained at screening. Include the history of any toxicities or allergy related to previous treatments.

### 6.3.2 Vital Signs

Vital signs (body temperature, respiratory rate, seated blood pressure and heart rate) will be recorded during the screening visit, Day -1, Day 11, Day 15 and at study discharge. Additionally, on Days 1, 4 and 8, seated blood pressure and heart rate will be measured 4 hours post AM dose in groups 1, 3, 4 and 5 and 4 hours post PM dose in group 2.

Blood pressure and/or heart rate values that meet exclusion criteria may be confirmed by repeat analysis at the screening visit and/or Day -1. In the event that the repeat blood pressure and/or heart rate value(s) do not exclude the subject, a third assessment should be taken approximately 5 minutes later. The subject may be enrolled if the third assessment does not meet exclusion criteria for blood pressure and/or heart rate.

Blood pressure and heart rate should be measure after the subject has been seated or supine quietly for at least 5 minutes.

Note: For any time point when vital signs and ECG are both required, the heart rate measurement from the ECG machine is to be entered in the CRF. At these time points it will not be necessary to measure heart rate by other means. However, for time points when an ECG will not be recorded but vital signs are to be measured, the heart rate is to be measured by other means (ie, Dynamap or manual count over 60 seconds) and that result entered in the CRF.

### 6.3.3 Physical Measurements

Height and weight will be measured and body mass index (BMI) calculated at screening as part of the physical exam. Weight will also be measure on Days -1, 8, 11, 15, and at study discharge.

### 6.3.4 Physical Examination

A physical examination will be performed at the screening visit, Days 1 (predose), 8, 11, 15 and at study discharge. If the screening physical examination is performed within 24 hours of dosing on Day 1, then a single examination may count as both the screening and predose evaluation.

### 6.3.5 Electrocardiograms

A 12-lead ECG will be recorded at screening, Day -1, Day 11 and at study discharge. Additionally, on Days 1, 4 and 8, a 12-lead ECG will be recorded 4 hours post AM dose in groups 1, 3, 4 and 5 and 4 hours post PM dose in group 2.

### 6.3.6 Adverse Event Monitoring

Subjects will be closely monitored throughout the study for adverse events and will not be discharged from the study until the investigator has determined that adverse events have either completely resolved or are not of clinical significance (refer to Section 7).

### 6.3.7 Laboratory Test Assessments

Blood and urine samples will be obtained at selected times (refer to Table 6.1) for clinical laboratory evaluations. Subjects are required to fast for at least 7 hours prior to the collection of specimens for clinical laboratory tests. A central laboratory will perform the analyses, unless results are needed immediately, then a local lab can be used. Reference ranges from these tests will be provided by the laboratory. Sample collection time (relative to dosing) should be maintained throughout the inpatient portion of the study. Samples should be collected prior to dosing. Samples for clinical laboratory tests for subjects assigned to group 2 can be collected in the AM, prior to the PM dosing.

Results of clinical laboratory test performed on Day -1 must be available prior to dosing.

The following clinical laboratory tests will be performed.

**Hematology**

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

**Serum Chemistry**

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin (if abnormal, direct
Fasting glucose
Total Protein
Albumin

bilirubin should be performed, except at screening)
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Creatinine
Creatinine Clearance (Screening only)
Blood Urea Nitrogen (BUN)
Uric acid
C-Reactive Protein (CRP)
Amylase (if abnormal, lipase should be performed, except at screening)
Sodium
Potassium
Chloride
Calcium
Phosphorus
Creatine kinase (CK), CK not to be drawn after day 11. If CK is 2 times the upper limit of normal, Troponin T should be performed (except at screening)

**Urinalysis**

Protein
Glucose
Blood
Leukocyte esterase
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

**Serology**

Serum for hepatitis C (reflex to HCV RNA if hepatitis C antibody positive) antibody, hepatitis B surface antigen, HIV-1, -2 antibody (screening only)

**Other Analyses**

Urine for drugs of abuse (screening and on Day -1)
Pregnancy test (WOCBP only: screening*, Days -1*, 4, 11 and at discharge).
RT/Pol genotype and HIV clade (screening)

*Lab result MUST be available prior to dosing

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 7.4 Laboratory Test Abnormalities).

## 6.4 Efficacy Assessments

Not applicable.

## 6.5 Pharmacokinetic Assessments

### 6.5.1 Pharmacokinetics: Collection and Processing

Tables 6.5.1A and 6.5.1B lists the sampling schedule to be followed for the assessment of pharmacokinetics. Further details of blood sample collection and processing will be provided to the site in the procedure manual.

**Table 6.5.1A: PK Sample Schedule (Groups 1, 3, 4 and 5 Only)**

| Study Day | Time (Event) Hour | Time (Relative To Last Dose) Hour:Min | BMS-626529 and RTV[a] |
|---|---|---|---|
| 1 and 8 | 0 (pre-AM dose) | 00:00 | x |
| 1 and 8 | 1 | 01:00 | x |
| 1 and 8 | 2 | 02:00 | x |
| 1 and 8 | 3 | 03:00 | x |
| 1 and 8 | 4 | 04:00 | x |
| 1 and 8 | 5 | 05:00 | x |
| 1 and 8 | 6 | 06:00 | x |
| 1 and 8 | 8 | 08:00 | x |
| 1 and 8 | 12* | 12:00 | x[b] |
| 8 | 13 | 01:00 | x |
| 8 | 14 | 02:00 | x |
| 8 | 15 | 03:00 | x |
| 8 | 16 | 04:00 | x[b] |
| 8 | 17 | 05:00 | x |
| 8 | 18 | 06:00 | x |
| 8 | 20 | 08:00 | x |
| 9 | 0 | 12:00 | x |

**Table 6.5.1A: PK Sample Schedule (Groups 1, 3, 4 and 5 Only)**

| Study Day | Time (Event) Hour | Time (Relative To Last Dose) Hour:Min | BMS-626529 and RTV[a] |
|---|---|---|---|
| 9 | 4 | 16:00 | x |
| 9 | 12 | 24:00 | x |
| 10 | 0 | 36:00 | x |
| 10 | 12 | 48:00 | x |
| 11 | 0 | 60:00 | x |
| 5, 6, 7 | 0 (pre-AM dose) | 00:00 | x |

*: Samples to be taken before evening dosing

[a] RTV will be measured in Group 1, 3 and 4 only

[b] Additional blood samples will be drawn on Day 8 for protein binding analysis

**Table 6.5.1B: PK Sample Schedule (Group 2 Only)**

| Study Day | Time (Event) Hour | Time (Relative To Last Dose) Hour:Min | BMS-626529 and RTV |
|---|---|---|---|
| 1 and 8 | 0 (pre-PM dose)* | 00:00 | x[a] |
| 1 and 8 | 1 | 01:00 | x |
| 1 and 8 | 2 | 02:00 | x |
| 1 and 8 | 3 | 03:00 | x |
| 1 and 8 | 4 | 04:00 | x[a] |
| 1 and 8 | 5 | 05:00 | x |
| 1 and 8 | 6 | 06:00 | x |
| 1 and 8 | 8 | 08:00 | x |
| 2 and 9 | 12 | 12:00 | x |
| 2 and 9 | 16 | 16:00 | x |
| 2 and 9 | 0 (pre-PM dose Day 2) | 24:00 | x |
| 10 | 0 | 36:00 | x |

**Table 6.5.1B: PK Sample Schedule (Group 2 Only)**

| Study Day | Time (Event) Hour | Time (Relative To Last Dose) Hour:Min | BMS-626529 and RTV |
|---|---|---|---|
| 10 | 12 | 48:00 | x |
| 11 | 0 | 60:00 | x |
| 5, 6, 7 | 0 (pre-PM dose)* | 00:00 | x |

*: Subject will receive study drug in the evening.
a: Additional blood samples will be drawn on Day 8 for protein binding analysis.

### 6.5.2 Pharmacokinetic Sample Analyses

The serial plasma PK samples will be analyzed for BMS-626529 and RTV by a validated LC/MS/MS assay. If warranted by further clinical investigation, BMS-626529 metabolites may also be analyzed. Plasma samples collected for BMS-626529 protein binding assay will be initially analyzed for Groups 3 and 5 only, and remaining samples will be stored for future analysis, if deemed appropriate.

### 6.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

## 6.6 Pharmacodynamics Assessments

Viral activity will be assessed by the magnitude and rate of change in plasma HIV RNA levels from baseline (predose Day 1). Blood samples from all subjects will be obtained for analyses of HIV RNA level at Screening, on Days 1 through 11, 15 and discharge. Samples should be collected prior to dosing (pre AM dose in groups 1, 3, 4, and 5; pre PM dose in group 2). The plasma collection time (relative to dosing) should be maintained throughout the inpatient portion of the study (Days 1 through 11).

CD4+ and CD8+ lymphocyte counts and percents will be assessed. Blood samples from all subjects will be obtained for CD4+ and CD8+ cell counts at Screening, Days 1, 8, 15

and discharge. Samples should be collected prior to dosing (pre AM dose in groups 1, 3, 4, and 5; pre PM dose in group 2). Collection time (relative to dosing) should be maintained throughout the inpatient portion of the study (Days 1 through 11).

RT/Pol genotyping to determine HIV clade will be performed. A plasma sample will be obtained at screening for RT/Pol genotype and HIV clade determination.

## 6.7 Pharmacogenomic/Pharmacogenetic Assessments

See Amendment 01 for pharmacogenomics blood sampling.

## 6.8 Outcomes Research Assessments

Not applicable.

## 6.9 Other Assessments

### 6.9.1 Exploratory Biomarkers

Plasma samples for HIV envelope genotyping and phenotyping will be collected at Screening, Days 1, 4, 8, 15 and discharge. Collection time (relative to dosing) should be maintained throughout the inpatient portion of the study (Days 1 through 11). Envelope phenotype will be determined on samples from Day 1. All other samples may be analyzed if deemed relevant.

Plasma samples for HIV co-receptor usage and neutralizing antibody activity will be collected at Screening, Days 1, 8, 15 and discharge. Collection time (relative to dosing) should be maintained throughout the inpatient portion of the study (Days 1 through 11). These samples may be analyzed if deemed relevant.

Plasma samples will also be collected for exploratory resistance analysis at Screening, Days 1, 8, 15 and discharge. These samples could be used for performing clonal analysis to detect or quantitate minor resistant variants or for viral culture, genotyping, or phenotyping of the HIV genome to determine sensitivity to additional therapeutic agents. These samples may be analyzed if deemed relevant.

Blood samples for activation marker and exploratory apoptotic markers analysis using PBMCs will be collected at Screening, Days 1, 4, 8, 15 and discharge in special tubes with special handling and shipping instructions. These samples may be analyzed if deemed relevant. Collection time (relative to dosing) should be maintained throughout the inpatient portion of the study (Days 1 through 11).

Further details of sample collection, processing and shipping will be provided to the site in the procedure manual.

# 7 ADVERSE EVENTS

## 7.1 Definitions

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

### 7.1.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious

outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE and must be reported accordingly.

Although overdose and cancer are not always serious by regulatory definition, these events should be reported on an SAE form and sent to BMS in an expedited manner.

All pregnancies, regardless of outcome, must be reported to the sponsor on a Pregnancy Surveillance Form, not an SAE form (see Section 7.6).

**NOTE:**

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

### 7.1.2 Nonserious Adverse Events

All AEs that are not classified as serious.

## 7.2 Assignment of Adverse Event Intensity and Relationship to Study Drug

The following categories and definitions of intensity as determined by a physician should be used for all BMS clinical study AEs:

- Mild (Grade 1) - Awareness of event but easily tolerated
- Moderate (Grade 2) - Discomfort enough to cause some interference with usual activity
- Severe (Grade 3) - Inability to carry out usual activity
- Very Severe (Grade 4) - Debilitating, significantly incapacitates subject despite symptomatic therapy

The following categories and definitions of causal relationship to study drug as determined by a physician should be used for all BMS clinical study AEs:

- Related: There is a reasonable causal relationship to study drug administration and the AE
- Not related: There is not a reasonable causal relationship to study drug administration and the AE

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

## 7.3 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to study drug, action taken, and treatment required. If treatment for the AE was administered, it should be recorded on the

appropriate CRF page. The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

### 7.3.1 Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing or within 30 days of the last visit for screen failures. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should notify BMS (or designee) of any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

Serious adverse events, whether related or unrelated to study drug, must be recorded on the SAE page of the CRF and reported within 24 hours to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be reported within 24 hours by confirmed facsimile transmission (fax). If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting. The SAE electronic CRF in the electronic data capture tool should not be used.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page of the CRF.

If an ongoing SAE changes in its intensity or relationship to study drug, a follow-up SAE report should be sent within 24 hours to the sponsor (or designee). As follow-up

information becomes available it should be sent within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

**SGS Contact Information:**

**SAE Facsimile Number:** PPD

**SAE Telephone Contact (24h emergency phone number):** PPD

### 7.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. When BMS has a written agreement with a local IRB/IEC, BMS will directly submit ESR(s). The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

### 7.3.3 Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

If an ongoing nonserious AE worsens in its intensity or its relationship to the study drug changes, a new nonserious AE entry for the event should be completed. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 7.3.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

All identified nonserious AEs must be recorded and described on the appropriate nonserious AE page of the CRF (paper or electronic).

## 7.4 Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF, or be submitted electronically from a central laboratory. In addition, the following laboratory abnormalities should also be captured on the nonserious AE CRF page (paper or electronic) or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

## 7.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 7.3.1 for reporting details.)

## 7.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized (See Section 4.2.1 for the definition of WOCBP).

Before enrolling WOCBP in this clinical study, investigators must review the sponsor-provided information about study participation for WOCBP. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

### 7.6.1 Requirements for Pregnancy Testing

All WOCBP MUST have a **negative** pregnancy test within 24 hours as specified in Section 6.1 **prior** to receiving the investigational product. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is

positive, the subject must not receive the investigational product and must not continue in the study.

Pregnancy testing must also be performed throughout the study as specified in Section 6.1 (see flow chart/time and events schedule) and the results of all pregnancy tests (positive or negative) recorded on the CRF or transferred electronically.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

### 7.6.2 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify the SGS medical monitor of this event, record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to SGS and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to SGS according to SAE reporting procedures described in Section 7.3.1.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

## 7.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the appropriate nonserious AE page of the CRF (paper or electronic) or SAE paper CRF page.

# 8 STATISTICAL CONSIDERATIONS

## 8.1 Sample Size Determination

The sample size evaluation is 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 one regimen group may suggest that the dose of BMS-663068 is sufficiently active against HIV to proceed with further development of the drug. If the BMS-663068 containing regimen has no effect, then administration of the regimen to 10 subjects (ARV naive or experienced) would provide a ≤1% probability to observe a mean $\log_{10}$ drop of ≥1. If the true population mean decrease from baseline in HIV RNA is ≥1.5 log10, then there would be a 99% probability that the observed mean decline from baseline would be ≥1 $\log_{10}$. In addition, 10 subjects within each group can 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 is 1 $\log_{10}$. Meanwhile, 10 subjects in each group can also provide 82% power to conclude the mean decreases in $\log_{10}$ HIV RNA from two groups are different if the true difference in population mean decreases from these two groups is 0.6 $\log_{10}$.

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

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

## 8.2 Populations for Analyses

All subjects who receive study medication will be included in the safety data set.

All available data from subjects who receive BMS-663068 will be included in the pharmacokinetic data set.

All available data from subjects for whom pharmacodynamic measurements are available at baseline and at least one other time will be included in the pharmacodynamic data set.

## 8.3 Endpoint Definitions

### 8.3.1 Safety Endpoint

Safety assessments will be based on adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance.

### 8.3.2 Pharmacokinetic Endpoint(s)

Pharmacokinetics of BMS-626529 and RTV will be derived from plasma concentration versus time data. The pharmacokinetic parameters to be assessed include:

| | |
|---|---|
| Cmax | Maximum observed plasma concentration |
| Ctrough | Trough observed plasma concentration |
| Tmax | Time of maximum observed plasma concentration |
| AUC(TAU) | Area under the concentration-time curve in one dosing interval |
| AUC(0-24h) | Area under the concentration-time curve over a 24-hour period following the AM dose (PM for Group 2) on Day 8 |
| Css,avg | Average steady-state plasma concentration, calculated as AUC(0-24h)/24 |
| T-HALF | Terminal half-life (after last dose only) |
| CLT/F | Apparent total body clearance |

| | |
|---|---|
| Vss/F | Apparent volume of distribution at steady-state |
| AI | Accumulation index; ratio of AUC(TAU) at steady-state to AUC(TAU) after the first dose |
| Protein binding (%) | Percent of BMS-626529 that are bound to total plasma proteins |
| IQ | Inhibitory quotient, calculated as the ratio of BMS-626529 in vivo exposure to in vitro measured protein binding adjusted $EC_{90}$. The following in vivo exposure measures will be used in evaluating IQ: Cmax, Ctrough and Css,avg. |

Individual subject pharmacokinetic parameter values will be derived by non compartmental methods by a validated pharmacokinetic analysis program.

### 8.3.3 Pharmacodynamic Endpoint(s)

Pharmacodynamic assessment will be based on change in HIV RNA. Additionally, CD4+ and CD8+ lymphocyte counts and percents will be assessed.

## 8.4 Analyses

### 8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated.

### 8.4.2 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

### 8.4.3 Efficacy Analyses

Not Applicable.

### 8.4.4 Pharmacokinetic Analyses

The multiple-dose pharmacokinetics of BMS-626529 following administration of BMS-663068 with or without RTV will be described by summary statistics for the pharmacokinetic parameters by regimen group, study day, dose time (AM or PM, Groups 1, 3, 4 and 5 only), antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]). Medians and ranges will be presented for Tmax. Means and standard deviations will be provided for T-HALF. Geometric means and coefficients of variation will be presented for Cmax, Ctrough, Css,avg, AUC(TAU), AUC(0-24), CLT/F, Vss/F and AI.

To assess the dependency on regimen, scatter plots of Cmax, AUC(TAU), and Ctrough versus regimen group will be provided by day and dose time (Groups 1, 3, 4 and 5 only). Time to steady-state will be evaluated by summary statistics of Ctrough (following AM doses except Group 2) by study day and by plot of geometric mean Ctrough versus study day.

Protein binding (%) for BMS-626529 will be evaluated by summary statistics and tabulated by regimen group. Inhibitory Quotient (IQ) of Cmax, Ctrough (both on Day 8 following AM regimens except Group 2) and Css-avg of BMS-626529 (defined in section 8.3.2) will be summarized and tabulated by regimen group.

Point estimates and 90% confidence intervals will be constructed for accumulation indices (ratio of Day 8 [AM doses except Group 2] vs. Day 1 for AUC(TAU), Cmax and Ctrough) by regimen group. These estimates will be generated using general linear models fitted to log-transformed data with study day as a fixed effect, and measurements within each subject as repeated measurements. Point estimates and 90% confidence intervals for differences at the log-scale will be exponentiated to obtain estimates and confidence intervals for ratios of geometric means in the original scale. No adjustments will be made for multiplicity.

Similar analysis will be used to access the effect of RTV on PK exposure of BMS-626529, by comparing the exposure of BMS-626529 in group 3 vs. group 5 and group 4 vs. group 5 with regimen groups as a fixed effect in the general linear models. The effects of diurnal PK variation (PM vs. AM) will also be assessed by the similar model for

Groups 1, 3, 4 and 5 only with time point (PM or AM) as a fixed effect and measurements within each subject as repeated measurements in the general linear models.

The multiple-dose pharmacokinetics of RTV when coadministered with various regimens of BMS-663068 will be described by summary statistics for the pharmacokinetic parameters by regimen group, study day, dose time (AM or PM, Groups 1 and 3), antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]). Medians and ranges will be presented for Tmax. Means and standard deviations will be provided for T-HALF. Geometric means and coefficients of variation will be presented for Cmax, Ctrough, Css, avg, AUC(TAU), AUC(0-24), CLT/F, Vss/F and AI.

### 8.4.5 Pharmacodynamic Analyses

Although the final decision on the further evaluation of BMS-663068 will be 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 one regimen group may suggest that that dose of BMS-663068 is sufficiently active against HIV.

The magnitude of the change in $\log_{10}$ HIV RNA levels will be assessed by summarizing changes from baseline, including 90% confidence intervals, at study day 2 through day 11 and at day 15, by regimen group and antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]). The primary assessment of the antiviral activity of BMS-663068 will be 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 will be provided. Two groups t-test will be used to test the differences in mean $\log_{10}$ decrease in HIV RNA at Day 9 between two regimen groups by antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]). Each individual's maximum $\log_{10}$ decrease from baseline in HIV RNA will be summarized by regimen group, antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]), and frequency distributions for maximum $\log_{10}$ decrease from baseline in HIV RNA will be provided by regimen group, antiretroviral

treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced])..

#### *8.4.5.1 Pharmacokinetics/ Pharmacodynamic Analyses*

The effect of BMS-626529 on PD measures (i.e., CD4+ and CD8+ T lymphocyte counts and percents and the corresponding changes in these parameters from baseline) will be assessed by summary statistics. Scatter plots will be used to assess the relationship between the changes from baseline in plasma HIV RNA and BMS-626529 $EC_{90}$ (determined from Day 1 sample), a threshold of protein binding adjusted $EC_{90}$ will be determined based on this scatter plot and summary statistics will be provided for the changes from baseline in plasma HIV RNA by group, excluding subjects with protein binding adjusted $EC_{90}$ above this threshold.

Scatter plots will also be used to assess the relationship between the changes from baseline in plasma HIV RNA and BMS-626529 IQs, and to assess the correlation between $\log_{10}$ changes from baseline in HIV RNA and IQs

### 8.4.6 Pharmacogenomic Analyses

See Amendment 01 for pharmacogenomics blood sampling assessments.

### 8.4.7 Outcomes Research Analyses

Not applicable.

### 8.4.8 Other Analyses

Summary statistics for exploratory biomarkers, such as but not limited to those stated in sections 6.6 and 6.9, and corresponding changes from baseline, or percent changes from baseline as appropriate, will be tabulated by regimen group, study day and time point. Possible associations between changes in exploratory biomarkers of interest and BMS-663068 dose or exposure will be explored graphically and by suitable statistical models, if appropriate. Some nonlinear models, such as but not limited to generalized least squares, will also be explored. Ad-hoc statistical analysis would be considered.

## 8.5 Interim Analyses

The primary analyses will be conducted after all subjects have completed the study and after the formal study database lock.

Interim analyses will be conducted for internal decision making. Data that may be included in the interim analysis are measures of antiviral activity, PK, and safety. Analyses will only consist of listings, summaries, and graphs, and no formal inferences requiring any adjustment to statistical significance levels will be performed.

In addition, a structural population PK and PK/PD model will be developed based on approximately 50% and repeated when 100% of PK data are available. This data will be combined with data from previous clinical studies with BMS-663068 to assist in internal decision making that could include, but is not limited to selecting possible phase IIb doses.

# 9 ADMINISTRATIVE SECTION

## 9.1 Compliance

### 9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

### 9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

THE INVESTIGATOR MUST NOTIFY BMS PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO BMS.

### 9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, study documentation, informed consent, and enrollment of WOCBP.

For sites using the BMS electronic data capture tool, each individual making entries and/or corrections on electronic CRFs must meet BMS training requirements and must

only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

For electronic CRFs, corrections are made through the BMS electronic data capture tool that generates an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The system also prompts the user to document reason for change that is also maintained in the audit trail.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

## 9.2 Records Retention

The investigator must retain study drug (those supplied by the sponsor or sourced by the investigator) disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

### 9.2.1 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the Pregnancy Surveillance Form. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

Paper CRFs must be completed legibly in ink. Subjects are to be identified by birth date and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank.

Electronic data transfer is acceptable.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

For paper CRFs, a correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

### 9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site

where study drug is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number and use date
- dates and initials of person responsible for the inventory /entry/ movement of each study drug
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted, broken)
- amount returned to the sponsor
- amount destroyed at study site, if applicable
- retain samples sent to third party for bioavailability/bioequivalence, if applicable

The sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

## 9.3 Destruction and Return of Study Drug

### 9.3.1 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor.

### 9.3.2 Return of Study Drug

Upon completion or termination of the study, all unused and/or partially used study drug that was supplied by the sponsor must be returned to BMS.

All study drug returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers (eg, patient kits that have clinical labels attached). Empty containers should not be returned to BMS. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused study drug, those that were supplied by the sponsor, should be arranged by the responsible Study Monitor.

## 9.4 Publications

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

# 10 GLOSSARY OF TERMS

| Term | Definition |
|---|---|
| Adverse Reaction | An adverse event that is considered by either the investigator or the sponsor as related to the investigational product |
| Expedited Safety Report | Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures. |
| SUSAR | Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC). |
| Unexpected Adverse Reaction | An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product) |

# 11 LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| AE | adverse event |
| ACLS | advanced cardiac life support |
| ADME | absorption, distribution, metabolism and elimination |
| AI | accumulation index |
| AIDS | acquired immunodeficiency syndrome |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| AV | atrioventricular |
| β-HCG | beta-human chorionic gonadotrophin |
| BDC | bile duct-cannulated |
| BMI | body mass index |
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| C | Celsius |
| C12 | concentration at 12 hours |
| CFR | Code of Federal Regulations |
| CK | creatine kinase |
| CLR | renal clearance |
| Cmax | maximum concentration |
| CRF | Case Report Form, paper or electronic |
| CTA | clinical trial agreement |
| D/C | discontinue |
| DSM IV | Diagnostic and Statistical Manual of Mental Disorders |
| $EC_{50}$ | 50% effective concentration |
| $EC_{90}$ | 90% effective concentration |
| ECG | electrocardiogram |
| eCRF | Electronic Case Report Form |
| eg | exempli gratia (for example) |
| ER | extended release |
| ESR | Expedited Safety Report |

| Term | Definition |
|---|---|
| et al | and others |
| FSH | follicle stimulation hormone |
| g | gram |
| GCP | good clinical practice |
| GI | gastrointestinal |
| GLP | good laboratory practice |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HRT | hormone replacement therapy |
| IB | investigator brochure |
| ie | id est (that is) |
| IEC | Independent Ethics Committee |
| IR | immediate release |
| IRB | Institutional Review Board |
| IQ | Inhibitory Quotient |
| IU | International Unit |
| kg | kilogram |
| LLN | lower limit of normal |
| LOQ | limit of quantitation |
| m | meter |
| mg | milligram |
| MA | marked abnormalities |
| MAD | multiple ascending dose |
| mL | milliliter |
| N/A | not applicable |
| NOAEL | no-observed-adverse-effect-level |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PBMC | peripheral blood mononuclear cell |
| Q12H | every 12 hours |
| QAM | Quaque die Ante Meridiem, every day before noon |
| QD | quaque die, once a day, once-daily |
| QHS | Quaque hora somni (every night) |
| QTcB | QT interval corrected for Bazett's |

| Term | Definition |
|---|---|
| RNA | ribonucleic acid |
| RTV | ritonavir |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SD | standard deviation |
| T-Half | half life |
| ULN | upper limit of normal |
| WOCBP | women of childbearing potential |

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# APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

## 1 INFORMED CONSENT PROCEDURES

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

### 1.1 Subjects Unable to Give Written Informed Consent

#### 1.1.1 Minors

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. (In the event that the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who

are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

### 1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

### 1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

### 1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject’s only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for

subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

### 1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

## 1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

# APPENDIX 2 DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

The following is taken from DSM-IV:

Diagnostic Criteria for Psychoactive Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1) Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect,
   b) Markedly diminished effect with continued use of the same amount of the substance.
2) Withdrawal, as manifested by either of the following:
   a) The characteristic withdrawal syndrome for the substance,
   b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3) The substance is often taken in larger amounts or over a longer period than was intended.
4) There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking) or recover from its effects.
6) Important social, occupational or recreational activities are given up or reduced because of substance use.
7) The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induce depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.

Criteria for Severity of Psychoactive Substance Dependence:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate: Symptoms or functional impairment between "mild" and "severe".

Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

In Partial Remission: During the past six months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past six months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

A. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring at any time in the same 12-month period:
    1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household).
    2) Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use).
    3) Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct).
    4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights).
B. The symptoms have never met the criteria for substance dependence for this class of substance.