Statistical Analysis Plan

1090387 / AI438006 / Version: Final, dated 07SEP2010

Trial identification:	**AI438006** **1090387**
Title:	Randomized, Open label, Multiple-Dose Study to Evaluate the Pharmacodynamics, Safety and Pharmacokinetics of BMS-663068 in HIV-1 Infected Subjects
Trial phase:	II A
Design:	Randomized, open label, multiple-dose regimens, parallel group study. Subjects will be randomized into one of 5 regimens.
Expected sample size:	50
Trial objectives:	Primary: 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: to assess: - the safety and tolerability of multiple regimens of BMS-663068 with and without RTV in HIV infected subjects - the effect of BMS-626529 following multiple regimens of BMS-663068 on CD4+ and CD8+ lymphocyte counts and percents - the PK of BMS-626529 following multiple regimens of BMS-663068 with and without RTV in HIV infected subjects - the diurnal variation in the PK exposures of BMS-626529 following multiple regimens of BMS-663068 with and without RTV in HIV infected subjects - the plasma protein binding for BMS-626529 - the relationships between change from baseline in log10 HIV RNA versus Inhibitory Quotient 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
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Version number:	Final
Version date:	07SEP2010

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1 INTRODUCTION

1.1 Trial objectives

Primary Objective

The primary objective of the trial is:

- 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 Objectives

The secondary objectives are:

- 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 log10 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 Objectives

The exploratory objectives are:

- 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

1.2 Design

This is a randomized, open label, multiple-dose parallel study. Subjects will undergo screening evaluations to determine eligibility within 28 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.

The approximate duration of the study is 81 days. Study participation includes a 28-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.

1.3 Expected sample size

A total of 50 patients will be enrolled in the study, namely 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.

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 log10 decrease in HIV RNA from baseline to Day 9 is normally distributed, with a standard deviation of 0.5, as estimated from AI430003.

1.4 Randomization and blinding

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 is prepared by SGS Biostat.

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.

1.5 Protocol amendments

Amendment 1 includes changes to permit the collection and storage of blood samples for use in future exploratory pharmacogenetic research. Bristol-Myers Squibb will use DNA obtained from the blood sample and health information collected from the main clinical trial, AI438006 to study the association between genetic variation and drug response. Bristol-Myers Squibb may also use the DNA to study the causes and further progression of HIV. Samples from this study may also be used in conjunction with pharmacogenetic research results from other clinical studies to accomplish this objective.

In amendment 2 following changes were made:

- Updated the statistician personnel and contact information.
- Incorporated Germany Competent Authority (BfArM) request to change the inclusion criteria of CD4+ counts ≥ 100 cells/μL to ≥ 200 cells/μL.
- Removed the statement that women of childbearing potential must be using an acceptable method of contraception for at least 8 weeks before dosing to be consistent with the inclusion criteria.
- In response to the comments received from the Ethics Committee of the Land Berlin, a clarification of the intent to exclude informed consent given by legally acceptable representatives (or witnesses) in the protocol is deemed necessary.
- In response to the comments received from the Ethics Committee of the Land Berlin, clarified that subjects who are unwilling to practice adequate infection protection will be excluded from this study.
- In response to the comments received from the Ethics Committee of the Land Berlin, added study stopping rules.
- Provided clarification that study evaluations need to be performed prior to study discharge or for subjects who are prematurely discontinued from the study.
- To assess Troponin T rather than Troponin I.
- Clarify that creatinine clearance needs to be calculated at screening.
- Serious Adverse Event (SAE) submission process per new standard operating procedure.

In amendment 3 following changes were made:

- Add secondary objective to characterize the PK of RTV.
- Changed the duration of study from 81 days to 88 days to accommodate an increase in the screening period for reporting of RT/Pol genotype.
- Changed the duration of the screening period from 28 days to 35 days to allow enough time for confirmation of Clade B infection in all subjects.
- Clarified EC90 as protein binding adjusted EC90.
- Added criteria that subjects who test positive for amphetamines (which, like cannabinoids, may be used for life style enhancement without meeting criteria for addiction) can be included in the study, unless they are excluded due to Exclusion criteria 2m in Section 4.2.2 (recent drug abuse).
- Changed exclusion criteria for absolute neutrophil count (ANC) 0.9 x lower limit of normal (LLN) to 0.7 x LLN. BMS-663068 and BMS-626529 do not appear to impact white blood cells (WBC) or ANC counts and this slight change to the exclusion criteria will avoid having to disqualify subjects based on clinically irrelevant variations in ANC between screening at Day -1.

- Removed footnote from clinical laboratory tests and blood (PBMC) collection that specified the collection should occur Pre-PM in group 2.
- Clarified that samples for clinical laboratory tests for subjects assigned to group 2 can be collected in the AM. Removed HIV-1 RNA analysis and CD4+ and CD8+ counts from this section since these samples need to be collected prior to dosing (ie. in the PM for group 2).
- Corrected spelling error.
- Add information for PK analyses of RTV.

Amendment 4 clarifies that interim analyses will be conducted for internal Bristol-Myers Squibb decision making that could include, but is not limited to selecting possible phase IIb doses.

1.6 Flow chart (V2.0 protocol)

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

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

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

Footnotes:

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
1. 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.

2 GENERAL SPECIFICATIONS

2.1 Analysis populations

Definition:
- All randomized population: all randomized subjects.
- Safety population: all randomized subjects who used the trial medication at least once.
- Pharmacokinetic population: all subjects who receive BMS-663068 and provided pharmacokinetic samples.
- Pharmacodynamic population: all subjects for whom pharmacodynamic measurements are available at baseline and at least one other time. Only Clade B subjects will be included in the population. Whether a subject is clade B or not will be derived from the protocol deviations.
- Pharmacokinetic/Pharmacodynamic: a combination of both populations.

The safety population will be used for the general descriptive part and for the safety part.
The Pharmacokinetic population will be used for the Pharmacokinetic analysis.
The Pharmacodynamic population will be used for the Pharmacodynamic analysis.
The Pharmacokinetic/Pharmacodynamic population will be used for the Pharmacokinetic /Pharmacodynamic relation analysis.

2.2 Variables and derived parameters

Pharmacokinetic variables:

- Cmax	Maximum observed plasma concentration
- Ctrough	Trough observed plasma concentration A composite Ctrough will be calculated as the geometric mean of all trough concentrations except the 12 h sample on Day 1 (24 h for group 2)
- 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 (after last dose only)
- Vz/F	Apparent volume of distribution based on the terminal phase (after last dose only)
- 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 biding adjusted EC_{90}. The

following in vivo exposure measures will be used in evaluating IQ: Cmax, composite Ctrough and Css,avg.

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

Safety assessments:
- adverse events
- laboratory safety
- vital signs
- ECG

2.3 Analysis timepoints

2.3.1 Allocation into analysis phases

Adverse events and concomitant therapies will be allocated into the following phases. For concomitant therapies a non-treatment-emergent analysis will be done. For adverse events, a treatment-emergent analysis will be done.

Phase	Start phase	End phase
Screening	Date of signing ICF	Date/time first intake of study medication – 1 minute
Treatment	Date/time first intake of study medication	Date/time last intake of study medication + 3 days(*)
Follow-up	Date/time last intake of study medication + 3 days + 1 minute	Trial termination date (*)

(*) Note that the last phase (in case of early termination) will always be closed by the trial termination date.

2.3.2 Treatment-emergent allocation of adverse events

A treatment-emergent way of allocation means that an event is allocated to an analysis phase according to its start date. If the event continues to be present during a subsequent analysis phase, it is not reported there again. So each event is reported exactly once. The **main allocation rule** is as follows: select the analysis phase for which "start phase ≤ event start ≤ end phase". In order to be able to do this, the start date of the event should be known. If this is not true, so if the start date(time) is only partially known or completely missing, then a worst-case allocation is performed as follows:
- The event start date(time) is completely unknown: the event will be allocated to the first treatment analysis phase in the trial;
- The date(time) is only partially known: then the event will be allocated to the first analysis phase for which the known part of the event start date makes sense:
    - Select all analysis phases for which the known parts satisfy the main allocation rule mentioned above.

- Pick the first treatment analysis phase from this selection. If there is no treatment analysis phase in the selection, then pick the first analysis phase of the selection.

Notes:
- Missing date(time) parts will not be imputed. The matching datetime field will remain missing.
- If variables would be derived from such incomplete dates, they would be set to "missing".
- If any of the event properties change in case of adverse events, it is recorded as a new event in the CRF and in the database. So if during a subsequent analysis phase the AE properties change, the event is reported as a new event.
- The assumption is that all analysis phase start and end dates are known, and also the dates of planned visit are known.

2.3.3 Non-treatment-emergent allocation of concomitant therapies

An event (e.g., a concomitant therapy) is allocated to EACH analysis phase during which the event is present. So each individual event can be reported more than once.
This way of allocation means that an event is allocated to each analysis phase during which the event was present, so not only to the analysis phase during which it started. An additional possibility is that the event may be still ongoing at the end of the trial, or that the event might even have started prior to trial start. Because there is no flag in the database to indicate whether the event started pre-trial or is still ongoing at the end of the trial, the following assumptions will be made:
- In case the start date is missing, it will be assumed that the event started prior to the trial.
- In case the end date is missing, it will be assumed that the event is still ongoing at the end of the trial.

The **main allocation rule** is as follows: select all analysis phases for which at least one of the following is true:
- "started prior to trial start" AND "still ongoing at trial end"
- "started prior to trial start" AND "start phase ≤ event stop (nonmissing)"
- "start phase ≤ start event ≤ phase end"
- "start event (nonmissing) < start phase" AND "event stop ≥ start phase"
- "start event (nonmissing) < start phase" AND "still ongoing at trial end"

If the start date(time) and/or stop date(time) is only partially known, then a worst-case allocation is performed as follows:
- If the event start date(time) is only partially known, then select all analysis phases that satisfy the above-mentioned general rules for the known date(time) parts.
- If the event stop date(time) is only partially known, then select all analysis phases that satisfy the above-mentioned general rules for the known date(time) parts.

Notes:
- Missing date(time) parts will not be imputed. The matching datetime field will remain missing.
- If variables would be derived from such incomplete dates, they would be set to "missing".
- The assumption is that all analysis phase start and end dates are known, and also the dates of planned visit are known.

2.3.4 Allocation into visit windows

The number of days in trial (relday) will be defined as:

relday = | *visit date – reference date + 1* if the visit is on or after the reference visit;
visit date – reference date if the visit is before the reference visit,
and where the reference day equals the first day of trial medication use.

Visits will be tabulated according to the planned visit number. No visit windows or time intervals will be used since visits are scheduled very quickly after one another. One exception to this rule is that baseline data may be imputed with earlier results (screening or unscheduled) if not available at the baseline visit. If this occurs, a footnote will be added.

The primary discussion of HIV RNA change from baseline will focus on day 9.

2.4 Handling of missing data

2.4.1 Missing values when computing percentages

Missing values will not be included in the denominator count when computing percentages.
Similarly, empty classes will not be shown in frequency tabulations.

2.4.2 Handling of values below (or above) a threshold

If the database contains values like e.g. “<0.04”, then for the descriptive statistics the value of the detection limit shall be used. In the above example, the value 0.04 will be used to replace the character value of “<0.04”.
Note that this rule only applies to safety data and to the HIV RNA (see also section 4.3.1).
For the purpose of calculating PK parameters, predose concentrations that are below the lower limit of quantification (BLQ), and concentrations prior to the first quantifiable concentration that are BLQ, will be set to zero.

2.4.3 Handling of unscheduled assessments or retests

Predose retests: use the LATEST one for the analysis.
Postdose retests: use the ORIGINAL/PLANNED one for the analysis. Retests or unscheduled samples will not be used in the descriptive statistics, but all be shown in listings. They will be used if there is a worst-case determination over a period of time.

2.4.4 HIV RNA viral load testing

For HIV RNA, multiple tests can be available: standard assay, ultra-sensitive assay and diluted sample assay.

If for a single sample multiple test results are available the following priority rules apply:
1: use left-censored result (<50)
2: use uncensored result: standard test has first priority; ultrasensitive second priority and diluted has third priority
3: use right censored result (> 100000)

2.4.5 Baseline

Baseline will be defined as the last non-missing measurement prior to the first study medication intake.

2.5 Validation model

SAS version 9.1 will be used for the analysis. The following statistical analysis validation models can be applied:

- Model A:
  Minimal validation. Review of the output, source code and program log by the person who designed/created the programs.
- Model B:
  Review of the output, source code and program log by an independent person (i.e., somebody else than the person who designed/created the programs).
- Model C:
  Review of the output, source code and program log by an independent person (i.e., somebody else than the person who designed/created the programs). This person will also reprogram the primary parameter(s) independently, and these results should match with the original analysis.
- Model D:
  Sponsor-specific.

The following validation model will be applied to this particular analysis:

☐ A
☒ B
☐ C: specifications of independent programming (e.g., for which parameters) are below:

- xxxxx
- xxxxx

☐ D

3 STATISTICAL METHODS

3.1 Planned analysis (protocol amendments included)

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 and provided pharmacokinetic samples 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.

Endpoint Definitions

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.

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 A composite Ctrough will be calculated as the geometric mean of all trough concentrations except the 12 h sample on Day 1 (24 h for group 2)
- 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 (after last dose only)
- Vz/F	Apparent volume of distribution based on the terminal phase (after last dose only)
- 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 EC90. The following in vivo exposure measures will be used in evaluating IQ: Cmax, composite Ctrough and Css,avg.

Protein binding adjusted EC90 for BMS-626529 will be derived from phenotypically measured individual EC50 values at baseline using the following formula:

Protein binding adjusted EC90 (ng/mL) = sc × mw × EC50 (µM) / fu

where sc is a scale factor relating EC50 to EC90 (sc = 5.5);
fu is the mean estimated unbound faction of BMS-626529 in vivo;
mw is the molecular weight of BMS-626529 free base (473.48 g/mole);
IC50 from monogram = EC50

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

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

Analyses
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.

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.

Efficacy Analyses
Not Applicable.

Pharmacokinetic Analyses
The multiple-dose pharmacokinetics of BMS-626529 and RTV following administration of BMS-663068 with or without RTV will be described by summary statistics (mean, SD, CV, median, minimum, maximum, geometric mean, geometric CV) for the pharmacokinetic parameters by regimen group, study day, dose time (AM or PM, Groups 1, 3, 4 and 5 only for BMS-626529; Groups 1 and 3 only for RTV), antiretroviral treatment history (ARV naive, ARV experienced, and combined [ARV naive + ARV experienced]).

To assess the dependency on regimen, scatter plots of BMS-626529 Cmax, AUC(TAU), AUC(0-24h), and composite Ctrough versus regimen group will be provided by dose time on Day 1 and on Day 8 (Groups 1, 3, 4 and 5 only). Time to steady-state will be evaluated by summary statistics of individual 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 summarized for all data, by sampling time and by regimen group. Inhibitory Quotient (IQ) of Cmax (on Day 8 following AM regimens except Group 2), composite Ctrough and Css,avg of BMS-626529 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 a mixed-effect model fitted to log-transformed data with study day as a fixed effect, and subject as random effect. 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 a mixed-effect model for Groups 1, 3, 4 and 5 only with time point (PM or AM) as a fixed effect and subject as random effect.

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 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, 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 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]). Additional analysis of HIV RNA beyond day 9 may be requested if HIV RNA continue to decline beyond Day 9 in the majority of individuals.

Pharmacokinetics/ Pharmacodynamic Analyses
The effect of BMS-626529 on PD measures (i.e., HIV RNA and 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 protein binding adjusted BMS-626529 EC90 (determined from Day 1 sample), a threshold of EC90 may 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 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 exposure parameters, and to assess the correlation between log10 changes from baseline in HIV RNA and IQs.

Outcomes Research Analyses
Not applicable.

Other Analyses
Summary statistics for exploratory biomarkers, such as but not limited to those stated in sections 6.6 and 6.9 of the protocol, 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 but are not in the scope of this analysis plan.

Interim Analyses
Data Summaries were added:
- on 50% of the sample size, including data up to day 15 for HIV RNA and CD4
- on 75% of the sample size, including data up to day 15 for HIV RNA and CD4
- on 100% of the sample size, including data up to day 15 for HIV RNA and CD4

No data summary on 25% of the sample was performed as no datasets were available at that time.
These summaries will only include patients with (either HIV or CD) data on day 15.
The final analysis will contain all data (up to trial termination) for all subjects.
The TLFs for these intermediate analyses are identified in this SAP with “+IA” in the TLF title.

3.2 Changes to the planned analysis

Only Clade B subjects will be included in the PD analysis population. This is because, based on in vitro data, PD and PK/PD analyses from non-Clade B subjects is anticipated to be substantially different from that of Clade B HIV.
For the inferential statistics in the PD analysis, the between-group comparison of the changes from baseline by means of a t-test is replaced by an ANCOVA model in order to correct for baseline (including baseline as a covariate in the model). This was done based on the EMEA Points to consider on adjustment for baseline covariates.

3.3 Further specifications

Stratification factor:
In case of a discrepancy between the recorded actual stratification and the stratification used for IVRS central randomization, the actual stratification as reported on the CRF randomization page will be used in the statistical analysis.

4 ANALYSIS DETAILS

All results will be presented per treatment group, unless specified otherwise. Listings will be ordered by treatment group, subject and time point (if applicable). The analysis population will be indicated in a subtitle.

4.1 *General characteristics*

The statistical analysis will be done for the safety population.
As descriptive statistics the mean, standard error, standard deviation, 90% confidence interval of the mean, minimum, maximum and median will be calculated.

4.1.1 Allocation

Listing GEN 1: Allocation: Randomization list

Listing of medication numbers, subject numbers, prior antiretroviral treatment history (stratification factor), date of randomization, treatment groups, country and site. Both the actual stratification factor and the one used for randomization will be listed, and the difference will be flagged.

4.1.2 Investigator information

Table GEN 1: Countries and sites: Tabulation

Tabulation of the number of subjects per country and site per treatment group and overall.

4.1.3 Subject disposition

Table GEN 2: Subject disposition: Descriptive statistics of the number of days in trial

Descriptive statistics of the number of days in trial per treatment group and per visit.

Table GEN 3: Subject disposition: Tabulation

Tabulation of number of subjects (per treatment group and overall):
- screened (i.e., who signed an ICF)
- not randomized and not treated
- randomized and not treated
- treated (= safety population)
- in the PD population
- in the PK population
- in the PK/PD population.

Listing GEN 2: Subject disposition: number of days in trial

Listing per subject of the number of days in trial for each visit, together with the actual visit dates and the trial termination date (= date of last contact).

Listing GEN 3: Subject disposition: trial phases

Listing per subject of the analysis phases in the trial, together with the start and end dates of each phase.

Listing GEN 4: Subject disposition: first and last contact in the trial

Date of first visit in the trial, date of last visit in the trial, date of last trial termination. Analysis population = all screened subjects.

4.1.4 Trial termination

Table GEN 4: Trial termination: tabulation

Tabulation per treatment group (and total) of completions/discontinuations, and the reasons for discontinuation.

Listing GEN 5: Trial termination

Listing per subject of the reason for completion/discontinuation, the number of days in trial at trial termination.

4.1.5 Protocol deviations

Protocol deviations will not be included in the database, and therefore not included in the analysis either. Medical Writing will receive a list of deviations from Data Management to include in the CSR.

Listing GEN 6: No-treatment subjects

Listing of the no-treatment subjects and the reason of being a no-treatment subject.

4.1.6 In- and exclusion criteria

Listing GEN 7: In- and exclusion criteria (violations)

Only criteria that are not met will be listed.

4.1.7 Demographic data and baseline disease characteristics

Demographic parameters only listed:
- subject initials
- date of signing informed consent
- date of signing pharmacogenetic informed consent
- date of birth

Continuous demographic parameters:
- age at screening (years)
- height (cm) at screening
- weight (kg) at screening
- body mass index BMI = (weight in kg) / (height in m)² (kg/m²), as calculated automatically in the eCRF.

Categorical demographic parameters:
- sex
- race
- drug abuse (urine drug screen)

Continuous baseline disease parameters:
- baseline CD4+ and CD8+ counts
- baseline HIV-1 RNA results
- baseline $\log_{10}$ HIV-1 RNA results
- duration of HIV infection (=baseline date - date of first confirmed positive HIV test+1)
- Baseline envelope phenotype at day 1
- EC50 and PBA EC90

Categorical baseline disease parameters:
- baseline HIV-1 RNA results (<5.000, [5.000-10.000[, [10.000-100.000[, ≥100.000)
- baseline CD4+ and CD8+ counts (<200, [200-500[, ≥500)
- Hepatitis infection status:
  - Hepatitis C antibody
  - Hepatitis B surface antigen
- HIV Serology screen
- ART treatment history (+date of first ARV intake and date of last ARV intake prior to screening)
- ART naïve / experienced (stratification factor)
- Exposed to HIV attachment inhibitor

Analysis:

Table GEN 5: Demographic data: descriptive statistics

Continuous parameters: descriptive statistics per treatment group and overall.
Categorical parameters: tabulation per treatment group and overall.
For each population.

Listing GEN 8: Demographic data

Listing per subject of all demographic parameters.

Table GEN 6: Baseline disease characteristics: descriptive statistics

Continuous parameters: descriptive statistics per treatment group and overall.
Categorical parameters: tabulation per treatment group and overall.
For each population.

Listing GEN 9: Baseline disease characteristics

Listing per subject of all baseline disease characteristics and date of first confirmed positive HIV-1 test.

Listing GEN 10: RT/Pol genotype

Listing per subject of all RT/Pol genotype data (including HIV RT and Pol genotypic resistance mutations).

Listing GEN 11: Envelope phenotype

Listing per subject of baseline envelope phenotype (EC50 and PBA EC90) at day 1.

4.1.8 Baseline physical examination

Table GEN 7: Physical examinations: tabulation

Tabulation per treatment group and overall.

Listing GEN 12: Physical examinations: abnormalities

Listing of the baseline physical examination results of abnormal findings only.

4.1.9 Concomitant therapy

Treatments will be reported in each analysis phase during which they were applied. I.e., a non-treatment-emergent allocation. The analysis phases are defined in §2.3.1, and the allocation algorithm in case of missing data is discussed in §2.4.
Concomitant therapies are coded using WHO-DRUG. In the tabulation, the generic term will be used. The ATC classification will not be used for analysis.

Table GEN 8: Concomitant therapies: tabulation

Tabulation of the generic terms per phase, treatment group and overall.

Listing GEN 13: Concomitant therapies

Listing per subject of all concomitant therapy data.

4.1.10 Diagnostic and medical treatment procedures

Table GEN 9: Diagnostic and medical treatment procedures: tabulation

Tabulation of the medical treatment used by the patients.

Listing GEN 14: Diagnostic and medical treatment procedures

Listing per subject of all medical treatment data.

4.1.11 Medical/Surgical history and concomitant diseases

Listing GEN 15: Medical history

Listing per subject of the (abnormal) medical history data (i.e., condition no longer present).

Listing GEN 16: Concomitant diseases

Listing per subject of the (abnormal) concomitant diseases data (i.e., condition still present).

4.1.12 Exposure

Parameters:

- total treatment duration = date of last drug administration – date of first drug administration + 1 day

Analysis:

Table GEN 10: Exposure: tabulation

Frequency tabulation per treatment group of the total treatment duration of BMS-663068 and ritonavir.

Listing GEN 17: Exposure

Listing per subject of all medications, number of units and times of intake per phase.

Listing GEN 18: Exposure: breakfast

Listing per subject of the start and stop time of breakfast.

Listing GEN 19: Exposure: snacks

Listing per subject of the start and stop time of the snack.

4.2 Pharmacokinetics

The final statistical analysis will be done on the Pharmacokinetics population.

Table PK 1: Actual PK blood sampling times

The actual blood sampling times relative to BMS-663068 administration will be tabulated by subject, day and group.

Table PK 2: BMS-626529 plasma concentrations

Individual values and descriptive statistics of BMS-626529 plasma concentration vs. the theoretical sampling time will be tabulated by regimen group, by day, by dosing time (groups 1, 3, 4 and 5). Descriptive statistics will be provided overall and by antiretroviral treatment history (ARV naïve or ARV experienced).

Table PK 3: Ritonavir plasma concentrations

Individual values and descriptive statistics of Ritonavir plasma concentration vs. the theoretical sampling time will be tabulated by regimen group, by day, by dosing time (groups 1 and 3). Descriptive statistics will be provided overall and by antiretroviral treatment history (ARV naïve or ARV experienced).

Figure PK 1: Average BMS-626529 plasma concentration vs. time profiles

Arithmetic mean (±SD if possible) of BMS-626529 plasma concentration vs. time profiles on linear and log linear scales, all regimens groups in the same graph (with different symbols), one graph by day, overall and by ARV history.

Figure PK 2: Individual BMS-626529 plasma concentration vs. time profiles, by regimen group

Spaghetti plots of individual BMS-626529 plasma concentration vs. time profiles on linear and log linear scales, all subjects in the same graph, one graph by regimen group and by day, solid lines for ARV naïve and dashed lines for ARV experienced.

Figure PK 3: Individual BMS-626529 plasma concentration vs. time profiles, by subject

Individual BMS-626529 plasma concentration vs. time profiles on linear and log linear scales, one graph by subject (with indication of the ARV history), all days in the same graph.

Figure PK 4: Average ritonavir plasma concentration vs. time profiles

Arithmetic mean (±SD if possible) of ritonavir plasma concentration vs. time profiles on linear and log linear scales, all regimens groups in the same graph (with different symbols), one graph by day, overall and by ARV history.

Figure PK 5: Individual ritonavir plasma concentration vs. time profiles, by regimen group

Spaghetti plots of individual BMS-626529 plasma concentration vs. time profiles on linear and log linear scales, all subjects in the same graph, one graph by regimen group and by day, solid lines for ARV naïve and dashed lines for ARV experienced.

Figure PK 6: Individual ritonavir plasma concentration vs. time profiles, by subject

Individual ritonavir plasma concentration vs. time profiles on linear and log linear scales, one graph by subject (with indication of the ARV history), all days in the same graph.

Table PK 4: BMS-626529 pharmacokinetic parameters

Individual values and descriptive statistics of BMS-626529 plasma pharmacokinetic parameters (including protein binding and IQs) will be tabulated by regimen group, by day and by dosing time where applicable. Descriptive statistics will be provided overall and by antiretroviral treatment history (ARV naïve or ARV experienced).

Table PK 5: Ritonavir pharmacokinetic parameters

Individual values and descriptive statistics of ritonavir plasma pharmacokinetic parameters will be tabulated by regimen group, by day and by dosing time where applicable. Descriptive statistics will be provided overall and by antiretroviral treatment history (ARV naïve or ARV experienced).

Figure PK 7: Dependency on regimen of BMS-626529 pharmacokinetic parameters

Scatter plots of BMS-626529 Cmax, AUC(TAU), AUC(0-24h) and Ctrough versus regimen groups, one graph by day (Day 1 and Day 8) and by dosing time (where applicable). Different symbols for ARV naïve and ARV experienced subjects.

Figure PK 8: Dependency on regimen of ritonavir pharmacokinetic parameters

Scatter plots of ritonavir Cmax, AUC(TAU), AUC(0-24h) and Ctrough versus regimen groups, one graph by day (Day 1 and Day 8) and by dosing time (where applicable). Different symbols for ARV naïve and ARV experienced subjects.

Figure PK 9: Steady-state assessment for BMS-626529 plasma concentration

Geometric mean of BMS-626529 Ctrough concentration vs. study day, all regimens groups in the same graph (with different symbols), overall and by ARV history.

Figure PK 10: Steady-state assessment for ritonavir plasma concentration

Geometric mean of ritonavir Ctrough concentration vs. study day, all regimens groups in the same graph (with different symbols), overall and by ARV history.

Table PK 6: Statistical assessment of the accumulation of plasma BMS-626529

Point estimates and 90% confidence intervals for the ratios of Day 8 vs. Day 1 for AUC(TAU), Cmax and Ctrough, One sub-table for each regimen group.

Table PK 7: Statistical assessment of the effect of RTV on BMS-626529 pharmacokinetic parameters

Point estimates and 90% confidence intervals for the ratios of group 3 versus group 5 and group 4 versus group 5 for AUC(TAU), Cmax and Ctrough (separate assessment after morning and evening administration). One sub-table for each comparison

Table PK 8: Statistical assessment of the diurnal variation of BMS-626529 pharmacokinetic parameters

Point estimates and 90% confidence intervals for the ratios of PM versus AM administration for AUC(TAU), Cmax and Ctrough. One sub-table for each regimen group.

4.3 Pharmacodynamics

The statistical analysis will be done for the Pharmacodynamic population.

4.3.1 Primary parameter: Log_{10} HIV RNA

The primary pharmacodynamic parameter is the change from baseline in *log_{10} HIV RNA* to day 9. No imputation will be perfomed in case of a missing value on day 9. All other time points will be regarded as secondary. Baseline is defined as day 1 predose. In case this is missing, the last non-missing assessment prior to first study medication intake will be used.

As descriptive statistics the mean, standard error, standard deviation, 90% confidence interval of the mean, minimum, maximum and median will be calculated.

For the quarterly summaries, all data up to and including day 15 will be included.

Assessments:
HIV-1 RNA analysis. Values below the limit of detection will be imputed by the value of the detection limit. This will be flagged in the listing.

Parameters:
- HIV RNA viral load
- log_{10} HIV RNA viral load
- changes from baseline in log_{10} HIV RNA (especially to day 9)
- largest decrease in log_{10} HIV RNA from day 2 up to and including day 15 (nadir)
- day when this largest decrease was achieved (day 2 up to and including day 15)

Analysis:

Figure PD 1: HIV log_{10} RNA: Subject profile plots of the actual values (+IA)

Subject profile plot of the actual values over time. Each subject is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis with the viral load will use a log10 scale. Solid symbols are used for viral loads under the detection limit.

Table PD 1: HIV RNA and HIV log_{10} RNA: Descriptive statistics of the actual values (+IA)

Descriptive statistics of the actual values (in original units as well as log_{10} transformed) per time point and per regimen group.

Figure PD 2: HIV log_{10} RNA: Subject profile plots of the changes from baseline (+IA)

Subject profile plot of the changes from baseline over time. Each subject is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change). Solid symbols are used for viral loads under the detection limit.

Figure PD 3: HIV log_{10} RNA: Mean plot of the changes from baseline (+IA)

Mean plot (with 90% CI) of the changes from baseline over time. Each regimen is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change).

Figure PD 4: HIV log_{10} RNA: Median plot of the changes from baseline (+IA)

Median plot of the changes from baseline over time. Each regimen is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change).

Figure PD 5: HIV log_{10} RNA: Scatter plots

Scatter plots of log10 change from baseline in HIV RNA at day 9 versus baseline. Regimen groups will be differentiated by different plot symbols.

Table PD 2: HIV log10 RNA: Descriptive statistics of the changes from baseline (+IA)

Descriptive statistics per time point, per regimen group of the changes from baseline.

Table PD 3: HIV log10 RNA: Inferential statistics of the changes from baseline (+IA)

Between-treatment comparison: ANCOVA to test the difference in mean log_{10} decrease in HIV RNA at day 9 between 2 regimen groups, including baseline as a covariate. No correction for multiplicity will be done. Also 90% confidence intervals of the mean treatment difference will be calculated. This analysis will be replicated including ARV history. The interaction between treatment and ARV history will be tested, and dropped from the model if $p<0.10$.

Within-group comparison versus baseline: paired t-test.

Table PD 4: HIV log10 RNA: Categorized changes from baseline (+IA)

Categories for the change in log10 HIV RNA per time point with following categories:
- decrease >3 log,
- decrease]2-3] log,
- decrease]1-2] log,
- decrease]0.5-1] log,
- decrease]0-0.5] log
- no change or increase.

Frequency tabulation per time point and per regimen group.

Table PD 5: HIV log_{10} RNA: Descriptive statistics on maximum log_{10} decrease from baseline in HIV RNA (+IA)

Descriptive statistics of the maximum log_{10} decrease from baseline in HIV RNA by regimen group.

Table PD 6: HIV log_{10} RNA: Inferential statistics on maximum log_{10} decrease from baseline in HIV RNA (+IA)

Between-group comparisons: ANCOVA to test the difference in mean log_{10} decrease in HIV RNA at day 9 between 2 regimen groups, including baseline as a covariate. No correction for multiplicity will be done. This analysis will be replicated including ARV

history. The interaction between treatment and ARV history will be tested, and dropped from the model if p<0.10.
Within-group comparison versus baseline: paired t-test.

Figure PD 6: HIV log_{10} RNA: Scatter plot of the maximum change from baseline in HIV RNA

Scatter plot of maximum log_{10} HIV RNA decrease from baseline versus the baseline log_{10} HIV RNA.

Table PD 7: HIV log10 RNA: Categorized maximum change from baseline (+IA)

Categories for the maximum change in log10 HIV RNA with following categories:
- decrease >3 log,
- decrease]2-3] log,
- decrease]1-2] log,
- decrease]0.5-1] log,
- decrease]0-0.5] log
- no change or increase.

Frequency tabulation per regimen group.

Table PD 8: HIV log_{10} RNA: Day of maximum log_{10} decrease from baseline in HIV RNA

Frequency table of the day of reaching the maximum log_{10} decrease from baseline in HIV RNA by regimen group.

Analysis per ARV treatment history:
Plots and descriptive statistics will be created for treatment-naïve and treatment-experienced subjects separately, and will be presented next to one another.

Table PD 9: HIV RNA and HIV log_{10} RNA: Descriptive statistics of the actual values by ARV treatment history (+IA)

See Table PD 1.

Figure PD 7: HIV log_{10} RNA: Scatter plot of change from baseline in HIV log_{10} RNA on Day 9 vs. Envelope Phenotype (Protein Binding Adjusted EC90) on Day 1 separated by ARV experience

Scatter plots of log_{10} change from baseline in HIV RNA at day 9 versus Protein Binding Adjusted EC90 of envelope phenotype at baseline separately by the ARV experience. Different plot symbols for the treatment regimens.
Perform a linear regression of log10 change on the Protein Binding Adjusted EC90, separated by the ARV experience, and provide the estimate and test results on the coefficient of the slope of the Protein Binding Adjusted EC90.

Figure PD 8: HIV log_{10} RNA: Mean plot of the changes from baseline by ARV treatment history (+IA)

Figure PD 9: HIV log_{10} RNA: Median plot of the changes from baseline by ARV treatment history (+IA)

Table PD 10: HIV log10 RNA: Descriptive statistics of the changes from baseline by ARV treatment history (+IA)

See Table PD 2.

Table PD 11: HIV log10 RNA: Inferential statistics of the changes from baseline by ARV treatment history (+IA)

See Table PD 3.

Table PD 12: HIV log10 RNA: Categorized changes from baseline by ARV treatment history (+IA)

See Table PD 4.

Table PD 13: HIV log_{10} RNA: Descriptive statistics on maximum log_{10} decrease from baseline in HIV RNA by ARV treatment history (+IA)

See Table PD 5.

Table PD 14: HIV log_{10} RNA: Inferential statistics on maximum log_{10} decrease from baseline in HIV RNA by ARV treatment history (+IA)

See Table PD 6.

Figure PD 10: HIV log_{10} RNA: Scatter plot of the maximum change from baseline in HIV RNA by ARV treatment history

Scatter plot of maximum log_{10} HIV RNA decrease from baseline versus the baseline log_{10} HIV RNA, separately by ARV treatment history category. Graphs will be presented next to one another.

Figure PD 11: HIV log_{10} RNA: Scatter plot of maximum HIV log_{10} RNA decrease from baseline vs. Envelope Phenotype (Protein Binding Adjusted EC90) on Day 1 separated by ARV experience

Scatter plots of maximum log_{10} HIV RNA decrease from baseline versus Protein Binding Adjusted EC90 of envelope phenotype on Day 1 separately by the ARV experience. Different plot symbols for the treatment regimens.
Perform a linear regression of log10 change on the Protein Binding Adjusted EC90, separated by the ARV experience, and provide the estimate and test results on the coefficient of the slope of the Protein Binding Adjusted EC90.

Table PD 15: HIV log10 RNA: Categorized maximum change from baseline by ARV treatment history (+IA)

See Table PD 4.

Table PD 16: HIV log_{10} RNA: Day of maximum log_{10} decrease from baseline in HIV RNA by ARV treatment history

Analysis listing:

Listing PD 1: HIV RNA viral load data (+IA)

Listing of all viral load data per subject and per treatment group. A flag will be added to indicate the timepoint of achieving an absolute HIV RNA nadir or <50c/ml or <400</ml.

4.3.2 CD4+ and CD8+ counts and percentages

As descriptive statistics the mean, standard error, standard deviation, 90% confidence interval, minimum, maximum and median of the parameters will be calculated.

Baseline = day 1 predose.

Assessments:
- CD4+ and CD8+ counts and percentages

Parameters:
- actual values
- changes from baseline

Analysis:

Figure PD 12: CD4+ and CD8+: Subject profile plots of the actual values (+IA)

Subject profile plot of the actual values over time. Each subject is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols.

Table PD 17: CD4+ and CD8+: Descriptive statistics of the actual values

Descriptive statistics of the actual values (counts and percents) per treatment group and per time point.

Figure PD 13: CD4+ and CD8+: Subject profile plots of the changes from baseline (+IA)

Subject profile plot of the changes from baseline over time. Each subject is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change).

Figure PD 14: CD4+ and CD8+: Mean plot of the changes from baseline (+IA)

Mean plot (with 90% CI) of the changes from baseline over time. Each regimen is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change).

Figure PD 15: CD4+ and CD8+: Median plot of the changes from baseline (+IA)

Median plot of the changes from baseline over time. Each regimen is represented by a line, showing data from day 1 (predose) up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change).

Table PD 18: CD4+ and CD8+: Descriptive statistics of changes from baseline (+IA)

Descriptive statistics of the changes from baseline per treatment group and per time point. No inferential statistics are planned.

Table PD 19: CD4+ and CD8+: Cross-tabulation of time points versus baseline

For CD4+, CD8+ cell counts: cross-tabulation per treatment group of each time point versus baseline of the categories < 200, 200-500, ≥ 500.

Analysis per ARV treatment history:
Plots and descriptive statistics will be created for treatment-naïve and treatment-experienced subjects separately, and will be presented next to one another.

Table PD 20: CD4+ and CD8+: Descriptive statistics of the actual values by ARV treatment history

Figure PD 16: CD4+ and CD8+: Mean plot of the changes from baseline by ARV treatment history (+IA)

Figure PD 17: CD4+ and CD8+: Median plot of the changes from baseline by ARV treatment history (+IA)

Table PD 21: CD4+ and CD8+: Descriptive statistics of changes from baseline by ARV treatment history (+IA)

See Table PD 18.

Table PD 22: CD4+ and CD8+: Cross-tabulation of time points versus baseline by ARV treatment history

Analysis listing:

Listing PD 2: CD4+ and CD8+ data

Listing of all CD4+, CD8+ data per subject and per treatment group.

4.4 Pharmacokinetics/pharmacodynamics relation

The statistical analysis will be done for the Pharmacokinetics/pharmacodynamics population.
As descriptive statistics the mean, standard error, standard deviation, 90% confidence interval of the mean, minimum, maximum and median will be calculated.

Assessments:
- BMS-626529 plasma concentration
- BMS-626529 EC_{50}
- BMS-626529 EC_{90} (generated with standard conversion factor applied to measured EC_{50})
- BMS-626529 Protein Binding Adjusted EC_{90}
- BMS-626529 IQs
- HIV RNA plasma HIV RNA

Parameters
- Largest decrease in plasma HIV RNA (days 2 up to and including day 15)

Analysis:

Figure PK/PD 1: PK/PD: scatter plot of changes from baseline in plasma HIV RNA and RNA nadir versus Protein Binding Adjusted BMS-626529 EC_{90}

Scatter plots will be made to assess the relationship between the log10 changes from baseline in plasma HIV RNA at day 9 and RNA nadir vs Protein Binding Adjusted BMS-626529 EC_{90}.

Table PK/PD 1: PK/PD: Descriptive statistics of changes from baseline of plasma HIV RNA

A threshold will be determined based on the scatter plot in Table PK/PD1. Descriptive statistics will be provided for the changes from baseline in plasma HIV RNA and log10 HIV RNA by treatment group, per time point and ARV treatment history, excluding subjects with Protein Binding Adjusted EC_{90} above the previously defined threshold.

Figure PK/PD 2: PK/PD: scatter plot of changes from baseline in CD4+ and CD8+ cell counts versus Protein Binding Adjusted BMS-626529EC_{90} and versus PK parameters

Scatter plots will be made to assess the relationship between the changes from baseline in CD4+ and CD8+ cell counts and Protein Binding Adjusted BMS-626529 EC_{90} and versus PK parameters.

Figure PK/PD 3: PK/PD: scatter plot of changes from baseline in plasma HIV RNA and RNA nadir versus BMS-626529 Iqs and versus PK parameters

To assess the relationship between the log10 changes from baseline in plasma HIV RNA at day 9 vs BMS-626529 IQs, scatter plots of log10 changes from baseline in plasma HIV RNA and RNA nadir versus BMS-626529 IQs and versus PK parameters will be made. Also the correlation between $\log_{10}$ changes from baseline in HIV RNA and RNA nadir vs IQs and vs PK parameters will be presented in a footnote of the graph.

Listing PK/PD 1: HIV RNA and PK parameters

Listing of the HIV RNA decrease and the PK parameters per treatment group.

4.5 Safety

The safety analysis will be done for the safety population.
The safety analysis will not present subgroup analyses by ARV treatment history.

4.5.1 Adverse events

Treatment-emergent principle:
An AE will only be reported in the phase where it started, and not in subsequent phases if the AE continues to be present. The reporting (analysis) phases are defined in §2.3.1, and the allocation algorithm in case of missing data is discussed in §2.4.

Worst-case principle:
When cross tabulating AE preferred terms versus an AE attribute (e.g., severity), the worst-case is always applied within each analysis phase. I.e., when a subject has two times the same AE preferred term in the same analysis phase, then the subject is reported only once: only with the worst severity. If this happens in two different analysis phases, the AE is reported twice: once in each analysis phase. This worst-case principle is not applied to the number of events. All events will be shown.

Definitions:
Tabulations will show:
- *N* = the number of subjects. In case a subject has multiple events of the same AE preferred term in the same reporting (analysis) phase, then the subject will only be counted once.
- *%* = percentage of N relative to the total number of subjects in the reporting (analysis) phase.

Other derived parameters:
- AE preferred term = 'NONE': the subject does not have an AE in the reporting (analysis) phase
- onset day = AE start date – analysis reference date + 1 (and is only defined when both dates are completely known)
- duration
  = AE stop date – AE start date + 1 (in case both dates are completely known)
  = trial termination date – AE start date + 1 (in case the start date is completely known, and the AE has not resolved yet at the end of the study. These observations will be flagged in the listing, e.g., as ">x days" instead of just "x days".)
  = missing in all other cases.

Coding:
Adverse event verbatims were coded using the MedDRA dictionary. The tabulations will show the system organ class and the preferred term.

Analysis:
The screening analysis phase will only be listed, unless specified otherwise.

Table SAF 1: Adverse events: Summary table

Tabulation per treatment group and per analysis phase (screening, treatment, follow-up, treatment and follow up) of the total number (and %) of subjects:
- with data;
- with at least one treatment-emergent AE;

- with at least one treatment-emergent SAE;
- with at least one treatment-emergent AE leading to death;
- with at least one mild (grade1) treatment-emergent AE;
- with at least one moderate (grade2) treatment-emergent AE;
- with at least one severe (grade3) treatment-emergent AE;
- with at least one very severe (grade4) treatment-emergent AE;
- with at least one severe or very severe (grade 3-4) treatment-emergent AE;
- with at least one treatment emergent AE for which the study treatment was permanently stopped;
- with at least one treatment emergent AE for which the study treatment was temporarily stopped;
- with at least one treatment emergent AE that is thought to be related to treatment;

Table SAF 2: Adverse events: Tabulation of all events

Tabulation of treatment emergent AE preferred terms per body class, per analysis phase and per treatment group.

Table SAF 3: Adverse events: Tabulation per intensity

Cross-tabulation of treatment emergent AE preferred terms versus their intensity. Exclude the 'NONE' from this table. Use the worst-case intensity per treatment emergent AE per subject. Per analysis phase and per treatment group.

Table SAF 4: Adverse events: Tabulation per action taken against study treatment

Tabulation of treatment emergent AE preferred terms versus the action taken against the study treatment. Exclude the 'NONE' from this table. Use the worst-case per treatment emergent AE per subject. Per analysis phase and per treatment group.
Part A): considering the action taken towards BMS-663068
Part B): considering the action taken towards Ritonavir

Table SAF 5: Adverse events: Tabulation of all treatment-related adverse events

Tabulation of treatment emergent AE preferred terms per body class, per analysis phase and per treatment group. Selecting only the treatment emergent AE that were treatment-related.

Table SAF 6: Adverse events: Tabulation of the intensity of all treatment-related adverse events

Cross-tabulation per analysis phase of treatment emergent AE preferred terms versus their intensity. Per body class and per treatment group. Use the worst-case intensity per treatment emergent AE per subject and per analysis phase, selecting only the AEs that were treatment-related.

Table SAF 7: Adverse events: Tabulation of the intensity of all not treatment-related adverse events

Cross-tabulation per analysis phase of treatment emergent AE preferred terms versus their intensity. Per body class and per treatment group. Use the worst-case intensity per treatment emergent AE per subject and per analysis phase, selecting only the AEs that were not treatment-related.

Analysis listings:

Listing SAF 1: Adverse events: Summary listing of all events (+IA)

Listing per subject of the treatment emergent AE preferred term, start and stop date with onset day and duration and the outcome (in case of serious adverse events), intensity, relation to the study treatment, action taken regarding the study treatment, concomitant therapy started because of the AE, and a seriousness flag.
In such a way that all information fits on one single line for each AE.

Listing SAF 2: Adverse events: All events

Listing per subject of the AE verbatim / preferred (coded) term / system organ class, start and stop date with onset day and duration and the outcome, intensity, relation to the study treatment, action taken regarding the study treatment, concomitant therapy started because of the AE, and a seriousness flag together with its details (hospitalization, life-threatening,…).

Listing SAF 3: Adverse events: Death (+IA)

Listing of all AEs resulting in death.

Listing SAF 4: Adverse events: Serious events (+IA)

Listing of all serious AEs.

Listing SAF 5: Adverse events: Events for which the study or the study treatment were permanently discontinued (+IA)

Listing of the AEs for which the study treatment was permanently discontinued, or for which the study was discontinued.

4.5.2 Laboratory safety: hematology and biochemistry

The analysis will be done on SI-converted values only.

Abnormality codes:
All values will be classified according to the test's normal ranges as below, within or above normal range. Values equal to the normal limits are still considered normal.

Worst-case abnormality
Per test and per subject, a worst-case post-baseline will be derived. This worst-case is defined as:
- (B) Below normal: at least one post-baseline assessment is below normal range, and no post-baseline assessment is above normal range.
- (A) Above normal: at least one post-baseline assessment is above normal range, and no post-baseline assessment is below normal range.
- (W) Within normal: all post-baseline assessments are within normal range.
- (A+B) Both above and below normal: at least one post-baseline assessment is below normal range, and another post-baseline assessment above normal range.
- (M) Missing, when there are no post-baseline assessments.

Local lab data and unscheduled visits (if any) are normally only listed but shall be used in the determination of the worst-case abnormality. Thus, all post-baseline lab results will be used for this worst-case.

Parameters to analyse:

- raw (observed) values;
- changes from reference;
- abnormality codes per time point
- worst-case on-treatment abnormality code

The reference assessment (baseline) will be the measurement the closest –but prior– to the first medication intake, and shown as 'Imputed Baseline' in the tables. As only measurements from the central lab will be considered for this, the reference assessment visit will usually be the screening visit, unless a pre-dose unscheduled assessment occurs after the screening assessment. The data from SYNLAB on day -1 will not be used as a reference.

Analysis:

Table SAF 8: Laboratory safety: Descriptive statistics of the actual values

Descriptive statistics of the actual values, sorted per test, per time point and per treatment group.

Table SAF 9: Laboratory safety: Descriptive statistics of the changes from baseline

Descriptive statistics of the changes from baseline, sorted per test, per time point and per treatment group.

Table SAF 10: Laboratory safety: Shift table of the abnormalities at each time point versus baseline

Frequency table showing per test, per time point and per treatment group the number of subjects in each of the possible combinations of normal regions at the two time points (from below normal to within normal, from above normal to above normal, etc.). I.e., the change from baseline in abnormality code.

Table SAF 11: Laboratory safety: Shift table of the worst-case abnormalities versus baseline

Frequency table showing per test and per treatment group the worst-case on-treatment abnormality code, cross-tabulated versus the baseline abnormality code.

Listing SAF 6: Laboratory safety: All test results

Listing per treatment group, per subject and per time point of all test results, flagging out-of-normal values. Flag the samples for which the subject had not been fasting for at least 7 hours prior to sampling.

Listing SAF 7: Laboratory safety: Abnormal test results

Listing per treatment group, per subject and per time point of all test results, selecting only the out-of-normal values. Flag the samples for which the subject had not been fasting for at least 7 hours prior to sampling.

Listing SAF 8: Laboratory safety: pregnancy tests

Listing of the pregnancy tests per treatment group.

Listing SAF 9: Laboratory safety: Comments

Listing of the lab comments.

4.5.3 Urinalysis

Table SAF 12: Laboratory safety: Cross-tabulation of the urinalysis results against baseline

Cross-tabulation per test, per time point and per treatment group of the urinalysis results against the baseline results.

Listing SAF 10: Laboratory safety: Urinalysis results

Listing of the urinalysis test results per subject.

4.5.4 ECG

Reference time point:
The reference assessment (baseline) will be the measurement the closest –but prior– to the first medication intake (=imputed baseline). If there are two assessments on day -1 (i.e. a 'day -1' assessment and an 'unscheduled' assessment), the unscheduled assessment will be taken as a baseline since this was a re-test of the day -1 assessment.

Parameter definitions:
The following **measurements** will be analysed:
- HR (bpm);
- PR (ms);
- QT (ms)
- QRS (ms);
- uncorrected QT (ms);

The following **HR-based corrections of the QT interval** will be analysed:
- Bazett's square-root corrected QT[1]: QTcB (ms) = QT (ms) $\times \sqrt{\frac{HR(bpm)}{60}}$
- Fridericia's cube-root corrected QT[2]: QTcF (ms) = QT (ms) $\times \sqrt[3]{\frac{HR(bpm)}{60}}$

If RR is missing, but HR is available from the same ECG reading, the following replacement will be made in the above formulas.

$$\frac{1000}{RR(ms)} = \frac{HR(bpm)}{60}$$

Corrected QT (QTc) will always be re-computed if already provided. Provided QTcs will only be listed.

If HR is missing, it will be calculated using RR (if available) and rounded to the integer value (see formula above). HR from the vital signs part (i.e., pulse) will not be used in this ECG analysis part. Recalculated HR values will be flagged in the listing.

Any roundings will be performed after computation of the applicable parameters, and before any further handling.

Abnormalities for the actual values:

The actual values will be categorized into abnormalities using the normal ranges defined in the table below. Values equal to the boundaries are still considered normal.

Parameter	Lower limit	Upper limit
HR, bpm	55 and change of < -15	100 and change of > +30
PR, ms	NAP	200
QRS, ms	50	120

Following ICH-E14, the actual values of the **uncorrected as well as the corrected**

QTs will also be categorised into:

≤ 450 ms

]450,480] ms

]480,500] ms

> 500 ms.

Abnormalities on the changes from baseline (QT and QTc parameters):
Abnormalities on the change from baseline will only be defined for corrected QT, as follows:

≤ 30 ms;
]30 ; 60] ms;
> 60 ms.

Only increases by > 30 ms will be considered as abnormalities.
Note: the QTc definitions for abnormalities follow the ICH E14 guidance[3].

Worst-case abnormality for HR, QRS and PR intervals:
Per parameter and per subject, a worst-case post-baseline will be derived. This worst-case is defined as:

- (B) Below normal: at least one post-baseline assessment is below normal range, and no post-baseline assessment is above normal range.
- (A) Above normal: at least one post-baseline assessment is above normal range, and no post-baseline assessment is below normal range.
- (W) Within normal: all post-baseline assessments are within normal range.
- (A+B) Both above and below normal: at least one post-baseline assessment is below normal range, and another post-baseline assessment above normal range.
- (M) Missing, when there are no post-baseline assessments.

All post-baseline assessments will be included in this derivation; also possible unscheduled assessments.

Worst-case abnormality for QT and QTc intervals:
Per parameter and per subject, a worst-case post-baseline will be derived. This worst-case is defined as the highest QT(c) value. This worst-case will be derived for both the absolute values as well as the changes from baseline. All post-baseline assessments will be included in this derivation; also possible unscheduled assessments.

Parameters to analyze:

- actual values;
- changes from baseline;

- abnormality classifications for the actual values;
- abnormality classification for the increases from baseline (only QT and QTc);
- worst-case abnormalities.

Analysis:

Table SAF 13: ECG: Descriptive statistics of actual values

Descriptive statistics per parameter, per time point and per treatment group of actual (raw) values.

Figure SAF 1: ECG: Mean plot of the changes from baseline

Mean plot (with SE bars) of the changes from baseline over time. Each regimen is represented by a line, showing data from imputed baseline up till day 15. Regimen groups will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change).
Separate plot for each parameter.

Figure SAF 2: ECG: Scatter plot of the actual QT(c) interval versus the plasma concentration

Scatter plots of the QT and QTc values at day 8 versus the BMS-626529 plasma levels at day 8. Different plot symbols for the treatment regimens.

Figure SAF 3: ECG: Scatter plot of the changes from baseline in QT(c) interval versus the plasma concentration

Scatter plots of the change from baseline in QT and QTc at day 8 versus the BMS-626529 plasma levels at day 8. Different plot symbols for the treatment regimens.
Perform a linear regression of the change from baseline in QT and QTc on the plasma levels, and provide the estimate and test results on the coefficient of the slope.
Add a horizontal reference line at change=0.

Figure SAF 4: ECG: Plots of mean QT and QTc and mean BMS-626529 concentration versus time since dosing

Plot per treatment regimen of the mean (without SE) change in QT and QTc, together with the mean BMS-626529 concentration. The left vertical axis should provide the change from baseline in QT or QTc, and the right vertical axis should provide the plasma levels.

Table SAF 14: ECG: Descriptive statistics of changes from baseline

Descriptive statistics per parameter, per time point and per treatment group of the changes from baseline.

Table SAF 15: ECG: Shift-table per time point of QRS and PR intervals

Frequency table showing per parameter, per time point and per treatment the number of subjects in each of the possible combinations of normal regions at the two time points (from below normal to within normal, from above normal to above normal, etc.). I.e., the change from baseline in abnormality code.

Table SAF 16: ECG: Shift-table of the worst-case QRS and PR intervals

Frequency table showing per parameter and per treatment group the worst-case on-treatment abnormality code, cross-tabulated versus the baseline abnormality code.

Table SAF 17: ECG: Shift-table per time point of QT and QTc intervals

Frequency table showing per parameter, per time point and per treatment the number of subjects in each of the possible combinations of values at the two time points. I.e., the change from baseline in abnormality code on the raw values.

Table SAF 18: ECG: Shift-table of the worst-case QT and QTc intervals

Frequency table showing per parameter and per treatment group the worst-case on-treatment abnormality code of the raw values, cross-tabulated versus the baseline abnormality code.

Table SAF 19: ECG: Tabulation per time point of changes in QT and QTc intervals

Frequency table showing per parameter, per time point and per treatment the number of subjects in each of the possible change from baseline categories.

Table SAF 20: ECG: Tabulation of the worst-case change in QT and QTc intervals

Frequency table showing per parameter and per treatment group the worst-case on-treatment change from baseline category.

Analysis listings:

Listing SAF 11: ECG: Actually measured intervals

Listing of ECG parameters (date/time performed, actual values, changes from baseline and abnormality codes).

Listing SAF 12: ECG: Morphology results

Listing of ECG morphology results.

Listing SAF 13: ECG: abnormalities

- Abnormalities reported by ECG reader;
- Abnormalities in ECG parameters (i.e. based on arithmetic criteria at start of this section).

4.5.5 Vital signs

Parameters:

- pulse (bpm): if the pulse is taken from the ECG HR, then this will be flagged in the listing.
- systolic blood pressure (mmHg)
- diastolic blood pressure (mmHg)
- Body temperature (°C)

- Weight (kg)
- Respiratory rate (bpm)

Note that vital signs can be taken in seated or supine (5 minutes) conditions, but this is not recorded in the eCRF.

Parameter definitions:
Normal ranges, applied to the vital signs parameters are listed below. Values equal to the limits of the normal range are still considered to be normal. There are no normal ranges for the body weight.

Parameter	Lower limit	Upper limit
Pulse, bpm	Value < 55 and change < -15	Value > 100 and change > 30
DBP, mmHg	Value < 55 and change < -20	Value > 90 and change > 20
SBP, mmHg	Value < 90 and change < -10	Value > 140 and change > 10
Temperature, °C	36.0	Value > 37.5 (99.5 °F), or change > 1.7 (3 °F)
Respiratory rate, bpm	8	Value > 16 or change > 10

Worst-case abnormality
Per parameter and per subject, a worst-case post-baseline will be derived. This worst-case is defined as:

- (B) Below normal: at least one post-baseline assessment is below normal range, and no post-baseline assessment is above normal range.
- (A) Above normal: at least one post-baseline assessment is above normal range, and no post-baseline assessment is below normal range.
- (W) Within normal: all post-baseline assessments are within normal range.
- (A+B) Both above and below normal: at least one post-baseline assessment is below normal range, and another post-baseline assessment above normal range.
- (M) Missing, when there are no post-baseline assessments.

This worst-case derivation will use all post-baseline assessments, including unscheduled time points.

Parameters to analyse:

- raw (observed) values;
- changes from reference;
- abnormality codes per time point
- worst-case on-treatment abnormality code

The baseline reference time point is last available measurement before first medication intake (=imputed baseline).

Analysis:

Table SAF 21: Vital signs: Descriptive statistics of actual values

Descriptive statistics per parameter, per time point and per treatment group of actual (raw) values.

Figure SAF 5: Vital signs: Mean plot of the changes from baseline

Mean plot (with SE bars) of the changes from baseline over time. Each regimen is represented by a line, showing data from imputed baseline up till day 8. Regimen groups

will be differentiated by different line colours and symbols. The Y-axis will show a horizontal reference line at 0 (= no change).
Separate plot for each parameter.

Figure SAF 6: Vital signs: Plots of mean vital signs and mean BMS-626529 concentration versus time since dosing

Plot per treatment regimen of the mean (without SE) change in vital signs, together with the mean BMS-626529 concentration. The left vertical axis should provide the change from baseline in vital signs, and the right vertical axis should provide the plasma levels.

Table SAF 22: Vital signs: Descriptive statistics of changes from baseline

Descriptive statistics per parameter, per time point and per treatment group of the changes from baseline.

Table SAF 23: Vital signs: Tabulation per time point of the abnormalities

Frequency tabulation per parameter, per time point and per treatment group of the abnormality codes.

Table SAF 24: Vital signs: Tabulation of the worst-case abnormalities

Tabulation per parameter and per treatment group of the worst-case on-treatment abnormalities.

Analysis listings:

Listing SAF 14: Vital signs: Actually measurements

Listing of VS parameters (date/time performed, actual values, changes from baseline and abnormality codes).
Values outside the normal ranges will be flagged, as well as pulse measurements taken from the ECG HR.

Listing SAF 15: Vital signs: Abnormalities

Listing of raw values, changes from baseline and the abnormality codes for observations outside the normal range.
This listing will select only the values outside of the normal range.

4.5.6 Physical examinations

Listing SAF 16: Physical examination: Abnormalities

Listing showing the abnormal physical examination results only.

5 REFERENCES

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3. ICH E14 The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. ICH Step 4: Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. London, May 2005.