IMPAACT P1020A
(DAIDS Document ID 10037)

Phase I/II, Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, Atazanavir, ATV, REYATAZ™) in Combination Regimens in Antiretroviral Therapy (ART)-Naïve and Experienced HIV-Infected Infants, Children, and Adolescents

A National and International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

This file contains the current IMPAACT P1020A protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #6, dated 23 July 2013
- Letter of Amendment #2, dated 20 December 2012
- Memo to Sites – HIV-1 RNA PCR Testing, dated 26 October 2011
- Clarification Memorandum #5, dated 19 October 2011
- Clarification Memorandum #4, dated 15 June 2011
- Clarification Memorandum #3, dated 2 August 2010
- Letter of Amendment #1, dated 4 December 2009
- Clarification Memorandum #2, dated 18 March 2009
- Clarification Memorandum #1, dated 13 January 2009
This is Clarification Memo #6 for IMPAACT P1020A "Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents" Version 6.0 dated December 21, 2007.

This Clarification Memo can be obtained from the P1020A Protocol Specific Web Page (http://www.impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1020A] web page you will have the option to click the PSWP tab.

The purpose of this memo is to inform sites participating in P1020A of the following:

1. Bristol-Myers Squibb (BMS) will stop manufacturing the 100 mg capsules of Atazanavir (ATV) in the near future. In order to prepare for this, subjects who are currently taking the 100mg capsules will be asked to either change the combination of capsules to achieve their current dose (if possible) or take a new adjusted dose. The new adjusted dose will be communicated to each site via the protocol pharmacologist, Dr Jennifer Kiser.

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at impaact.teamp1020a@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1020A.
DATE: December 20, 2012


“Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents”

DAIDS ES # 10037

TO: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1020A

FROM: IMPAACT P1020A Protocol Team

THE FOLLOWING INFORMATION IMPACTS THE P1020A STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY ALSO IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

UPON RECEIVING FINAL IRB/EC AND ANY OTHER APPLICABLE REGULATORY ENTITY (RE) APPROVAL(S) FOR THIS LoA, SITES SHOULD IMPLEMENT THE LoA IMMEDIATELY. SITES ARE STILL REQUIRED TO SUBMIT A LoA REGISTRATION PACKET TO THE DAIDS PROTOCOL REGISTRATION OFFICE (PRO) AT THE REGULATORY SUPPORT CENTER (RSC). SITES WILL RECEIVE A REGISTRATION NOTIFICATION FOR THE LoA ONCE THE DAIDS PRO VERIFIES THAT ALL THE REQUIRED LoA REGISTRATION DOCUMENTS HAVE BEEN RECEIVED AND ARE COMPLETE. A LoA REGISTRATION NOTIFICATION FROM THE DAIDS PRO IS NOT REQUIRED PRIOR TO IMPLEMENTING THE LoA. A COPY OF THE LoA REGISTRATION NOTIFICATION ALONG WITH THIS LETTER AND ANY IRB/EC CORRESPONDENCE SHOULD BE RETAINED IN THE SITE’S REGULATORY FILES.

This letter of amendment can be obtained from the P1020A Protocol Specific Web Page Protocol Specific Webpage (https://impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number.

The purpose of this letter of amendment (LOA) is to address the following issues:

a) Remove the requirement for an intensive pharmacokinetic (PK) visit if the subject changes from powder to capsule formulation.

As of 12/20/12, protocol P1020A will no longer require, or perform, any intensive PK studies for subjects remaining on study drug. Previously, if subjects on powder were being transitioned to capsule atazanavir, the team pharmacologist (Dr. Jennifer Kiser) would provide an initial dosing recommendation. Then, approximately one week after starting capsule formulation at the recommended dose, the subject would undergo a 24 hour intensive PK visit. If the PK results were satisfactory, subjects in the United States would have an off study visit, and continue on capsule atazanavir (on study drug), but off study. Subjects in South Africa would also have an intensive PK study, and if satisfactory, would remain on study drug (capsule ATV) and on study (Phase II of the study).
As of 12/20/12, the protocol team will still offer dosing recommendations for subjects transitioning to capsule formulation, but no PK studies will be done. Subjects in the U.S. should start the capsule formulation at the **approved capsule dosing only** (per the team’s guidance) at the time of the off study visit. Subjects in South Africa should continue on capsule ATV, on study.

This will affect the following areas of the protocol:

Section 5.11 – BMS-232632 powder formulation and BMS-232632 powder formulation + ritonavir

b) An electrocardiogram (ECG) will no longer be required at the change from powder to capsule formulation

This will affect the following areas of the protocol:

Appendix IA – footnote 21

c) For sites using locally supplied ritonavir, all formulations of ritonavir are acceptable (solution, tablet, capsule).

These updates will be made in the next version of the protocol. Please contact the protocol team at impaact.teamp1020A@fstrf.org if you have any questions concerning this correspondence.

Thank you for your participation in P1020A.
To: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1020A

From: IMPAACT P1020A Protocol Team

Date: October 26, 2011

Re: Message to Sites Participating in IMPAACT P1020A "Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents" Version 6.0 dated December 21, 2007

Please note that in regard to item #3 in Clarification Memo #5, the term ‘study laboratories’ refers to the laboratories where sites have been sending specimens for HIV-1 RNA PCR testing throughout the protocol. In South Africa, the lab is Contract Laboratory Service in Johannesburg (LDMS 350), and in the US, the lab is Children’s Hospital of Los Angeles (LDMS 130). Sites should continue to send specimens for HIV-1 RNA PCR testing to these laboratories.

Please contact the protocol team at actg.teamp1020@fstrf.org if further clarification is necessary. Thank you for your interest and participation in IMPAACT P1020A.

Sincerely,

The P1020A Protocol Team
This is Clarification Memo #5 for IMPAACT P1020A "Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents" Version 6.0 dated December 21, 2007.

This Clarification Memo can be obtained from the P1020A Protocol Specific Web Page (http://www.impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1020] web page you will have the option to click the PSWP tab.

The purpose of this memo is to inform sites participating in P1020A of the following:

1. Bristol-Myers Squibb (BMS) will stop manufacturing the 50 mg capsules of Atazanavir (ATV) in the near future. In order to prepare for this, the 150 mg and 300 mg ATV capsules will be made available to the study sites through the Clinical Research Products Management Center (CPRMC). The 100 and 200 mg capsules will continue to be supplied.

2. Ritonavir will no longer be supplied to study sites through the CPRMC. Sites will purchase ritonavir from commercial sources and will be reimbursed by BMS. The sites must continue to keep accountability records so that the lot numbers of ritonavir dispensed to which SID numbers can be tracked.

3. Use of the Roche Amplicor Assay for HIV-1 RNA PCR is not required. Study laboratories may use any viral load platform for which they are CAP/CLIA-approved (US) or DAIDS-VQA approved (South Africa).

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1020@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1020A.
DATE: 15 June 2011
RE: CLARIFICATION MEMO #4 for P1020A – Regarding the change in packaging for Atazanavir powder and change in Ritonavir formulation
TO: IMPAACT Principal Investigators & Study Coordinators at Sites Participating in P1020A
FROM: P1020A Protocol Team

This is Clarification Memo #4 for IMPAACT P1020A "Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents" Version 6.0 dated December 21, 2007.

This Clarification Memo can be obtained from the P1020A Protocol Specific Web Page (http://www.impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1020] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to inform sites participating in P1020A that the supply for Atazanavir (ATV) powder for oral solution in bottles will be switched to sachet packaging. The current bottle supply of ATV powder is scheduled to expire in September 2011 and it will not be extended. Therefore, sites will begin transitioning to the sachet packaging. Below, you will find pertinent product information:

<table>
<thead>
<tr>
<th>Product Description and Dosage Form</th>
<th>Potency</th>
<th>Primary Packaging (Volume)/Label Type</th>
<th>Secondary Packaging (Qty)/Label Type</th>
<th>Appearance</th>
<th>Storage Conditions (per label)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (ATV) powder for oral use</td>
<td>50 mg/sachet</td>
<td>1.5 g sachet/open label with text and symbols printed directly on sachet and cross-referencing to outer carton</td>
<td>Outer carton containing 30 sachets/open label booklet label cross-referencing to the sachet label</td>
<td>Sachet: aluminum foil with text and symbols printed directly on the sachet Outer carton: white cardboard with booklet label attached</td>
<td>15 - 25°C (59 - 77°F)</td>
</tr>
</tbody>
</table>

Example of dosing using the sachet: A child receiving a 350 mg dose (7 scoops) will now receive 7 sachets per dose.

Ritonavir will also be supplied as white film-coated 100 mg tablets. This should be stored at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature]. Disperse in original container or USP equivalent tight container (60 mL or less). For patient use: exposure of this product to high humidity outside the original or USP equivalent tight container (60 mL or less) for longer than 2 weeks is not recommended.
Changes from Atazanavir powder in bottles to sachets, along with any changes in Ritonavir formulation, will be documented on the TXW0097-PACTG P1020A Treatment Record.

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1020@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1020A.
This is Clarification Memo #3 for IMPAACT P1020A "Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents" Version 6.0 dated December 21, 2007.

This Clarification Memo can be obtained from the P1020A protocol specific web page (http://www.impaactgroup.org/p1020A-protocol-specific-web-page). The username is impaact and the password is cure (all lower case). The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to provide instruction for sites participating in P1020A, using Zerit® for Oral Solution or Zerit® (stavudine) Capsules. Due to the discontinuation of Zerit® for Oral Solution and the disruption of Zerit® Capsule production by Bristol-Meyers Squibb, sites are instructed to use any FDA approved or tentatively approved formulation of stavudine oral solution or stavudine capsules. The following websites are provided as a useful resource.


Website for FDA tentatively approved antiretrovirals: http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1020@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1020A.
To: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1020A

From: IMPAACT P1020A Protocol Team

Date: December 4, 2009


DAIDS ES #:   10037

THE FOLLOWING INFORMATION IMPACTS THE P1020A STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY ALSO IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

PLEASE FILE THIS LETTER AND ANY IRB/EC CORRESPONDENCE IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES. YOU ARE NOT REQUIRED TO SUBMIT THESE DOCUMENTS TO THE PROTOCOL REGISTRATION OFFICE UNLESS THE CHANGES RESULT IN A CHANGE TO THE INFORMED CONSENT FOR YOUR SITE.

The following letter of amendment may be obtained from the P1020A Protocol Specific Webpage of the IMPAACT Website (http://www.impaactgroup.org/P1020A-protocol-specific-web-page). The username is: impaact and the password is: cure (all lower case). The document is available under ‘Current Protocol Related Documents’.

The purpose of this letter is to allow for modifications in a subject’s treatment regimen if required by toxicity to one of the two NRTI agents. This amendment applies only to subjects who have completed at least 56 weeks of therapy, and have successfully completed the 56 week intensive pharmacokinetic evaluation.

If the site team feels that a change of one of the NRTI agents is warranted based on toxicity (example: lipodystrophy, or ongoing anemia) that can be attributed to a NRTI, and the site team feels it is the subject’s best clinical interest to remain on atazanavir,
then such a change will be allowed. The NRTI that is to be used must be chosen from: abacavir, lamivudine, emtricitabine, stavudine, zidovudine or didanosine. The use of tenofovir is not allowed based on its impact on atazanavir pharmacokinetics. If a subject’s treatment regimen is changed, please notify the team of the change and document that information on the appropriate case report form.

Section 4.62 changed to read: Abacavir sulfate (ABC, Ziagen\textsuperscript{R}) for the first 56 weeks of therapy

Section 4.63 changed to read: All antiretroviral therapies other than the regimens described in this study for the first 56 weeks of therapy

This information will be incorporated into the next protocol version when a new version is issued. Please contact the protocol team at actg.teamp1020@fstrf.org if you have any questions about the information provided in this letter.
TO: IMPAACT Principal Investigators and Study Coordinators
FROM: IMPAACT P1020A Protocol Team
DATE: March 18, 2009
RE: CLARIFICATION MEMO #2 for IMPAACT P1020A

This is Clarification Memo #1 for IMPAACT P1020A "Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents" Version 6.0 dated December 21, 2007.

This Clarification Memo can be obtained from the P1020A protocol specific web page (http://www.impaactgroup.org/p1020A-protocol-specific-web-page). The username is impaact and the password is cure (all lower case). The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to correct an error in the Step II enrollment instructions.

1. Inclusion Criterion 4.31 currently states that any South African subject enrolled into either part of Step I, who is virologically successful by Week 96 of the last study subject enrolled into the respective part of Step I will enroll into step II. Inclusion criterion 4.31 is in disagreement with the last sentence of Section 6.431 which states that if the Protocol Chair, the site investigator, and the parents decide that it is in the best interest of the subject to stay on his/her current treatment, he/she will be allowed to continue on study, on study treatment. The intent was to allow all Step I South African subjects currently on treatment to continue on treatment.

2. Exclusion criteria 4.42 states that a South African subject who meets any of the original enrollment exclusions, including section 4.2 exclusions cannot continue onto Step II. Step 1 exclusion criterion 4.27 disallows any grade ≥ 2 laboratory values at BASELINE. Since most subjects on study drug have grade 2 elevations of total bilirubin, and there is no ‘baseline visit’ for Step II, this criteria would prohibit most Step I subjects from moving on to Step II.

Both section 4.31 and section 4.42 were inadvertently included in version 6.0 and are against the intent of Step II, which was to allow enrollment of all Step I subjects currently (and safely) on treatment. Sites are instructed to disregard both criteria.

These revisions will be incorporated into the next version of the protocol if it is amended. Please contact the protocol team at actg.teamp1020@fstrf.org if you have any questions concerning this correspondence.

Thank you for your participation in IMPAACT P1020A.

P1020A Protocol Team
This is Clarification Memo #1 for IMPAACT P1020A "Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS 232632, ATAZANAVIR, ATV, REYATAZ) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents" Version 6.0 dated December 21, 2007.

This Clarification Memo can be obtained from the P1020A protocol specific web page (http://impaact.s-3.com/members/ps/1020a/ps1020a.htm). The username is impaact and the password is cure (all lower case). The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to correct an error in the second paragraph of Section 6.41 and the Schedule of Evaluations (Footnote 14 of appendices IB and IC). Both sections incorrectly state that ALL subjects must have two follow-up study visits at weeks 4 and 8 after the End of Step I study visit. Inadvertently language was entered in the second paragraph of Section 6.41 and footnote 14 that reiterated the follow up requirement pertaining only to subjects who come off Step 1 due to toxicity. All other subjects stopping Step I at the time of study closure are not required to have the two follow up visits after the end of study visit.

Sites are instructed to omit these two follow up visits. Step 1 is ending 1/31/09, in the Unites States only, for all subjects on capsule formulation of atazanavir (with or without ritonavir boosting).

These revisions will be incorporated into the next version of the protocol if it is amended. Please contact the protocol team at actg.teamp1020@fstrf.org if you have any questions concerning this correspondence.

Thank you for your participation in IMPAACT P1020A.

P1020A Protocol Team
IMPAACT P1020A

PHASE I/II, OPEN-LABEL, PHARMACOKINETIC AND SAFETY STUDY OF A NOVEL PROTEASE INHIBITOR (BMS-232632, ATAZANAVIR, ATV, REYATAZ™) IN COMBINATION REGIMENS IN ANTIRETROVIRAL THERAPY (ART)-NAÏVE AND EXPERIENCED HIV-INFECTED INFANTS, CHILDREN, AND ADOLESCENTS

A National and International Multicenter Trial of the Pediatric AIDS Clinical Trials Group

Sponsored by:

The United States of America National Institute of Allergy and Infectious Diseases

Pharmaceutical Support Provided by:

Bristol-Myers Squibb

The U.S.A. Food and Drug Administration Investigational New Drug Number, IND # 60, 878

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Version 6.0
FINAL
12/21/07
IMPAACT P1020A PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to actg.teamp1020@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1020@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For site registration questions, e-mail actg.protreg@fstrf.org. For Adverse Event Reporting (AER) questions, e-mail actg.adr@fstrf.org or call 1-800-537-9979. To order study drug, call the Clinical Research Products Management Center at (301) 294-0741. For randomization or enrollment questions, call (716) 834-0900. Additional contact information can be found in the “Pediatric AIDS Clinical Trials Group Protocol Contact List” on the IMPAACT website (http://IMPAACT.s-3.com/members/contacts.htm [username = impaact; password = cure])

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### GLOSSARY

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>Lamivudine, Epivir®</td>
</tr>
<tr>
<td>ACTU</td>
<td>AIDS Clinical Trial Unit</td>
</tr>
<tr>
<td>AER</td>
<td>Adverse event report</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATV</td>
<td>Atazanavir, BMS-232632</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BID</td>
<td>Twice a day</td>
</tr>
<tr>
<td>BMS-232632</td>
<td>Atazanavir, Reyataz™</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>CD4</td>
<td>T Cell Type</td>
</tr>
<tr>
<td>CDC</td>
<td>(United States) Center for Disease Control</td>
</tr>
<tr>
<td>CHBH</td>
<td>Chris Hani Baragwanath Hospital (Soweto, South Africa)</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CI/F</td>
<td>Clearance</td>
</tr>
<tr>
<td>CMAX</td>
<td>Maximum Observed Concentration</td>
</tr>
<tr>
<td>CMIN</td>
<td>Minimum Observed Concentration</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRPMC</td>
<td>(United States) Clinical Research Products Management Center</td>
</tr>
<tr>
<td>d4t</td>
<td>Stavudine, Zerit®</td>
</tr>
<tr>
<td>ddI</td>
<td>Didanosine, Videx®</td>
</tr>
<tr>
<td>DAIDS</td>
<td>(United States) Division of AIDS</td>
</tr>
<tr>
<td>DMC</td>
<td>(United States) Data Management Center</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EC</td>
<td>Effective Concentration</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EFV</td>
<td>Efavirenz, Sustiva®</td>
</tr>
<tr>
<td>FDA</td>
<td>(United States) Food and Drug Administration</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyltranspeptidase</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>---------</td>
<td>------------</td>
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<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High-density lipoprotein-cholesterol</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IC</td>
<td>Inhibitory Concentration</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonization</td>
</tr>
<tr>
<td>IDL</td>
<td>Intermediate-density lipoprotein</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational new drug</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function test</td>
</tr>
<tr>
<td>MCC</td>
<td>(South Africa) Medicines Control Council</td>
</tr>
<tr>
<td>MTCT</td>
<td>Mother To Child Transmission</td>
</tr>
<tr>
<td>NIAID</td>
<td>(United States) National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NIH</td>
<td>(United States) National Institutes of Health</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>PAB</td>
<td>Pharmaceutical Affairs Branch of DAIDS</td>
</tr>
<tr>
<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Group</td>
</tr>
<tr>
<td>PBMC</td>
<td>Peripheral Blood Mononuclear Cells</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>PID</td>
<td>Subject Identification Number</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic(s)</td>
</tr>
<tr>
<td>po</td>
<td>By mouth/Per Oral</td>
</tr>
<tr>
<td>PR</td>
<td>On an electrocardiogram tracing, the interval between the beginning of P wave and end of the Q wave</td>
</tr>
<tr>
<td>q</td>
<td>Every</td>
</tr>
<tr>
<td>QRS</td>
<td>On an electrocardiogram tracing, the interval between the beginning of Q wave and end of the S wave</td>
</tr>
<tr>
<td>QT</td>
<td>On an electrocardiogram tracing, the interval between the beginning of Q wave and end of the T wave</td>
</tr>
<tr>
<td>QTc</td>
<td>On an electrocardiogram tracing, the interval between the beginning of Q wave and end of the T wave, corrected for heart rate</td>
</tr>
</tbody>
</table>
RAB  Regulatory Affairs Branch of DAIDS
RNA  Ribonucleic Acid
ROC  Regulatory Operations Center
RTV  Ritonavir, Novir®

S.A.  South Africa
SAE  Serious Adverse Event
SAF  Sodium acetate-acetic acid-formalin
SDMC Statistical and Data Management Center
SID  Study Identification Number
SQV  Saquinavir, Fortase®-Soft Gel

$t_{1/2}$  Half-life
TDF  tenofovir disoproxil fumarate, Viread®
TID  Three times a day

ULN  Upper Limit of Normal
U.S.A. United States of America

WB  Western Blot
ZDV  Zidovudine, AZT, Retrovir®
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SUMMARY OF CHANGES FOR IMPAACT P1020A VERSION 6.0

All changes from Version 5.0 appear in boldface type in Version 6.0 of the protocol, including correction of typographic errors, updated information, and other changes that do not affect regulatory or study subject consent. Information from Letters of Amendment #1 (09/20/04), #3 (09/26/05), #4 (12/19/05), and #6 (07/03/07) and Clarification Memo’s #1 (09/13/04), #2 (11/12/04), #4 (02/16/05), #5 (03/29/05), and #6 (11/17/05) are included.

The following is a summary list of the changes made in the protocol:

1. Protocol Team Roster was updated to include new team members and correct member information.

2. The Schema was revised to include the new sample size and specific age criterion for the re-opening of study Group 5A and accrual information for Groups 1-8. This is also reflected in Section 6.211.

3. Throughout the protocol patient was changed to subject.

4. Study Flow Chart #3 was added for study Group 5A.

5. Section 1.104 “Rationale for Addition of Cohort 5A” was added.

6. Section 3.0 was updated to include information regarding the re-opening of subgroup 5A for, extending the period of follow-up for groups 1, 2, 5 and 6 until the powder formulation is locally available.

7. The title of section 4.1 was changed to read, “Inclusion Criteria for (Group 5A) Step 1”.

8. Section 4.11 was updated to include the age criterion for Group 5A.

9. Section 5.1 was updated to include information on extending follow-up for subjects in groups 1, 2, 5, and 6; and allowing subjects to switch from powder to capsule formulation.

10. Section 5.11 was updated to include information and instructions for sites to allow subjects to switch from the powder to capsule formulation of atazanavir. Table 11 was added to provide information for converting atazanavir powder dosage to atazanavir capsule dosage.

11. Throughout, tables were renumbered due to the addition of Table 11.

12. Section 5.12 was updated to include NRTI-toxicity related information.
13. Section 5.21 was revised to account for the color change of the 200mg formulation-strength of BMS-232632.

14. Sections 5.32-5.33 were revised to include language to allow site pharmacists at IMPAACT CTUs in US and South Africa to obtain ritonavir solution through commercial resources.

15. Section 6.213 was updated to include the definition of Cmin.

16. Section 8.15 was inserted to include the rationale for adding Group 5A.

17. Appendix I-B was updated to correct blood volume and study visit interval errors.

18. Appendix I-C was added for Step I evaluations beyond Week 280 and to allow subjects to continue on study until the study end date of January 31, 2009.

19. Appendix I-D was added for US subjects who are on the powder formulation and for all South African subjects; starting January 31, 2009.

20. Blood draw priorities were added to Appendices IB-ID.

21. Appendix II-C includes an updated toxicity table for grading ECG changes. The following typographical error was corrected: 98% percentile was changed to read 98th percentile.

22. Appendix III-C includes updated contact information for Don Decker.

23. Appendix IV-A includes updated information regarding the local laboratories.

24. Appendix IV-B includes updated laboratory and designated contact information.

25. Appendix V includes updated shipment information for all PK samples.

26. Appendix VI was updated to include information and instructions to sites on how to return ECG equipment.

27. Appendix X:

   - Under “What Does My Child Have to Do If My Child Is In This Study?”: The following paragraphs were added:
     Your baby is being asked to participate in Version 6.0 of this study. In this version, children who are 90 to 180 days old will receive BMS-232632. Your baby will remain on the study until BMS-232632 is approved and available in your local area. The study staff will inform you when it becomes available.
Children who are already enrolled in the study will be allowed to remain in the study until BMS-232632 is approved and available in both the United States and South Africa.

If your child is 2 years old and taking the powder form of the study drug, your child will be allowed to switch to the capsule form of the study drug. Your child will be allowed to take the capsule after they have completed week 56 PK test. This test will check to the amount of medicine that is in your child’s blood.

- Under “What Does My Child Have to Do If My Child Is In This Study?”: Under Entry Visit: The second paragraph was revised to read:
  In this version, the study will begin by enrolling five subjects. These initial subjects may establish the dose or BMS-232632 alone or in combination with ritonavir for each group. However, a second set of five subjects may be needed.

- Under “How Many People Will Take Part In This Study?”: The first sentence was revised to read:
  About 5 children will take part in this version of the study. A total of 183 children are already in this study and are on study drugs.

28. Appendix XI, fact sheet and template consent form for Specimen Storage at Repositories funded by the National Institutes of Child Health and Human Development (NICHD), was added.

29. Throughout, PACTG was changed to IMPAACT
PHASE I/II OPEN-LABEL, PHARMACOKINETIC AND SAFETY STUDY OF A NOVEL PROTEASE INHIBITOR (BMS-232632, ATAZANAVIR, ATV, REYATAZ™) IN COMBINATION REGIMENS IN ANTIRETROVIRAL THERAPY (ART) - NAIVE AND EXPERIENCED HIV-INFECTED INFANTS, CHILDREN, AND ADOLESCENTS

DESIGN: Phase I/II, open-label multicenter study of BMS-232632 as part of combination antiretroviral regimens.

SAMPLE SIZE:
- Minimum of 72 evaluable subjects for Part A (A minimum of 20 from South Africa).
- Minimum of 85 evaluable subjects for Part B (A minimum of 40 from South Africa).

POPULATION: HIV-infected infants, children, and adolescents ages 91 days to 21 years, who are either ART-naive or ART-experienced.

STRATIFICATION: Study groups are stratified by age, BMS-232632 formulation, and country (U.S.A. or South Africa).

REGIMENS: Step I:

Part A: BMS-232632 in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) [excluding abacavir sulfate (ABC, Ziagen®) and tenofovir disoproxil fumarate (TDF, Viread®)]. Each study group is managed independently following a dose escalation algorithm for BMS-232632 with initial doses at 310, 415, 520, and 620 mg/m².
- Group 1 [91 days to 2 years of age (less than or exactly 730 days)]: BMS-232632 powder (CLOSED TO ACCRUAL Total N=8).
- Group 2 [2 years and 1 day (731 days or more) to 13 years of age]: BMS-232632 powder (CLOSED TO ACCRUAL Total N=11).
- Group 3 [2 years and 1 day (731 days or more) to 13 years of age]: BMS-232632 capsules. (CLOSED TO ACCRUAL, Total N=31).
- Group 4 [13 years and 1 day to 21 (not including the 22nd birthday) years of age]: BMS-232632 capsules. (CLOSED TO ACCRUAL, Total N=35).

Part B: BMS-232632 + ritonavir in combination with two NRTIs [excluding abacavir sulfate (ABC, Ziagen®) and tenofovir disoproxil fumarate (TDF, Viread®)]. Each study group will be managed independently following a dose escalation algorithm for BMS-232632 at the 310mg/m².
- Group 5 [91 days to 2 years of age (less than or exactly 730 days)]: BMS-232632 powder. (CLOSED TO ACCRUAL TOTAL N=21).
- Group 5A [91 to 180 days of age]: BMS-232632 powder. Minimum n=5.
SCHEMA (Cont.)

- Group 6 [2 years and 1 day (731 days or more) to 13 years of age]: BMS-232632 powder. (CLOSED TO ACCRUAL Total N=26)
- Group 7 [2 years and 1 day (731 days or more) to 13 years of age]: BMS-232632 capsules. (CLOSED TO ACCRUAL Total N=29)
- Group 8 [13 years and 1 day to 21 (not including the 22nd birthday) years of age]: BMS-232632 capsules. (CLOSED TO ACCRUAL Total N=21)

Dose Finding Algorithm: To establish a final BMS-232632 dose for a study group, at least 10 evaluable subjects (U.S.A. and S.A.) taking the same BMS-232632 dose that satisfies both safety and pharmacokinetic criteria are required.

Step II:

This study step is only for subjects in South Africa who are virologically responding at the completion of Step I.

TREATMENT DURATION:

- Step I: U.S.A. and South Africa, this step will end 96 weeks after the last subject is enrolled into one of the study groups for each part of the study. U.S.A. subjects will go off-study after this study step, and South African subjects will continue into Step II.
- Step II: South Africa, this step will end when BMS-232632 is approved in South Africa, and it is available for distribution to subjects.

PRIMARY OBJECTIVES:

1. To determine the pharmacokinetic profile and dosing schedule of the capsule formulation for BMS-232632 and BMS-232632 + ritonavir in combination with two NRTIs in HIV-infected children and adolescents.
2. To determine the pharmacokinetic profile and dosing schedule for the powder formulation of BMS-232632 and BMS-232632 + ritonavir in combination with two NRTIs in HIV-infected infants and young children.
3. To determine the safety and tolerability of BMS-232632 and BMS-232632 + ritonavir in HIV-infected infants, children, and adolescents.

SECONDARY OBJECTIVES

1. To assess the antiviral activity of BMS-232632 and BMS-232632 + ritonavir containing regimens as measured by viral load response and duration of maximum response when given to protease inhibitor treatment-experienced and -naive study subjects.
2. To assess the development of virologic resistance as measured by genotypic and phenotypic assays during treatment with BMS-232632 and BMS-232632 + ritonavir.
3. To assess the relationship between the results of baseline phenotypic and genotypic resistance assays and virologic response.
4. To assess the relationship between systemic exposure to BMS-232632 and BMS-232632 + ritonavir, subject-reported adherence, and virologic response (Only for U.S.A. subjects).
5. To evaluate the relationship of pharmacokinetics, as collected according to a population strategy, to pharmacodynamically-linked variables.
6. To assess the changes in immunologic function as measured by T cell-subset analysis and markers of cellular activation in relation to initiating or changing antiretroviral therapy (ART).
7. To assess the long-term safety and tolerability of BMS-232632 and BMS-232632 + ritonavir in South African HIV-infected infants, children, and adolescents (Step II).
STUDY FLOW CHART #1—PART A (Step I)

IMPAACT P1020A Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, atazanavir, ATV, Reyataz™) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents

Note: All groups have been managed independently from each other

Abacavir sulfate (ABC, Ziagen®) and tenofovir disoproxil fumarate (TDF, Viread®) will be excluded as NRTI options for the subject’s regimen under IMPAACT P1020A.

Enroll five subjects per group to establish BMS-232632 dose in each study group. Data will be pooled across countries.

Accepted BMS-232632 dose (Based on PK and safety criteria)

Accrue five more subjects using this accepted starting dose for BMS-232632 in a given study group

Re-evaluate starting dose based on PK criteria but with a N_{eval}=10. Data will be pooled across countries.

To establish a final BMS-232632 dose for a study group, at least 10 evaluable subjects taking the same BMS-232632 dose that satisfies both safety and pharmacokinetic criteria will be required

Unacceptable BMS-232632 dose

Follow diagram 1 in section 6.212 until BMS-232632 dose is found

Unacceptable BMS-232632 dose for these 10 subjects
STUDY FLOW CHART #2—PART B (Step I)

IMPAACT P1020A Phase I/II Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, Atazanavir, ATV, Reyataz™) in Combination Regimens in Antiretroviral Therapy (ART) - Naive and Experienced HIV-Infected Infants, Children, and Adolescents

Note: All groups will be managed independently from each other

Group 5 (closed) (91 days of age to ≤2 years of age): Minimum of 10 patients from U.S. and 10 from S.A. receiving BMS-232632 powder + ritonavir + 2 NRTIs

Group 6 (closed) (>2 to ≤13 years of age): Minimum of 10 subjects from U.S. and 10 from S.A. receiving BMS-232632 powder + ritonavir + 2 NRTIs

Group 7 (closed) (>2 to ≤13 years of age): Minimum of 10 subjects from U.S.A. and 10 from S.A. receiving BMS-232632 capsule + ritonavir + 2 NRTIs

Group 8 (closed) (>13 to ≤21 years of age): Minimum of 10 subjects from U.S.A. and 10 from S.A. receiving BMS-232632 capsule + ritonavir + 2 NRTIs

Enroll five subjects per group to establish BMS-232632 dose in each study group. Data will be pooled across countries.

Accepted BMS-232632 dose (Based on PK and safety criteria)

Accrue five more subjects using this accepted starting dose for BMS-232632 in a given group

Re-evaluate starting dose based on PK criteria but with a N_{eval}=10. Data will be pooled across countries.

Unacceptable BMS-232632 dose

Follow diagram 1 in section 6.212 until BMS-232632 dose is found

Unacceptable BMS-232632 dose for these 10 subjects

To establish a final BMS-232632 dose for a study group, at least 10 evaluable subjects taking the same BMS-232632 dose that satisfies both safety and pharmacokinetic criteria will be required.

Abacavir sulfate (ABC, Ziagen®) and tenofovir disoproxil fumarate (TDF, Viread®) will be excluded as NRTI options for the subject’s regimen under IMPAACT P1020A.
Enroll minimum five subjects in Group 5A to establish BMS-232632 dose in each study group. Data will be pooled across countries.

Accepted BMS-232632 dose (Based on PK and safety criteria)

Unacceptable BMS-232632 dose

Adjust dosage and enroll an additional 5 subjects at the new dose
1.0 INTRODUCTION

1.1 General Background

State of the art management of HIV-infected children and adults dictates the use of combination therapies, generally consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI) (1, 2). However, the available treatment regimens for children are limited. There are few PIs available in formulations appropriate for young children. Moreover, many children are beginning to experience virologic failure on their present PI-containing regimens due to incomplete virologic suppression, which invariably leads to drug resistance and virologic rebound.

Poor adherence to complicated treatment regimens is an important factor that significantly impacts the choice of drug combinations, as well as subsequent virologic response. Based on parental reports taken in clinical HIV practice in the developed world, more than 30% of families describe themselves as poorly compliant with their children’s medication schedules, and over 50% of children with a poor response to combination therapy were noncompliant (3, 4). The development of potent combination therapies with proven efficacy but less complicated dosing schedules is critical to improving the outcome for HIV-infected children in all parts of the world.

There are seven U.S.A. Food and Drug Administration (FDA)-approved PIs for use in the United States: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir/ritonavir, and atazanavir (only for adults). Cross-resistance among them develops to variable degrees.

New PIs that retain virologic activity against strains harbored by treatment-experienced subjects and those with different toxicity profiles are desperately needed. BMS-232632 potency for inhibition of HIV-1 has been proven in adults and was approved for this population in May of 2003.

Recent data from adult studies suggest baseline viral resistance patterns (based on genotypic assays) may predict poor response to salvage regimens; their ability to predict a positive response is less clear (5). Preliminary data suggest that phenotypic analysis of viral resistance may also predict outcome of salvage therapy (6, 7). New technologic advances have led to the ability to obtain genotypic and phenotypic resistance data with a reasonable turnaround time.
1.2 Current Antiretroviral Treatment for Pediatric Population in South Africa

There are 1.1 million births in South Africa each year (8). With a 24.6% HIV-1 seroprevalence rate in pregnant women, 250,000 infants are exposed to HIV each year. In the absence of intervention to prevent mother-to-child transmission of HIV, the vertical transmission rate is estimated to be between 25-40%.

In Soweto, near Johannesburg, the HIV epidemic has had a profound impact on child mortality. Chris Hani Baragwanath Hospital (CHBH) admits 6,000 children annually. In 1992, 7% of pediatric deaths were HIV related, rising to over 50% in 1997 (9). In-hospital mortality at CHBH has risen from 3.9% in 1992 to 11.1% in 2001, and the rise is attributable to HIV infection. HIV-related pediatric admissions increased from 30% in 1996 to 38% by 2000, where 48% were under 15 months of age (10, 11).

Currently in South Africa, nation-wide there are 10 programs where children access antiretroviral treatment in the public service. Only a very small percent of children requiring treatment are accessing this currently. Even in wealthy countries, antiretroviral therapy (ART) for infants is complicated by paucity of appropriate formulations, relative lack of pharmacokinetic data and uncertainties about long-term ART. In resource-limited countries barriers to treatment implementation also include cost, medical expertise, and health care infrastructure.

Use of ART in pregnancy has resulted in dramatic reduction of pediatric HIV infection in developed countries. In developing countries affordable short course regimens to prevent Mother to Child Transmission (MTCT) have demonstrated a 47% reduction in transmission (12). Nonetheless, because of the large numbers of HIV-infected women attending antenatal clinics and a transmission rate of 13% with nevirapine-based intervention, a significant number of children in resource-poor settings will still acquire HIV via vertical transmission and be in need of ART.

Without ART, African children have a 26-45% mortality rate by their first year of life and a 35-59% mortality rate by their second birthday. Very few survive until their fifth birthday unlike in industrialized countries where there is only a 26% mortality rate by the child’s fifth birthday. Studies assessing simpler, more applicable regimens are urgently required to establish ART in resource-poor settings.

1.3 BMS-232632 (Atazanavir, ATV, Reyataz™) Background

1.3.1 General

BMS-232632 is an azapeptide aspartyl PI manufactured by Bristol-Myers Squibb (BMS) and undergoing phase II and III studies in HIV-infected adults. *In vitro*, BMS-232632 is a highly potent inhibitor of laboratory and
clinical strains of HIV-1 at submicromolar concentrations. BMS-232632 exhibits no inhibition of human aspartyl proteases, and its potency is retained in the presence of human serum (13).

Dose-ranging studies conducted in healthy volunteers determined that single doses of 100 mg up to 1200 mg are well tolerated. These studies also determined a half-life ranging between 2.9 and 6.5 hours. The drug was well absorbed, and doses of 300 mg or more sustained plasma levels above the 50% effective concentration after 24 hours (14).

1.32 Resistance Information

Laboratory resistance data suggest that BMS-232632 retains activity against HIV resistant to other PIs, and HIV that develops resistance to BMS-232632 remains sensitive to several other PIs. The primary mutation selected after multiple passages in culture with BMS-232632 is N88S. However, several additional mutations are required for significant resistance. HIV with a 20-fold decrease in sensitivity to BMS-232632 exhibited mutations at codons 88, 71, 46, and 32. This strain exhibited no change in sensitivity to saquinavir or amprenavir, with mild decreases in sensitivity to nelfinavir (15-fold change), indinavir (5-fold change) and ritonavir (3-fold change). HIV with high-level resistance to BMS-232632 (188-fold decrease in sensitivity), contained mutations at codons 88, 84, 71, 46, 33 and 32 and retained sensitivity to saquinavir (13).

Conversely, HIV resistant to other PIs remains sensitive to BMS-232632. HIV resistant to indinavir (24-fold decrease in sensitivity) and ritonavir (71-fold decrease) exhibited only slight decreases in sensitivity to BMS-232632. The same was true for HIV with significant resistance to nelfinavir (35-fold decrease) and amprenavir (82-fold decrease) (13).

1.33 Animal Studies

In animal toxicology studies, BMS-232632 was well tolerated following oral administration for 6 months at doses of up to 900 mg/kg/day in rats and 180 mg/kg/day in dogs. Area Under the Curve (AUC) levels at these doses were approximately 1.4 to 8.4 times the exposure observed in the studies with healthy humans receiving 600 mg QD for a week. Other non-clinical toxicity studies with BMS-232632 found that a single oral dose of up to 400 mg/kg was well tolerated in mice. A 2-week oral toxicity study in dogs at doses of 10, 30, or 75 mg/kg/day found no BMS-232632-related clinical, ophthalmologic, or electrocardiographic abnormalities. Furthermore, this study found no drug-related effects on body weight, food and water
consumption, organ weight, gross pathology, or histopathology and no morphologic evidence of systemic toxicity (13).

BMS-232632 was also evaluated in rats and dogs for potential central nervous system (CNS) effects. These studies concluded that no effects on the CNS were observed in rats at doses of up to 1200 mg/kg/day, and no clearly direct effects on the CNS were observed in dogs at doses of up to 360 mg/kg/day (13).

BMS-232632 is metabolized in the liver by the CYP3A4 isozyme. Rat, dog, or human liver microsomal incubations established that BMS-232632 undergoes oxidative metabolism by this isozyme. Furthermore, results from rat and dog studies determined that the half-life of this drug averaged 1 hour for rats and 0.5 hours for dogs. These data suggest that the liver may have a significant role in the clearance of BMS-232632 (13).

Relative bioavailability studies using the powder and capsule formulations of BMS-232632 are being conducted by BMS. Preliminary data from one of these studies, in dogs receiving the powder formulation with/without Tween, determined that the formulation without Tween had a bioavailability similar to that of the capsule formulation, in contrast to the Tween-based formulation. The powder formulation with tween had a significantly reduced bioavailability when compared to the capsule or the non-tween powder formulations (13).

The Preliminary PK results from a BMS pilot bioavailability study (AI424-025) that evaluates the utility of a powder formulation versus the standard capsule formulation for BMS-232632 concluded that the bioavailability of BMS-232632 from the powder formulation, administered with applesauce or water, and from the capsule contents mixed with applesauce is similar to that from the capsule formulation, and that 400 mg-QD is well tolerated (15).

BMS-232632 was also evaluated for its potential genotoxicity in a battery of genetic toxicology studies. There were no observed mutagenic effects in the bacteria mutagenicity-screening assay or in the Ames reverse mutation system (13, 15).

1.34 Human Studies

Preliminary data in healthy human participants suggest that the drug’s pharmacokinetic profile is favorable for once-daily dosing. In single dose studies, concentrations of BMS-232632 were above the adjusted 90%
inhibitory concentration (IC90) for 24 hours at doses of 400 mg, and 600 mg.

In multidose studies in healthy adults, mean steady-state half-life ranged from 4.0 to 7.7 hours at doses of 200 and 400 mg daily. Mean trough levels reached steady-state within 3 days. Plasma concentrations were above the IC90 for 24 hours at both 400 mg and 600 mg doses (13).

Data from BMS studies AI424-012 and BMS AI424-013, in which subjects received BMS-232632 at a 400 mg dose QD with food, are summarized in Table 1:

<table>
<thead>
<tr>
<th>BMS Study</th>
<th>CMIN Range</th>
<th>CMIN Mean Value</th>
<th>CMIN CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI424-012 (high-fat meal)</td>
<td>85-780 ng/mL</td>
<td>366 ng/mL</td>
<td>64%</td>
</tr>
<tr>
<td>AI424-013 (low-fat meal)</td>
<td>12-840 ng/mL</td>
<td>220 ng/mL</td>
<td>84%</td>
</tr>
</tbody>
</table>

Of the total 35 subjects in both studies (AI424-012: 20 subjects, AI424-013: 15 subjects), 33 had BMS-232632 levels of > 60 ng/mL at 24 hours post-steady-state dose, and the other 2 subjects had detectable levels of 12 ng/mL and 48 ng/mL (13).

The administration of BMS-232632 with a high-fat meal resulted in a 35% increase in AUC but no change in the CMAX. When BMS-232632 was given with meals, the variability in AUCs was significantly reduced, from 69% in the fasted state to 37% with a light meal and 43% with a high-fat meal. The administration of didanosine (ddI) with BMS-232632 resulted in a fourfold reduction of the AUC and CMAX of BMS-232632. When these two medicines were administered at least one hour apart, such reduction was not noted (13).

A nucleoside interaction study, AI424-004, was conducted to evaluate the combination therapy regimens of BMS-232632 with/without ddI and stavudine (d4T). Subjects received oral doses of BMS-232632; ddI and d4T; BMS-232632, ddI, and d4T; or ddI and d4T followed by BMS-232632 an hour later. The analysis of the data collected in this study concluded that ddI when co-administered with BMS-232632 influenced the kinetics of BMS-232632; however, when separated by one hour, ddI did not influence
the kinetics of BMS-232632. BMS-232632 did not influence the kinetics of either ddI or d4T (13).

The interaction of BMS-232632 with saquinavir was assessed in A1424-012, a randomized, open-label study. This study concluded that, for a constant dose of BMS-232632 (400 mg) co-administered with saquinavir doses of 800, 1200 and 1600 mg, there was a corresponding increase in the steady state AUC values for saquinavir. The terminal elimination half-life values for saquinavir alone were comparable to values obtained when it was co-administered with BMS-232632. Furthermore, the administration of saquinavir at doses of up to 1600 mg concurrently with BMS-232632 at a 400 mg dose did not affect the pharmacokinetics of BMS-232632 (13).

The total number of HIV-infected subjects who have been treated with BMS-232632 in three ongoing studies is approximately 600 (15). These subjects, all adults, have received 200 mg, 400 mg, 500 mg or 600 mg, given as a capsule formulation. Preliminary results from one of this studies, BMS-AI424-007, of a phase II study of the antiviral efficacy and clinical safety of BMS-232632 in HIV-infected adults, indicate that the antiviral efficacy of this drug is comparable to that of other PIs, with a median viral load reduction of 1.5 log_{10} after 2-week monotherapy and a 2.5 log_{10} decrease in viral load through 16 weeks after the start of two nucleosides. In this study, 88 subjects total were evaluable at 2 weeks, and 70 were evaluable at Week 16. The proportion of subjects with viral loads less than or equal to 400 c/mL was 60%, and the proportion with viral loads less than or equal to 50 c/mL was 40%. The subjects in this study were treatment-naïve adults (with less than 4 weeks of prior NRTI treatment or less than 1 week of prior NNRTI or PI treatment) with baseline HIV RNA levels across all arms of 4.8 log_{10} (all subjects had baseline viral loads >30,000 c/mL) and a median CD4 cell count of 386 cells/mL (13, 15).

The only significant laboratory abnormality noted in these adult studies has been hyperbilirubinemia. However, hyperbilirubinemia has been managed by dose reduction while maintaining virologic activity. Subjects with Gilbert’s trait exhibited the highest levels of bilirubin elevation. In addition, there appeared to be a dose-dependent relationship in terms of the frequency and degree of elevation of bilirubin levels. Bilirubin levels returned to normal values within 3 days of discontinuation of the study drug (13, 16).

Unreleased information from the interim results of BMS-AI424-007, in Stage I with 92 subjects (entry criteria: HIV RNA ≥ 5,000 and < 200,000 c/mL with minimum CD4 ≥100 cells) and in stage II with 320 subjects (entry criteria: HIV RNA ≥ 2,000 and < 750,000 c/mL with minimum CD4...
≥75 cells) recorded ten serious adverse experiences (SAE) and 14 SAE for stages I and II, respectively (11). In stage I of this study to date, five subjects have developed Grade 4 hyperbilirubinemia that required dose reduction, seven subjects developed clinical jaundice and 32 subjects developed hyperbilirubinemia within the first 60 days of treatment. Table 2 summarizes some of the recorded side effects reported in the unreleased interim results of BMS-AI424-007 (16).

**TABLE 2. Recorded Adverse Experience from the Interim Results of BMS-AI424-007**

<table>
<thead>
<tr>
<th>Recorded Adverse Experience</th>
<th>Stage I (N&lt;sub&gt;total&lt;/sub&gt;= 92 subjects) (entry criteria: HIV RNA ≥5,000 and &lt;200,000 c/mL with minimum CD4 ≥100 cells)</th>
<th>Stage II (N&lt;sub&gt;total&lt;/sub&gt;=230 subjects) (entry criteria: HIV RNA ≥2,000 and &lt;750,000 c/mL with minimum CD4 ≥75 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconjugated hyperbilirubinemia Grade 1-2 (400 mg dose of BMS-232632)</td>
<td>41% of the subjects</td>
<td>60% of the subjects</td>
</tr>
<tr>
<td>Unconjugated hyperbilirubinemia Grade 3-4 (400 mg dose of BMS-232632)</td>
<td>23% of the subjects</td>
<td>13% of the subjects</td>
</tr>
<tr>
<td>ALT/SGPT elevations</td>
<td>Not correlated with hyperbilirubinemia</td>
<td>BMS-232632 AT 400 mg dose: 29% for Grade1-2, and 4% Grade 3-4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29% of the subjects</td>
<td>17% of the subjects</td>
</tr>
<tr>
<td>Headache</td>
<td>17% of the subjects</td>
<td>14% of the subjects</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15% of the subjects</td>
<td>16% of the subjects</td>
</tr>
</tbody>
</table>

No obvious relationship between the pharmacokinetic parameters of CMAX, CMIN, or AUC and the HIV RNA log drop was discerned when a linear regression technique was performed upon data generated in the intense PK subset of subjects (n=29) of AI424-007. This finding was not unexpected as the success of therapy depended upon viral susceptibility to BMS-232632. The phenotyped viral samples appeared very susceptible. The short duration of exposure (the analyzed data were generated within the first four weeks of initiation of therapy) also precluded differentiation among doses (16).

The pharmacokinetic data generated in the detailed PK subset of subjects (n=29) of AI424-007 were very variable with CV values of about 70%; the fasted state of the subjects may have contributed to the variability. Subsequently, studies in healthy subjects (amended protocol AI424-007 and AI424-013) showed improvement in both the exposure (increased) and variability (decreased) with the coadministration of food. Of 29 trough values in the fasted, AI424-007 study, 11 were below the 59 ng/mL.
threshold, whereas in the fed state, 33 of 35 trough values were >60 ng/mL (combined AI424-012 and AI424-013 study data) (16).

Despite the lack of finding a significant relationship in AI424-007, pharmacokinetic/pharmacodynamic relationships have been generated elsewhere. It was demonstrated in an in-vitro hollow fiber system, whose pharmacokinetic exposure was modeled with Phase I human PK data (AI424-006), that the dynamically-linked variable to viral suppression (as measured by p24 antigen response in a cell system) appeared to be time above a threshold concentration. This finding translated to complete suppression of HIV p24 production once the threshold was exceeded for >80% of the dosing interval (17, 18).

1.35 BMS – 232632 (Atazanavir, ATV, Reyataz™) plus Ritonavir (RTV)

Background

As of January 2003, more than 1500 HIV-infected individuals have received BMS-232632 alone or in combination with ritonavir in Phase II/III studies. The most common adverse event remains an elevation of bilirubin levels; about 10% of adults on 200 mg, 400 mg, or 300 mg BMS-232632 + 100 mg ritonavir have developed jaundice of any grade; and 2 - 8% have developed scleral icterus.

BMS-232632 exposure is substantially increased by adding ritonavir (RTV). BMS conducted a study in healthy volunteers to determine the PK interaction of BMS-232632 and ritonavir at 300 and 100 mg QD respectively. The PK studies were conducted after 10, 15, and 20 days of treatment. The PK results are described in Table 3 (19).

### TABLE 3. Steady-State PK Interaction of BMS-232632 + ritonavir in Healthy Study Participants

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Mean</th>
<th>Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-232632 (300 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>3288</td>
<td>1.96 (1.78, 2.16)</td>
</tr>
<tr>
<td>AUC(TAU) (ng.h/mL)</td>
<td>16874</td>
<td>3.75 (3.48, 4.05)</td>
</tr>
<tr>
<td>BMS-232632 (300 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>3288</td>
<td>1.86 (1.69, 2.05)</td>
</tr>
<tr>
<td>AUC(TAU) (ng.h/mL)</td>
<td>16874</td>
<td>3.38 (3.13, 3.65)</td>
</tr>
<tr>
<td>Ritonavir (100 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2468</td>
<td>2386</td>
</tr>
<tr>
<td>AUC(TAU) (ng.h/mL)</td>
<td>15760</td>
<td>14844</td>
</tr>
</tbody>
</table>

n = 30 healthy volunteers
Another BMS study, also in healthy volunteers, established that co-administration of BMS-232632 + ritonavir increases the exposure of BMS-232632 several-fold in comparison to the administration of BMS-232632. The following table (Table 4) summarizes the results of the study (20).

**TABLE 4. Steady-State PK Interaction of BMS-232632 + ritonavir in Healthy Study Participants at two different doses of BMS-232632 and Ritonavir**

<table>
<thead>
<tr>
<th>Treatment* (mg) QD</th>
<th>$C_{\text{max}}$ ** (ng/mL)</th>
<th>$T_{\text{max}}$ *** (h)</th>
<th>$C_{\text{min}}$ ** (ng/mL)</th>
<th>AUC(TAU)** (ng*h/mL)</th>
<th>T-ALF** (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-232632 (200)</td>
<td>1480 (420)</td>
<td>2.50</td>
<td>33 (20)</td>
<td>7556 (2356)</td>
<td>4.53 (0.86)</td>
</tr>
<tr>
<td>BMS-232632 (200)+ ritonavir (100)</td>
<td>2876 (1353)</td>
<td>2.50</td>
<td>378 (286)</td>
<td>25780 (13989)</td>
<td>8.36 (2.20)</td>
</tr>
<tr>
<td>BMS-232632 (200)+ ritonavir (200)</td>
<td>4433 (758)</td>
<td>2.50</td>
<td>597 (237)</td>
<td>36256 (6418)</td>
<td>10.64 (3.27)</td>
</tr>
<tr>
<td>BMS-232632 (400)</td>
<td>5367 (1516)</td>
<td>2.50</td>
<td>159 (104)</td>
<td>29357 (8052)</td>
<td>5.28 (1.32)</td>
</tr>
<tr>
<td>BMS-232632 (400)+ ritonavir (100)</td>
<td>7754 (1060)</td>
<td>2.50</td>
<td>1023 (293)</td>
<td>70345 (10520)</td>
<td>7.04 (1.78)</td>
</tr>
<tr>
<td>BMS-232632 (200)+ ritonavir (200)</td>
<td>7156 (1195)</td>
<td>2.50</td>
<td>1419 (555)</td>
<td>70406 (13800)</td>
<td>9.68 (2.70)</td>
</tr>
</tbody>
</table>

*Two groups of sixteen subjects received BMS-232632 for six days at 200 mg and 400 mg QD. BMS-232632 PK profile was drawn on Day 6. On Day 7, each group was subdivided to receive ritonavir, at 100 or 200 mg QD. PK profile of BMS-232632 was drawn on Day 16. **Mean (S.D.) reported. ***Median reported.

The PK interaction of BMS-232632 + ritonavir has also been evaluated in HIV-infected subjects, who had failed several ART-regimens. Some of this study’s conclusions established that at Week 2 of treatment with BMS-232632 + ritonavir 300 QD and 100 mg, respectively, the PK parameters for the combination were similar to the data obtained in healthy volunteers. The following table (Table 5) summarizes the PK results of this trial (21).
TABLE 5. Week 2 PK Parameters of BMS-232632 + ritonavir in HIV-infected Subjects Who Had Failed Several ART-Regimens.

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>BMS-232632 Week 2</th>
<th>ritonavir Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>4,422</td>
<td>886</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>3 (2–5)</td>
<td>3 (2–8)</td>
</tr>
<tr>
<td>AUC24 (ng.h/mL)</td>
<td>46,073</td>
<td>7,011</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/mL)</td>
<td>636</td>
<td>43</td>
</tr>
<tr>
<td>C24 (ng/mL)</td>
<td>696</td>
<td>50</td>
</tr>
</tbody>
</table>

n = 10 HIV-infected adults

In the BMS-034 study, treatment-naïve subjects were randomized to BMS-232632 400 mg versus EFV 600 mg once a day, in combination with ZDV + 3TC BID. Each treatment arm enrolled just over 400 subjects. At 48 weeks of treatment, 70% of BMS-232632-treated subjects, and 64% of EFV-treated subjects had RNA levels <400 copies/mL. In this study, the rate of discontinuations due to adverse events was 6% in the BMS-232632 arm and 8% in the EFV arm. As expected, the main adverse event in the BMS-232632 treated arm was increased bilirubin (33% Grade 3-4, compared to 1% in EFV arm) and jaundice (5% in BMS-232632 arm, 0 in EFV arm) (13).

In BMS-043 study, subjects failing one prior PI containing regimen were randomized to BMS-232632 400 mg once a day versus Kaletra™ (400 mg lopinavir/100 mg ritonavir), combined with two NRTIs. There were approximately 115 evaluable subjects enrolled onto each arm. Baseline mean RNA level was 4.14 log₁₀, and CD4 cell count 268 copies/mL; 7% of the initial subjects discontinued from each arm. At 24 weeks, there was a mean decrease of 1.5 log₁₀ in the BMS-232632 treated group, compared to a decrease of just over 2 logs in the Kaletra™ treated group. Sixty percent of the BMS-232632 treated group had a viral load <400 copies/mL at 24 weeks. In this study, 3% of the BMS-232632 treated subjects experienced jaundice, and 20% had a Grade 3 or 4 elevation of bilirubin (13).

In BMS-045 study, 300 mg of BMS-232632 was used in combination with 100 mg ritonavir, compared to BMS-232632 400 mg/saquinavir 1200 mg QD or Kaletra™ (400 mg lopinavir/100 mg ritonavir) BID. Subjects had failed at least two treatment combinations, with experience to at least one agent in each class of drugs. Subjects were at first maintained on their NRTIs, and then changed at Week 2 to tenofovir and one NRTI plus the
PIs. More than 110 subjects were treated on each arm. At Week 16, the mean viral RNA decrease was 2.0 log\textsubscript{10} in the Kaletra™ arm, 1.85 in the BMS-232632 + ritonavir arm, and 1.61 in the BMS-232632 arm. The proportion achieving RNA levels less than 400 copies/mL was nearly equivalent in the BMS-232632 + ritonavir and the Kaletra™ arm, and less in the other alone arm. The discontinuation rate due to adverse events was 4% in the BMS-232632 + ritonavir arm, 10% in the BMS-232632 + saquinavir arm and 6% in the Kaletra™ arm. 6% of subjects on the boosted BMS-232632 regimen had jaundice, 45% Grade 3-4 bilirubin compared to 2% on the Kaletra™ arm and 17% on the BMS-232632 + saquinavir) (13).

1.4 Safety Update for BMS-232632 Doses Higher than 400 mg

In BMS Phase II/III sponsored trials, the rate of Grade 4 hyperbilirubinemia (>5x ULN) ranges from 2% for BMS-232632 400 mg QD for experienced subjects, 7% for naïve subjects, and 8% for subjects on BMS-232632 (300 mg) + ritonavir (100 mg) QD (13).

A total of 510 antiretroviral HIV-infected subjects received at least one dose of BMS-232632 in combination with other antiretroviral therapies, and 301 subjects received a comparator treatment in combination with other antiretroviral therapies (Table 6). Of the subjects treated with BMS-232632, 222 received BMS-232632 400 mg, 142 received BMS-232632 400 mg/saquinavir, and 119 received BMS-232632 300 mg pharmacologically enhanced with ritonavir 100 mg (22).
TABLE 6. Number of Antiretroviral Treatment-Experienced Treated Subjects in Safety Analyses in Phase II/III Clinical Studies of BMS-232632

<table>
<thead>
<tr>
<th>BMS-232632-Containing Regimens</th>
<th>lopinavir/ritonavir</th>
<th>NFV</th>
<th>ritonavir/ saquinavir</th>
<th>All Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>400 mg</td>
<td>400 mg/ saquinavir</td>
<td>300 mg/ ritonavir</td>
<td>600 mg/ saquinavir</td>
</tr>
<tr>
<td>N</td>
<td>222</td>
<td>142</td>
<td>119</td>
<td>27</td>
</tr>
</tbody>
</table>

Source: Updated Summary of Clinical Safety (Table 5.4.1A)
Includes 63 subjects treated first with NFV in AI424008 and then with BMS-232632 400 mg in AI424044.

In antiretroviral HIV-infected experienced subjects treated in Study AI424043, 69% of subjects treated with BMS-232632 and 79% of subjects treated with lopinavir/ritonavir reported one or more clinical adverse event (AE) of any grade, regardless of relationship to study therapy. The most common clinical AEs, infection, headache, and nausea, occurred with comparable frequency for both BMS-232632 and the comparator regimen, lopinavir/ritonavir. There were few differences in the incidence of treatment-related Grade 2 - 4 clinical AEs between the BMS-232632 and lopinavir/ritonavir regimens with the exception of higher incidences of jaundice in BMS-232632-treated subjects and allergic reaction, diarrhea, and gastritis in lopinavir/ritonavir-treated subjects (22).

In Study AI424045, 64% of subjects treated with BMS-232632 300/ritonavir, 73% of subjects treated with BMS-232632 400/saquinavir, and 75% of subjects treated with lopinavir/ritonavir reported one or more clinical AE of any grade. The most common clinical AEs, infection, headache, and nausea, occurred with comparable frequency in all three regimens. Except as noted, the incidence and patterns of treatment-related Grade 2 - 4 clinical AEs were comparable between the BMS-232632 300/ritonavir and lopinavir/ritonavir treatment regimens and higher on the BMS-232632 400/saquinavir treatment regimen. Among BMS-232632-treated subjects, a higher incidence of scleral icterus, jaundice, and myalgia were observed in the BMS-232632 300/ritonavir regimen, and a higher incidence of nausea, vomiting, and rash were observed in the BMS-232632 400/saquinavir regimen. A
higher incidence of diarrhea was observed among lopinavir/ritonavir-treated subjects (22).

The number of antiretroviral treatment-experienced subjects who discontinued treatment due to one or more AEs was infrequent and evenly distributed among the BMS-232632 and the lopinavir/ritonavir comparator treatment regimens of Studies AI424043 (1% BMS-232632 vs. 3% lopinavir) and AI424045 (3% BMS-232632/ritonavir, 5% BMS-232632/saquinavir and 3% lopinavir/ritonavir). Among antiretroviral treatment-experienced subjects, SAEs were infrequent and evenly distributed among the BMS-232632 and the lopinavir/ritonavir comparator treatment regimens of AI424043 (6% BMS-232632 vs. 5% lopinavir) and AI424045 (5% BMS-232632/ritonavir, 7% BMS-232632/saquinavir and 3% lopinavir/ritonavir). The majority of SAEs were judged by the Investigators to be unrelated to BMS-232632 or lopinavir/ritonavir (22).

A total of three deaths were reported in antiretroviral treatment-experienced subjects: two deaths (2/510, 0.4%) in subjects treated with BMS-232632 (congestive heart failure and homicide), and one death (1/264, 0.4%) in a subject treated with lopinavir/ritonavir (aneurysm, subdural hematoma and renal failure). None of the deaths were due to events that were considered by the Investigators to be related to BMS-232632 or lopinavir/ritonavir (22).

The safety experience associated with BMS-232632 + ritonavir regimen has been assessed directly in BMS Study AI424045. The safety data are summarized in Table 7. Additional safety experience supporting higher exposure can be derived from BMS Studies AI424007, AI424008/44, and AI424009/41 that included doses of BMS-232632 500 mg QD (AI424007) and BMS-232632 600 mg QD (AI424008/44, and AI424009/41). The key safety experience from these studies pertinent to the doses higher than 400 mg QD is also included in Table 7 (22).
### TABLE 7. Summary of Safety of BMS-232632 at Doses Greater than 400 mg/day

<table>
<thead>
<tr>
<th>Number of Subjects (%)</th>
<th>BMS Study AI424043 BMS-232632 400 mg/day (N = 144)</th>
<th>BMS Study AI424045 BMS-232632 300 mg/day/RTV (N = 119)</th>
<th>BMS Study AI424007 BMS-232632 500 mg/day (N = 107)</th>
<th>BMS Study AI424008/44 BMS-232632 600 mg/day (N = 195)</th>
<th>BMS Study AI424009/41 BMS-232632 600 mg/day (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time on BMS-232632 Therapy (weeks)</td>
<td>24</td>
<td>15</td>
<td>92</td>
<td>110</td>
<td>56</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>99 (69)</td>
<td>76 (64)</td>
<td>100 (93)</td>
<td>185 (95)</td>
<td>25 (93)</td>
</tr>
<tr>
<td>Selected Adverse Events&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>25 (17)</td>
<td>15 (13)</td>
<td>24 (22)</td>
<td>59 (30)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (17)</td>
<td>15 (13)</td>
<td>36 (34)</td>
<td>44 (23)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Rash</td>
<td>19 (13)</td>
<td>7 (6)</td>
<td>24 (22)</td>
<td>43 (22)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>14 (10)</td>
<td>17 (14)</td>
<td>16 (15)</td>
<td>43 (22)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (10)</td>
<td>19 (16)</td>
<td>33 (31)</td>
<td>37 (19)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Lipodystrophy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13 (9)</td>
<td>4 (3)</td>
<td>9 (8)</td>
<td>30 (15)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Peripheral Neurologic Symptom</td>
<td>13 (9)</td>
<td>8 (7)</td>
<td>22 (21)</td>
<td>49 (25)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (8)</td>
<td>7 (6)</td>
<td>12 (11)</td>
<td>21 (11)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (8)</td>
<td>6 (5)</td>
<td>5 (5)</td>
<td>16 (8)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Pain Abdomen</td>
<td>11 (8)</td>
<td>6 (5)</td>
<td>28 (26)</td>
<td>53 (27)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9 (6)</td>
<td>2 (2)</td>
<td>10 (9)</td>
<td>19 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Scleral Icterus</td>
<td>9 (6)</td>
<td>11 (9)</td>
<td>5 (5)</td>
<td>26 (13)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (6)</td>
<td>5 (4)</td>
<td>22 (21)</td>
<td>21 (11)</td>
<td>8 (30)</td>
</tr>
</tbody>
</table>
TABLE 7. Summary of Safety of BMS-232632 at Doses Greater than 400 mg/day

<table>
<thead>
<tr>
<th>BMS Study</th>
<th>Number of Subjects (%)</th>
<th>Number of Subjects (%)</th>
<th>Number of Subjects (%)</th>
<th>Number of Subjects (%)</th>
<th>Number of Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI42403</td>
<td>BMS Study AI424043</td>
<td>BMS Study AI424045</td>
<td>BMS Study AI424007</td>
<td>BMS Study AI424008/44</td>
<td>BMS Study AI424009/41</td>
</tr>
<tr>
<td>BMS-232632</td>
<td>400 mg/day (N = 144)</td>
<td>300 mg/day/RTV (N = 119)</td>
<td>500 mg/day (N = 107)</td>
<td>600 mg/day (N = 195)</td>
<td>600 mg/day (N = 27)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7 (5)</td>
<td>7 (6)</td>
<td>3 (3)</td>
<td>30 (15)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Grade 3 - 4 Laboratory Abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/SGPT</td>
<td>8/143 (6)</td>
<td>3/119 (3)</td>
<td>8/104 (8)</td>
<td>12/195 (6)</td>
<td>4/27 (15)</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>4/143 (3)</td>
<td>1/119 (&lt;1)</td>
<td>8/104 (8)</td>
<td>7/195 (4)</td>
<td>3/27 (11)</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>31/143 (22)</td>
<td>48/119 (40)</td>
<td>56/104 (54)</td>
<td>129/195 (66)</td>
<td>13/27 (48)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>3 (3)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Any Serious Adverse Event</td>
<td>9 (6)</td>
<td>6 (5)</td>
<td>21 (19)</td>
<td>28 (14)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Any Discontinuation due to Adverse Event</td>
<td>2 (1)</td>
<td>3 (3)</td>
<td>15 (14)</td>
<td>22 (11)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Discontinuation due to hyperbilirubinemia</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>2 (2)</td>
<td>6 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

a Treatment-emergent clinical AEs (Grade 1 - 4), regardless of relationship to treatment. AEs selected based on Grade 2 - 4 AEs considered at least possibly related to BMS-232632 treatment observed in ≥ 1% of all BMS-232632-treated subjects (see Section 1.4).

b Reported term; no prospective definition

c Includes one subject with “Jaundice Sclera”.

1.5 BMS-232632 (Atazanavir, ATV, Reyataz™) ECG Events Background

The potential of BMS-232632 to induce prolongation of PR- and QTc- intervals was noted in BMS study AI424-040. This study was an open-label, randomized, three-way crossover study to evaluate the pharmacokinetics and safety of BMS-232632 administered with a light meal to healthy study participants (23).

In this study, 24 HIV-negative healthy adult volunteers (22 men and 2 women) received the following three treatments with no washout in one of six randomly assigned sequences:

- 200 mg BMS-232632 capsule QD for five days
- 400 mg BMS-232632 capsule QD for five days
- 800 mg BMS-232632 capsule QD for five days

One subject discontinued the study after Day 7, two more after Day 10, for reasons not related to the medication. However, one subject discontinued the study after Day 10 due to PR-prolongation associated to study drug. This subject was monitored until the PR interval normalized, and went off study on Day 14 (23).

Mean PR baselines were similar across dose levels. Mean PR (post-dose) tended to increase with increasing dose. The mean PR changes from baseline increased with increasing dose (23).

The study found that fifty-eight percent (58%) of the subjects (12 males and 2 females) had prolongation of the PR interval to >200 msec on at least one ECG at one or more dose levels. In most cases, PR prolongation was mild (<250 msec). Five subjects had PR≥250 msec, all of them at the 800 mg dose level; marked PR prolongation (>400 msec) was observed in one of these subjects, a female. The mean PR peaked, for all dose levels, at 2.5 hours after dosing (median T_max=2.0 h) (23).

As for the QTc-interval, the mean QTc baselines were similar across dose levels. The mean QTc peaked, for all dose levels, at six hours after dosing (median T_max=2.0 hours). No study subject had a QTc>500 msec, no male subject had QTc>450 msec and no female subject had QTc>470 msec. Two male subjects had QTc>430 msec (one at 200 mg dose level, one at 800 mg dose level). Mean QTc (post-dose) intervals were larger for the 800 mg dose group, than for the 200 and 400 mg dose groups. Mean QTc (post-dose) intervals for the 200 and 400 mg dose groups were similar. Fifty percent (50%) of the subjects (11 males and 1 female) had at least one QTc change from baseline ≥30 msec; most of these occurred at the 800 mg dose level. The mean QTc changes from baseline were larger for the 800 mg dose group.
than for the 200 and 400 mg dose group (14). No subject had a QTc change from baseline of >60 msec (23).

Table 8 summarizes the changes in QTc-interval for all subjects in the study, and Figure 1 plots the mean PR-intervals versus the time since dosing.

Table 8: Listing of Subjects with Change from Baseline QTc Max to QTc Max ≥ 30 msec

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subject’s Gender</th>
<th>Study Day</th>
<th>ΔQTc Max (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
<td>Male</td>
<td>15</td>
<td>38.50</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>15</td>
<td>40.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>15</td>
<td>46.00</td>
</tr>
<tr>
<td>400 mg</td>
<td>Male</td>
<td>10</td>
<td>43.50</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>10</td>
<td>30.00</td>
</tr>
<tr>
<td>800 mg</td>
<td>Male</td>
<td>10</td>
<td>52.00</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10</td>
<td>40.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>5</td>
<td>33.50</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>5</td>
<td>51.50</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>10</td>
<td>41.00</td>
</tr>
</tbody>
</table>

ΔQTc Max = Change from Baseline QTc Max to QTc Max
FIGURE 1. Plot of Mean PR Versus Time Since Dosing

Note: Vertical bars represent one standard error of the mean.
The study concluded that there were dose- and concentration-dependent effects on QTc- and PR-intervals prolongation that were most apparent at the 800 mg dose of BMS-232632. However, no subject had a QTc > 500 msec or an increase in QTc > 60 msec at any dose level. No male subject had a QTc > 450 msec and no female subject had a QTc > 470 msec at any dose level. First degree AV block (PR>200) msec developed in at least one ECG in 58% of subjects. REG REVIEWly, there were no SAEs associated QTc or PR prolongations. One female subject discontinued due to PR prolongation (23).

Following the notification of ECG changes in adult subjects related to taking BMS-232632, the IMPAACT P1020A protocol team requested ECGs from all subjects enrolled in the study. Of the approximately 30 subjects on whom ECGs were performed, three subjects were noted to have asymptomatic prolongation of the PR-interval. No pediatric subject to date has had prolongation of the QTc-interval (24).

The number of BMS-232632-treated subjects with on-study PR interval prolongations > 200 msec was increased by one subject (BMS-232632 600 mg treatment regimen in Study AI424044). The frequency of subjects with a first degree atrioventricular block (PR interval > 200 msec) was comparable among regimens (BMS-232632 400 mg, 5.9%; BMS-232632 300 mg/ritonavir 100 mg, 4.3%; NFV, 10.4%; EFV, 3.0%; Kaletra™, 5.2%). No subject experienced atrioventricular block greater than first degree.

Following is the table (Table 9) summarizing all on-study PR-interval prolongation Phase II/III studies conducted by BMS. These data are from the latest safety update for BMS-232632 (25).

Additionally, at the U.S.A. FDA Advisory Committee for BMS-232632 in May 2003, two SAEs related to cardiac conduction and re-polarization problems were discussed. The first one was in a 49 year old male who presented three syncopal episodes and was taken to the emergency room, where his ECG revealed a prolonged QT interval. And the second one involved a 50 year old man with history of abnormal ECGs, who experienced a Grade 3 shortness of breath on Day 11 of the study receiving BMS-232632. A prolonged PR interval was noted on presentation. This subject died three days later from cardiac arrest. Both of these adult subjects receiving BMS-232632 were also taking verapamil, a calcium channel blocking agent prescribed for hypertension. Due to the possible relationship of BMS-232632, the concomitant antiretrovirals and verapamil with these SAEs, the IMPAACT P1020A Team decided to include verapamil in the list of disallowed medications for the study (26).
### TABLE 9. On-Study PR Interval Prolongation by Category - All Phase II/III Studies (17)

<table>
<thead>
<tr>
<th>PR Interval (msec)</th>
<th>Number with PR interval prolongation / Number Assessed (%)</th>
<th>AI424041</th>
<th>AI424044</th>
<th>AI424034</th>
<th>AI424043</th>
<th>AI424045</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMS-232632 Combined N = 152</td>
<td>NFV N = 48</td>
<td>BMS-232632 400 mg/day N = 173</td>
<td>BMS-232632 600 mg/day N = 127</td>
<td>BMS-232632 400 mg/day N = 353</td>
<td>EFV N = 329</td>
</tr>
<tr>
<td>≤ 200</td>
<td>144/152 (95)</td>
<td>43/48 (90)</td>
<td>158/173 (91)</td>
<td>109/127 (86)</td>
<td>336/353 (95)</td>
<td>319/329 (97)</td>
</tr>
<tr>
<td>&gt; 250</td>
<td>0/152 (0)</td>
<td>0/48 (0)</td>
<td>2/173 (1)</td>
<td>0/127 (&lt; 1)</td>
<td>1/353 (&lt; 1)</td>
<td>1/329 (&lt; 1)</td>
</tr>
</tbody>
</table>
1.6 **Adverse Events in Part A of IMPAACT P1020A in the U.S.A.**

As of November 21, 2002, the most common BMS-232632-related adverse event has been an elevation of bilirubin levels. Additionally, asymptomatic changes in ECG parameters, i.e., PR interval, heart rate and QTc intervals, have been closely monitored.

Following is a summary of the bilirubin and reported ECG adverse events that have been observed as of November 2002:

- Eight subjects had total bilirubin levels greater than 5.1 x ULN (TABLE XI and TABLE XIV). This has been the most common adverse event.

- Eleven subjects had asymptomatic prolongation of PR intervals above protocol defined limits. Eight were Grade 1 prolongation, and three were Grade 2.

- Seven subjects experienced heart rates lower than protocol defined limits.

- Two subjects had prolongation of QTcB interval above than protocol defined limits.

- One subject had a Grade 1 QRS duration.

1.7 **HIV Antiretroviral Resistance Background**

Incomplete suppression of HIV replication is attributable to numerous factors including limited potency of the antiretroviral regimen, poor adherence, pharmacological issues, and the emergence of drug resistance. Although it has not been definitely proven that clinical deterioration is due to the emergence of drug-resistant variants, *in vitro* and *in vivo* evidence strongly support such a relationship. To date, no antiretroviral has been developed for which HIV has been unable to evolve resistance. Once multi-drug resistance is present, viral suppression becomes extremely difficult.

To measure and define HIV resistance is a complex problem and is the topic of intense research. Central to its complexity is the biology of this virus. HIV circulates as a swarm of quasi-species—a highly variable genetic mixture constantly changing and increasing in complexity over time as well as space. Each of the viral variants is genotypically, antigenically, and phenotypically unique. The genetic diversity of HIV depends on the number of replication cycles (on the order of 1,011 virions per day), the mutation rate per replication cycle (on the order of 3 x 10^{-5} per base pair per replication cycle), recombination and the evolutionary fitness, i.e., the selective replicative advantage or disadvantage possessed by the variant virus. Given the
mutation rate of HIV and the dynamics infection, on average, every possible single-point mutation occurs between $10^4$ and $10^5$ times per day. Thus, when antiviral drug selective pressure is applied to the viral quasi-species, preexisting resistant minor viral species rapidly emerge (27). Persistent viral replication permits further viral evolution resulting in high-level resistance by the acquisition of cumulative mutations.

Another factor contributing to the difficulty of testing for HIV resistance is an incomplete understanding of the interaction of the multiple genotypic changes. Resistance to ART has been mapped to mutations in the target genes of the antiretroviral drugs, e.g., protease (PR) and reverse transcriptase (RT). However, the genotypic pathways associated with antiretroviral resistance can vary in vitro and in vivo depending on viral strain, cell line, or prior antiretroviral exposure. Mutations selected by drugs in combination can be different from those observed with monotherapy. In addition, in vitro studies suggest that mutations selected for by one antiretroviral can re-sensitize a resistant virus to another antiretroviral (phenotypic reversal) (28). New resistance mutations are continually being identified, posing a challenge to the interpretation of genotypic assays. Recently, two novel mutations, E44D and V118I, were identified as being selected by ZDV and were found to confer partial resistance to lamivudine in the absence of the M184V mutation (29). Moreover, when these novel mutations were present together with other ZDV resistance mutations (41L, 67N, 210W, and 215Y) the IC50 to lamivudine increased nine-fold (29).

There are at least two types of genotypic mutations that have been associated with antiretroviral resistance. Primary mutations are those that alter binding of the drug to its target and result in an increase in the amount of drug necessary to inhibit the enzyme. These mutations tend to be antiretroviral specific and can vary within a class. Secondary or compensatory mutations increase the level of resistance by improving the fitness of viruses carrying primary mutations. Usually secondary mutations have little or no effect on the level of resistance in the absence of primary mutations, and they tend to be less antiretroviral specific. Secondary mutations can occur at the target gene as well as the site of action of the encoded protein. For example, PIs can select for mutations not only in protease but also at the cleavage sites in gag-pol polyprotein.

Polymorphisms or naturally occurring variants at other codons in the PR and RT genes further complicate the analysis of antiretroviral resistance. The PR gene has nearly 48% variation at its codons compared with the consensus sequence, and PI resistance mutations can be found in PI-naive individuals (30). These polymorphisms may modulate the phenotype that results when primary and/or secondary mutations are present, leading to an apparent discordance between genotype and phenotype. This discordance most likely...
results from an incomplete understanding of all possible mutational interactions. The significance of these baseline polymorphisms in determining treatment outcome has yet to be defined.

Cross-resistance between agents of the same class has emerged as an important barrier to viral suppression in ART experienced individuals. Mutations in RT have been associated with resistance to several, even all, members of the NRTI and NNRTI classes. Such is the case of the RT mutation 151M in combination with three or four additional mutations, or the insertion of additional amino acids between RT codons 69 and 70, resulting in broad NRTI resistance. Cross-resistance among PIs appears to be ubiquitous. Analysis of viral isolates from 1500 PI-treated subjects found cross-resistance in 77% to 95% of viruses that displayed >10-fold resistance to indinavir, ritonavir, nelfinavir, or saquinavir (31). Although the most common initial primary mutations differ among PIs (e.g., V82, I84, or L90 for indinavir or ritonavir; G48, I84, or L90 for saquinavir; D30, I84, or L90 for nelfinavir; and I50 for amprenavir), there is considerable overlap in the compensatory secondary mutations (L10, M46, L63, A71, N88). It is believed that the presence of these secondary mutations "prime" for resistance to other PIs.

Finally, it has been observed that a significant number (20% to 50%) of subjects with virologic failure do not have detectable genotypic or phenotypic resistance (32).

Two approaches to detecting and measuring HIV antiretroviral resistance exist. Genotypic methods detect changes in the nucleotide sequence of HIV. These changes are compared with the consensus sequence and known resistance mutations. Phenotypic methods determine the concentration of drug that inhibits viral replication \textit{in vitro} by 50% (IC50) or 90% of a control (either a drug-sensitive wild type virus or virus in the absence of antiretroviral drugs). These assays can be performed with virus isolated by traditional methods, peripheral blood mononuclear cell (PBMC) co-culture, or on viruses constructed using recombinant DNA methods. In the latter methods, RT and PR are amplified from plasma HIV RNA to create infectious viruses, which are then assayed in cell lines. The recombinant approach is easily adapted to a high throughput format and is therefore available commercially. Both methodologies for determining HIV resistance - genotypic and phenotypic approaches - provide complementary information and have distinct advantages and disadvantages. All the currently available assays share the following limitations:

1. they are relatively insensitive to the presence of minority species, and
2. they are subject to the technical limitations in the RT-PCR step required to amplify the RT and PR genes.
Genotypic resistance assays have the relative advantage of being faster, cheaper, and easier to perform than current phenotypic assays. In addition, sentinel mutations may be detectable by the genotypic assay before a shift in drug susceptibility is apparent. However, the genotypic approach presupposes that the genetic basis of resistance has been determined and that consequences of mutational interactions can be predicted. Neither of these assumptions is entirely correct as discussed previously. In IMPAACT P1020A, genotypic analysis will be performed using the ABI HIV Genotyping System.

Phenotypic assays have the advantages of providing susceptibility data even if the genetic basis of resistance is unknown, assessing the net effect of different mutations on drug susceptibility and empirically determining cross-resistance. Theoretically, phenotypic assays should be more informative in cases where complex resistance is likely (e.g., multiple mutations, mutational interactions). However, current phenotypic assays are difficult to perform, time-consuming, and expensive. In IMPAACT P1020A, ViroLogic will be performing the phenotypic assays.

There is evidence prospective as well as retrospective, in favor of the clinical value of antiretroviral resistance testing. The VIRADAPT study was a randomized trial of genotyping versus standard of care in the management of subjects with plasma HIV RNA levels of > 10,000 copies/mL despite at least 3 months of therapy on a PI-containing triple therapy regimen. At 6 months the genotyping arm had a mean plasma HIV RNA reduction of 1.5 log copies/mL compared with a 0.65 log reduction in the control arm (p=0.015). In addition, 32.3% of the subjects in the genotyping arm had plasma HIV RNA levels of < 200 copies/mL versus 14% in the control arm (p=0.048). Follow-up of subjects in the genotyping arm indicated that the benefits persisted for 48 weeks. Subjects in the control arm were offered genotyping at 24 weeks and had declines in plasma HIV RNA levels similar to those seen in the genotyping arm. There was no difference in the virologic outcome at Week 48 between the two arms (33).

The Genotypic Antiretroviral Resistance Testing (GART) study was a randomized trial of genotyping versus standard of care for subjects failing a PI-containing regimen (34). Subjects assigned to the genotyping arm had a 1.19 log decrease in plasma HIV RNA at Week 12, compared to 0.61 log decrease in the control arm (0.00001). Although both the VIRADAPT and the GART studies have methodological flaws, such as algorithms that resulted in more aggressive treatment for subjects in the genotyping arm, they do provide preliminary support for the utility of these assays.
There are numerous retrospective studies that have determined that genotype and phenotype are predictors of subsequent virologic response; however, they found that resistance assays were better at predicting failure than success. Furthermore, most of these studies were small, with relatively brief follow-up and variable definitions of virologic response.

1.8 Preliminary Information from Partial Resistance Data in Part A of IMPAACT P1020A in the U.S.A.

Genotypic and phenotypic resistance tests are mandated at screening since most of the study candidates who want to enroll in IMPAACT P1020A have considerable antiretroviral experience. Prior to this amendment, a significant number of study candidates who had resistance testing were found to be ineligible on the basis of genotypic and/or phenotypic analysis. Forty percent of the children who had received two or more protease inhibitors were ineligible by phenotypic results, i.e. the IC50 of virus >10 fold resistant to BMS-232632. The team has also observed that resistance to BMS-232632 is related to phenotypic resistance to other antiretrovirals, mostly PIs. And, that high level resistance to the majority of antiretrovirals in all classes of medications is not infrequent (35).

In a preliminary analysis of IMPAACT P1020A data, phenotypic resistance to BMS-232632 and other antiretrovirals (ARV) was assessed in 40 subjects undergoing screening for protocol IMPAACT P1020A. Phenotypic resistance scores (PRS) were calculated as the Log10 of the ratio of subject versus wild type IC50s. Thirty-six of the 40 subjects had genotypic testing. The results indicate that heavily treated pediatric subjects exhibited relatively high levels of resistance to BMS-232632. Cross-resistance with other protease inhibitors (PI) was such that 94% of the variance in BMS-232632 phenotypic resistance scores could be predicted on the basis of cross-resistance with other PIs. These findings should be interpreted with caution since they come from exploratory analyses involving multiple comparisons, where some results may have been due to chance. The relationship between drug history and resistance patterns will continue to be evaluated as more data become available (36).

1.9 Adherence Background and Rationale for U.S.A. Sites

Advancements in antiretroviral drug treatments for HIV-infected children and adolescents are hindered by subject non-adherence. Decisions about dosing levels and drug combinations are based on the assumption that subjects will take the drug(s) as prescribed. However, this assumption may be ill founded, as there is evidence to suggest that 50% to 80% of pediatric subjects with a chronic illness are non-adherent to varying degrees (37). Further, as the complexity of drug regimens increases, so does the probability
that non-adherence will occur (37, 38). Thus, it is critical to the integrity of
drug study outcomes to assess adherence.

To date, there is no gold standard for the assessment of adherence.
Adherence assessment strategies commonly used are self-report, pill counts,
electronic monitoring, urine and serum assays, and the addition of tracers to
liquid medications. Each of these methods is imperfect and subject to error.

The more accurate methods are more expensive and labor intensive, as are
combinations of these methods. However, due to the critical nature of the
problem, the IMPAACT Adherence Subcommittee has piloted two measures
of self-reported adherence for subjects in the U.S.A.: Adherence Modules 1
and 2. Self-reported data are clearly subject to a number of biases, but,
within the context of large clinical trials, self-report provides a pragmatic
means for estimating adherence rates.

IMPAACT Adherence Module 1 is designed to quantify the proportion of
prescribed antiretroviral drugs actually taken within the 3 days prior to the
assessment. Adherence Module 2 is designed to capture self-reported reasons
for non-adherence linked with each drug. A preliminary analysis of 125
subjects enrolled in IMPAACT 377 indicated that, overall, the modules
performed well (39). Seventy percent of subjects reported complete
adherence (CA), 25% reported partial adherence (PA), and 5% reported non-
adherence (NA). Adherence did not differ by treatment arm, age, or
knowledge of HIV infection status. Adherence rates were lower for white
children than for non-white children (40% versus 73% CA, respectively,
p=0.048) and did not differ between African-American and Hispanic
children. The medication with the poorest adherence rate was nelfinavir
(68% CA). This rate was significantly lower than the rates for d4T (82%,
p=0.02) and nevirapine (83%, p=0.03). Problems were most frequently
reported with ritonavir and nelfinavir. These included taste, refusal, and
scheduling problems. Adherence was associated with virologic response:
complete HIV suppression (< 400 RNA copies/mL) was achieved in 68% of
subjects with CA and in only 42% with PA (p=0.03). CA was seen in 92%
of subjects with a 2 log drop in viral load and in 64% with a < 2 log drop in
viral load (p=0.03) (40).

The U.S.A. IMPAACT Adherence Modules can not be implemented in South
Africa, since they are not applicable as written due to cultural and socio-
economical differences between U.S.A. and South Africa. The IMPAACT
P1020A Version 6.0 does not include any adherence measurement tools for
South Africa. South African investigators will continue monitoring
adherence as part of the standard clinical care, as is customary for any
subject at the site but without a mandate for reporting to the IMPAACT
P1020A study.
1.10 Study Rationale

1.101 General Study Rationale

The current management of HIV-infected subjects dictates the use of antiretroviral agents in combination drug therapy regimens. These regimens combine different antiviral targets and pharmacological profiles, with the goal of increasing the efficiency, decreasing the toxicity, and delaying the development of resistance for the individual drug (13). This synergistic effect expressed by combination drug therapy regimens is one of the main reasons for the evaluation of BMS-232632. The availability of a powder formulation and the once-daily dosing schedule makes BMS-232632 an attractive agent for inclusion in pediatric treatment regimens.

IMPAACT P1020A is designed to provide pharmacokinetic data to guide dosing recommendations for BMS-232632 in infants, children, and adolescents. During the study, the safety and tolerance of BMS-232632 will be closely monitored, and preliminary virologic efficacy data will be obtained. Intensive pharmacokinetic data will be obtained from all subjects on Day 7, and at Week 56\(^2\). Twenty-four-hour intensive PK will be repeated 14 days after any BMS-232632 dose adjustment (other than those due to body weight based adjustments). To increase the accuracy of the data collected, all pharmacokinetic samples will be analyzed in real time.

The utility of target AUC values with real-time dose adjustments was demonstrated by IMPAACT 382. In BMS sponsored adult trials, a once daily 400-mg dose of BMS-232632 resulted in the majority of subjects having trough levels above the IC\(90\) (approximately 60 ng/mL, when adjusted for human serum protein binding). The expected intersubject variability for AUC values is 30% to 50%. Thus, the IMPAACT P1020A team decided on a minimum acceptable AUC value of 15,000 ng.h/mL for the study, believing that this value will provide trough levels in the range of the minimum trough target of 60 ng/mL. In light of the previously mentioned expected variability of AUC values of up to 50%, the protocol team set a population AUC target for BMS-232632 at 45,000 ng.h/mL. An AUC value of 45,000 ng.h/mL was selected as it would cover the

\(^2\) Intensive pharmacokinetics at week 56 will be performed as per week 1 PK; however, dose adjustments, if needed, will be for individuals only. No group-dose adjustments will be done based on week 56 PK data.
approximately 2-fold higher rate of hepatic clearance observed in young children versus adults taking protease inhibitors. Further, this exposure (projected from PK simulations) is similar to that of 600 mg QD, well tolerated by adult subjects in BMS AI424-008. Subjects with lower AUC values than these minimum levels will have BMS-232632 dose adjustments. Repeat pharmacokinetic studies will be performed 14 days after dose adjustment to confirm adequate AUC values.

The observed dose-dependent QTc and PR prolongation found in AI424-040 BMS study warrant continued ECG monitoring in IMPAACT P1020A. A larger clinical experience will allow an assessment of the clinical significance of these findings. Academic experts in cardiac electrophysiology were consulted for recommendations that lead to Version 3.0 of the protocol.

1.102 Rationale for Opening IMPAACT P1020A in South Africa

BMS-232632 is a novel protease inhibitor (PI), with pharmacokinetic parameters that support once daily dosing, a low pill burden for subjects, and convenient powder formulation for younger children. The once daily dosing is a distinct advantage for BMS-232632 in the global fight against HIV infection. Easier to follow antiretroviral regimens may improve adherence in resource-poor settings. This PI is also an attractive agent to bring into the field based on its acceptable safety profile and its lack of effect on cholesterol and triglyceride levels, as evidence in adult studies conducted by BMS.

The protocol team believes that in order to establish the correct dosing for this PI, it is very important to develop preliminary data in other countries (besides the United States of America), where people are infected with non-clade B HIV virus.

1.103 Rationale for BMS-232632 + ritonavir Approach

The IMPAACT P1020A team decided to amend the protocol based on the data of studies in healthy and HIV-infected adults receiving BMS-232632 plus ritonavir QD, data already discussed in the study background section. This amendment gives a new dosing algorithm using a low dose of ritonavir as a boosting agent for BMS-232632. This approach is meant to increase the chances of virologic response of highly ART-experienced subjects.

The boosted approach is being evaluated rather than continue with higher doses of BMS-232632 alone, since this approach has not been
completely successful. The protocol team set an AUC target of 45,000 ng.h/mL, with a $C_{\text{min}} \geq 60$ ng/mL based on adult PK data. The protocol stated the starting dose for BMS-232632 for each of the four study groups in Part A would be acceptable when five subjects receive a given BMS-232632 dose and:

- no subject had AUC < 15,000 ng.h/mL,
- at least 4 of the 5 subjects reached an AUC > 30,000 ng.h/mL, and
- at least 4 of the subjects reached $C_{\text{min}} \geq 60$ ng/mL.

Additionally, the starting dose would be considered safe for that study group if:

- none of these five subjects experienced life threatening toxicities,
- fewer than two of these five subjects experienced non-life-threatening Grade 3 or 4 toxicity (apart from bilirubin) attributable to study treatment; and,
- fewer than three of these five subjects had bilirubin levels higher than 5.1 x ULN.

Note:
See Section 8.32 for additional information about the PK algorithm.

Groups 1 and 2 had already failed the highest available dose of BMS-232632, 620 mg/m$^2$ and closed to accrual. Group 3 is evaluating the 520 mg/m$^2$ dose and Group 4 is evaluating the 620 mg/m$^2$ dose.

Table 10 summarizes the BMS-232632 initial doses per each one the four study groups in Part A that have failed the PK criteria, no group has failed the safety criteria.
### TABLE 10. Initial Doses BMS-232632 that Have Failed PK Criteria as per Protocol Versions 1.0, 2.0, and 3.0

<table>
<thead>
<tr>
<th>Group Number and Description (N=5)</th>
<th>Dose Level mg/m²</th>
<th>Dose Median mg</th>
<th>Dose Median mg/m²</th>
<th>AUC Median ng.h/mL</th>
<th>AUCs &lt;15,000 ng.h/mL</th>
<th>AUCs &gt;30,000 ng.h/mL</th>
<th>Cmin Median ng/mL</th>
<th>Cmin ≥ 60 ng/mL</th>
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<tbody>
<tr>
<td>1</td>
<td>310</td>
<td>100</td>
<td>329</td>
<td>6,354</td>
<td>3</td>
<td>1</td>
<td>16.8</td>
<td>1</td>
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<tr>
<td></td>
<td>620</td>
<td>500</td>
<td>584</td>
<td>32,435</td>
<td>1</td>
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<td>314</td>
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<td>2</td>
<td>91.5</td>
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<td>620</td>
<td>450</td>
<td>587</td>
<td>34,875</td>
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<td>138</td>
<td>5</td>
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<td>300</td>
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<td>33,070</td>
<td>0</td>
<td>3</td>
<td>173</td>
<td>5</td>
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<td>2</td>
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<td>400</td>
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<td>600</td>
<td>369</td>
<td>28,634</td>
<td>2</td>
<td>2</td>
<td>19.6</td>
<td>2</td>
</tr>
</tbody>
</table>

Only preliminary virologic efficacy data are available for IMPAACT P1020A. By October 2002, based on data from 44 heavily ARV treatment-experienced subjects within the four dosing groups of Part A, BMS-232632 was shown to have substantial antiviral activity. The majority of subjects had at least a 1 log₁₀ decline in HIV RNA at Week 24 [six (14%) subjects discontinued due to treatment failure]. Rather than continuing with higher doses of BMS-232632 in Group 3, which is evaluating the 520 mg/m² dose, the team decided that if this dose level does not meet the PK and safety criteria, no evaluation of the higher 620 mg/m² dose level will be done. For Group 4 is evaluating the 620 mg/m² dose level, and the team believes that this dose level may meet the PK and safety criteria for most adolescents.

The initial dose of BMS-232632 for the boosting approach will be 310 mg/m² and 100 mg/m² of ritonavir. The BMS-232632 dosing will be capped at 800 mg for the 310 mg/m² starting dose, and at 1000 mg for all other starting doses. Ritonavir will be capped at 100 mg.

1.104 Rationale for Addition of Cohort 5A
Group 5 of IMPAACT P1020A was designed to enroll infants and children 91 days to 2 years of age receiving atazanavir powder plus 100 mg/m² of ritonavir solution. Unfortunately, only two (both from the United States) infants between 3 and 6 months of age in this dosing cohort were enrolled as of 1/31/2007. Both infants had atazanavir exposures below our protocol defined target AUC of 30,000 ng*hr/mL. For PID 670634, aged 6 months, the AUC and C24 on 264 mg/m² were 7,347 ng*hr/mL and 126 ng/mL, respectively. For PID 450397, aged 3.6 months, the AUC and C24 were 14,909 ng*hr/mL and 120 ng/mL, respectively on 182 mg/m². The FDA has requested enrollment of at least 4-5 additional infants between 3-6 months of age to further define the pharmacokinetics, dosing, safety and efficacy of atazanavir in this age group. For version 6.0, a dosing subset of Group 5 (Group 5A) will open to infants 3-6 months of age. Inclusion and exclusion criteria remain as per previous versions of the protocol with the exception of the age criterion. The IMPAACT P1020A dosing strategy and pharmacokinetic and safety algorithm will apply to Group 5A infants. A minimum of five infants will be enrolled at the 310 mg/m² starting dose. The protocol team will apply the safety and pharmacokinetic algorithm, and then determine if additional dose adjustments are necessary. If the five infants meet safety and pharmacokinetic criteria at the initial 310 mg/m² starting dose, the dose will be accepted for this age cohort and and Group 5A will close to enrollment. However, if the pharmacokinetics in these first five infants are highly variable, the team may allow the enrollment of additional infants at the same dose to further define the pharmacokinetics in this 3-6 month age group. Alternatively, if these first five infants have consistently high or low exposures then the starting dose will be adjusted, and an additional minimum of five infants will be enrolled at the new dose. The starting dose for Group 5A will be adjusted using the same algorithm applied to previous cohorts. Refer to Tables 12-16 in Section 5.12 for the appropriate starting dosage.

2.0 STUDY OBJECTIVES AND HYPOTHESES

2.1 Primary Objectives and Hypotheses

2.1.1 To determine the pharmacokinetic profile and dosing schedule for the capsule formulation of BMS-232632 or BMS-232632 + ritonavir in
combination with two NRTIs\(^3\) in HIV-infected children and adolescents.

Hypothesis: Based on a standard dose generated from adult studies, a once-daily dose of BMS-232632 and BMS-232632 + ritonavir in adolescents and children (to be established in this study) will result in > 80% of the subjects having AUCs within the target range.

2.12 To determine the pharmacokinetic profile and dosing schedule for the powder formulation of BMS-232632 and BMS-232632 + ritonavir in combination with two NRTIs in HIV-infected infants and young children.

Hypothesis: Based on a standard dose generated from adult studies, a once daily dose of BMS-232632 and BMS-232632 + ritonavir in infants and children (to be established in this study) will result in >80% of subjects with AUCs within the target range.

2.13 To determine the safety and tolerability of BMS-232632 and BMS-232632 + ritonavir in HIV-infected infants, children, and adolescents.

Hypothesis: Based on dose ranging studies, BMS-232632 and BMS-232632 + ritonavir will be well tolerated, with no more than 20% of subjects experiencing Grade 3 or higher adverse events.

2.2 Secondary Objectives and Hypotheses

2.21 To assess the antiviral activity of BMS-232632 and BMS-232632 + ritonavir containing regimens as measured by viral load response and duration of maximum response in PI-experienced and -naive subjects.

Hypothesis: BMS-232632 and BMS-232632 + ritonavir, containing combination therapy will result in significant viral load response and durable virologic suppression in PI-experienced and -naïve subjects.

2.22 To assess the development of virologic resistance as measured by genotypic and phenotypic assays during treatment with BMS-232632 and BMS-232632 + ritonavir.

Hypothesis: The development of virologic resistance during therapy with BMS-232632 and BMS-232632 + ritonavir will be primarily seen

\(^3\) Abacavir (ABC, abacavir sulfate, Ziagen®) is excluded as one of the NRTIs options for the child’s regimen under IMPAACT P1020A.
in subjects with incompletely suppressed viral replication and will consist of predicted genotypic mutations.

2.23 To assess the relationship between the results of baseline phenotypic and genotypic resistance assays and virologic response.

Hypothesis: Virologic response will be inversely related to the degree of baseline phenotypic resistance and the number of baseline PI genotypic mutations.

2.24 To assess the relationship between systemic exposure to BMS-232632 and BMS-232632 + ritonavir, subject reported adherence, and virologic response (For U.S.A. subjects).

Hypothesis: Adherence will be closely related to systemic exposure and virologic response. Adherence will be better than that reported in protocol IMPAACT 377, because of the simplified dosing scheme in IMPAACT P1020A.

2.25 To evaluate the relationship of pharmacokinetics, as collected according to a population strategy, to pharmacodynamically-linked variables.

2.26 To assess the changes in immunologic function as measured by T cell-subset analysis and markers of cellular activation in relation to initiating or changing antiretroviral therapy (ART).

2.27 To assess the long-term safety and tolerability of BMS-232632 and BMS-232632 + ritonavir in South African HIV-infected infants, children, and adolescents (Step II).

3.0 STUDY DESIGN

IMPAACT P1020A is a Phase I/II, national and international, multicenter, open-label study of BMS-232632 and BMS-232632 + ritonavir-containing combination therapies for ART-naive and -experienced subjects. Children and adolescents from the age 91 days to 21 years will be enrolled into the study.

The study is divided in two steps. Step I is open in the U.S.A. and South Africa and is the BMS-232632 alone or in combination with ritonavir dosing finding step of the study. Step I is also divided into two parts, Part A or BMS-232632 dose finding part, and Part B or BMS-232632 + ritonavir dose finding part. Step II will only be open to South African subjects who are virologically responding to treatment when the last enrollee into either part of Step I (Part A or Part B) has
completed 96 weeks of treatment (end of Step I). Step II will continue in South Africa until BMS-232632 is approved and readily available by individual prescription as an off-study medication.

**IMPAACT P1020A, Version 5.0, closed to accrual on January 24, 2007; total accrual was 183 subjects.** As part of Protocol P1020A, Version 6.0, a dosing subset of Group 5 will re-open and enroll infants 91 to 180 days of age. With the exception of the age criterion, the study regimen, inclusion and exclusion criteria will remain as per Version 5.0.

To ensure continued access to the powder formulation after the original projected study end date (January 2009), the follow up period for groups 1, 2, 5 and 6 will continue until the powder formulation has FDA approval and is available locally. Study visits will occur every 12 weeks, and will include safety laboratory evaluations.

Subjects older than 2 years in Groups 1, 2, 5 and 6, receiving atazanavir powder may change to atazanavir capsules, if they have completed the week 56 intensive pharmacokinetic study visit and have met protocol defined AUC and PK criteria. Sites should notify the P1020A protocol team of their intent to switch a subject from powder to capsule, and follow the additional instructions in section 5.11.

The primary endpoint is to determine the pharmacokinetic profile and optimal dosing schedule of the capsule and powder formulations of BMS-232632 and BMS-232632 + ritonavir in combination with two NRTIs in HIV-infected children and adolescents. IMPAACT P1020A is designed to determine appropriate doses of BMS-232632 and BMS-232632 + ritonavir for four strata, defined with respect to age and BMS-232632 formulation, and country of enrollment (U. S. or South Africa).

Subjects are stratified into groups representing subject populations, which may require different dose levels, and the dose finding algorithm will be applied independently to each study group. The dose finding algorithm will be applied for the combined accruals in both countries. However, a minimum of 10 evaluable subjects from the U.S.A. and 10 evaluable subjects from South Africa will be enrolled into each study group at the REG REVIEW dose of BMS-232632 for that study group.

Current recommendations for initiating ART in treatment-naive subjects call for the use of three-drug regimens. Treatment-naive subjects in IMPAACT P1020A will begin therapy with two NRTIs in addition to BMS-232632 or BMS-232632 +
ritonavir. The NRTIs will be chosen at the discretion of the investigator based on the subject’s age and ability to tolerate the drug dosing and formulation.

Children with prior ART experience will also be able to enter the study. Previously treated children entering must be able to receive at least two new NRTIs or have genotypic evidence of sensitivity to at least two NRTIs. Children with treatment experience with an NNRTI are eligible. As BMS-232632 is expected to be efficacious in many subjects with prior treatment experience with PIs, subjects failing treatment with their first PI-containing regimens will be eligible for the study. Subjects with treatment experience with more than one PI will have a baseline viral phenotypic assay performed; if it indicates a less than 10-fold loss of sensitivity to BMS-232632, enrollment into the study will be allowed.

U.S.A. Subjects will be administered IMPAACT Adherence Modules 1 and 2 at Weeks 12, 24, 48, 72, 96, and every 24 weeks thereafter until the last subject enrolled in the study has reached Week 96 of his/her treatment. The respondent will be the individual identified as being primarily responsible for administering the drug regimen. In most cases, this will be the primary caregiver and the Pediatric version of the Adherence Modules will be administered. In some cases, the subjects themselves will be identified as taking primary responsibility for drug administration, and, in those cases, the Adolescent version of Adherence Module 2 will be used. Selection of the appropriate version of Adherence Module 2 will be left to the discretion of site personnel. Once the Adolescent version has been used, it will continue to be used in subsequent administrations for consistency.

In summary, IMPAACT P1020A will assess the activity, safety, and tolerability of BMS-232632 and BMS-232632 + ritonavir in combination with two NRTIs.

4.0 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

4.1 Inclusion Criteria for (Group 5A) Step I:

4.11 Age: 91 days to **180 days of age**.

4.12 A confirmed diagnosis of HIV infection defined by the current definition of the IMPAACT Virology Core Laboratory Committee. The current (April 00) definition requires two separate peripheral blood specimens from different days, and each specimen must be positive. The two positive results may be obtained in any combination of the following:

---

4 Abacavir (ABC, abacavir sulfate, Ziagen®) is excluded as one of the NRTIs options for the child’s regimen under IMPAACT P1020A.
• at any age: HIV culture, HIV-DNA PCR, or Plasma HIV RNA value ≥ 10,000 copies/mL
• age >4 weeks: neutralizable HIV p24 antigen (regular or ICD)
• age >18 months: licensed ELISA with confirmatory Western Blot

This definition may be updated by the IMPAACT Virology Core Laboratory Committee at any time. The IMPAACT P1020A will update the sites if these assays or their combination is modified. The protocol will always use the current definition of confirmed HIV-infection.

4.13 Viral load ≥ 5,000 copies/mL

4.14 Any CDC clinical classification and immune status.

4.15 Antiretroviral treatment naïve or experienced study candidates must be able to add two new NRTIs as part of their new therapy in this protocol, or have genotypic evidence of sensitivity to two NRTIs (the NRTIs must be used in combinations recommended in the Guidelines for the Use of Antiretroviral Agents in Pediatric and Adolescent HIV Infection).

If the study candidate has previously received treatment with ddC, ddI will not be considered a new NRTI for his/her new regimen under this protocol, and vice-versa.

Abacavir sulfate (ABC, Ziagen®,) and tenofovir disoproxil fumarate (TDF, Viread®) will be excluded as NRTI options for the subject’s regimen.

Sites must send an e-mail to the protocol team at actg.teamp1020@fstrf.org, establishing the candidate's PID#, date of birth (DOB), and ART-history. This information is required to determine if genotypic testing is needed. Sites must receive authorization, for each candidate, from the protocol team before proceeding with screening.

4.16 Study candidates must show evidence of retained phenotypic sensitivity to BMS-232632 (resistance index ratio of less than 10) when the subject has failed (after at least 12 weeks of therapy) two or more courses of PI containing regimens.
Sites must send an e-mail to the protocol team at actg.teamp1020@fstrf.org, establishing the candidate's PID#, date of birth (DOB), and ART-history. This information is required to determine if phenotypic testing is needed to confirm eligibility. Sites must receive authorization, for each candidate, from the protocol team before proceeding with screening.

4.17 Demonstrated ability and willingness to swallow study medications.

4.18 Study candidate, parent or legal guardian able and willing to provide signed informed consent.

4.19 Female participants who are sexually active and able to become pregnant must use two methods of birth control. Hormonal birth control alone (e.g. pills, shots, or slow release inserts placed under the skin) would not be considered adequate. An effective, medically accepted barrier method of contraception [e.g., female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm, intrauterine device (IUD), others] must also be used during the study. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission. Use of an IUD may increase the risk of pelvic inflammatory disease.

4.110 Males participating in the study must not attempt to impregnate a female, or participate in sperm donation programs. Males engaging in sexual activity that could lead to pregnancy must use a condom.

4.111 Study candidates with a history of undefined syncope will require a complete cardiac conduction evaluation at screening [e.g., ECG, 24-hour monitoring (Holter), and exercise test (if age appropriate)]. This evaluation must rule-out any cardiac conduction abnormalities (e.g., exclusion criteria 4.210 to 4.214).

4.2 Exclusion Criteria for Step I:

4.21 Active hepatitis.

4.22 Presence of an acute serious/invasive infection requiring therapy at the time of enrollment.

4.23 Hypersensitivity to any component of the formulation of BMS-232632.

4.24 Chemotherapy for active malignancy.
4.25 Pregnancy or breastfeeding.

4.26 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the clinician's opinion, would compromise the outcome of this study.

4.27 Any laboratory or clinical toxicity $\geq$ Grade 2 at entry$^5$

4.28 Documented history of cardiac conduction abnormalities, or significant cardiac dysfunction.

4.29 History of undefined syncope that can not be ruled out as related to cardiac conduction abnormalities$^6$.

4.210 Family history of prolonged QTc-interval syndrome, Brugada syndrome, or right-ventricular (RV) dyplasia.

4.211 Corrected QTc-Interval > 440 msec at screening.

4.212 Prolonged PR-Interval $>0.200$ seconds (200 ms) on ECG at screening (Study candidates $\geq$13 years of age).

4.213 PR-Interval $>98^{th}$ percentile on ECG at screening (Study candidates $<13$ years of age). Use Appendix VIII “Table to Determine 98$^{th}$ Percentile for PR-Intervals in Subjects $<13$ of Age”.

4.214 Cardiac rhythm abnormalities:
   - A type I second-degree atrioventricular (AV) block (Mobitz type I heart-block) occurring during waking hours on ECG at screening.
   - A type II second-degree AV-block (Mobitz type II heart-block) at any time on ECG at screening.
   - A complete AV-block at any time on ECG at screening.
   - A heart rate less than the 2$^{nd}$ percentile for age of the normal heart rate range (See Appendix IX) on ECG at screening.

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$^5$ Due to the long window of time allowed/needed (up to six weeks when genotypic and/or phenotypic testing is required), between the Screening Visit and the Entry Visit, the protocol team decided to establish this exclusion criterion at entry rather than at screening. Hematology, chemistries, liver function tests, lipid profile, and urinalysis must be checked at entry and results received before enrollment of the child into the study. Children must not receive study medications before getting confirmation of no Grade 2 laboratory or clinical toxicities at Entry Visit.

$^6$ Children with a history of undefined syncope will require a complete cardiac conduction evaluation at screening [e.g. ECG, 24-hour monitoring (Holter), and exercise test (if age appropriate)]. This evaluation must rule-out any cardiac conduction abnormalities (e.g. exclusion criteria 4.210 to 4.214).
4.215 Prolonged therapy with intravenous pentamidine for acute *Pneumocystis Carinii* Pneumonia (PCP) within three months of entry.

4.3 **Inclusion Criteria for Step II**

4.31 Any South African subject enrolled into either part of Step I, who is virologically successful by Week 96 of the last study subject enrolled into the respective part of Step I.

4.32 Female participants who are sexually active and able to become pregnant must continue using two methods of birth control. Hormonal birth control alone (e.g., pills, shots, or slow release inserts placed under the skin) would not be considered adequate. An effective, medically accepted barrier method of contraception [e.g., female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm, intrauterine device (IUD), others] must also be used during the study. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission. Use of an IUD may increase the risk of pelvic inflammatory disease.

4.33 Males who continue participation in the study must not attempt to impregnate a woman, or participate in sperm donation programs. Males engaging in sexual activity that could lead to pregnancy must use a condom.

4.4 **Exclusion Criteria for Step II**

4.41 A South African subject who meets any of the criteria for treatment discontinuation by Week 96 of the last subject enrolled into either part of Step I (see Section 6.4 Criteria for Treatment Discontinuation).

4.42 A South African subject who meets any of the exclusion criteria (Section 4.2) from Step I by Week 96 of the last subject enrolled into either part of Step I.

4.5 **Allowed Medications**

4.51 Any medication prescribed by study subject’s clinician, which is not listed in section 4.6 will be allowed in the study.

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7Ongoing treatment with once a month aerosolized pentamidine for prophylaxis is allowed.
4.52 Study subjects receiving intravenous gamma-globulin treatment, will be allowed in the study.

4.53 Study subjects receiving chronic steroids will be allowed in the study.

4.6 **Disallowed Medications**

4.6.1 Tenofovir disoproxil fumarate (TDF, Viread®)

4.6.2 Abacavir sulfate (ABC, Ziagen®).

4.6.3 All antiretroviral therapies other than the regimens described in this study

4.6.4 All investigational drugs

4.6.5 Systemic cytotoxic chemotherapy

4.6.6 Chronic acetaminophen use (e.g., Tylenol®), defined as more than 3 doses per day, for more than 7 days.

4.6.7 Treatment with any of the following medications within 180 days prior to entry:
- anabolic steroids
- megestrol acetate
- interleukin
- interferon
- thalidomide
- growth hormone

4.6.8 Disallowed medications due to their incompatibility with protease inhibitors:
- alprazolam
- amiodarone
- astemizole
- bepridil
- bupropion
- carbamazepine
- cisapride
- clorazepate
- clozapine
- diazepam
- dexamethasone
- encainide
- estazolam
- ergot alkaloids and derivative
- flecainide acetate
- flurazepam
- ketoconazole
- isotretinoin
- itraconazole
- meperidine
- midazolam
- phenobarbital
- phenytoin
- pimoide
- piroxicam
- propafenone
- propoxyphene
- quinidine
- rifabutin
- rifampin
- terfenadine
- triazolam
- zolpidem

4.69 Grapefruit juice.

4.610 Treatment with intravenous pentamidine\(^8\).

4.611 Verapamil.

4.7 Enrollment Procedures

Prior to implementation of this protocol, each site must have the protocol document and the consent form approved by its local Institutional Review Boards (IRB)/Ethics Committee (EC). Each site must be registered with and approved by the DAIDS/Regulatory Compliance Center Protocol Registration Office. Protocol Registration must be approved before any study participant can be enrolled in this study.

4.71 Enrollment Procedures for Step I

Sites interested in participating in IMPAACT P1020A, must send an e-mail to the team at actg.teamp1020@fstrf.org establishing the candidate's PID#, date of birth (DOB), and ART-history. Sites

\(^8\) Treatment with once a month aerosolized pentamidine for prophylaxis is allowed.
must receive authorization from the protocol team before proceeding with screening.

Enrollment slots will be granted only to a study candidate who:

- receives permission to proceed with the Screening Visit,
- accepts the notification for availability of slot and complete the Screening Visit within two weeks of receipt of the slot (Sites MUST e-mail the protocol team to accept the slot and to complete the Screening Visit)
- meets the study inclusion criteria.

Sites should contact the protocol team at actg.teamp1020@fstrf.org with any screening timeline deviations. A slot may be re-called if deviations from the timeline are not approved by the protocol team.

Study candidates will be enrolled in IMPAACT P1020A by SDAC/DMC registration screens. Entry evaluations must be completed within 72 hours prior to study drug initiation. Study drug(s) must begin within 72 hours of registration (see Appendix I for schedule of screening, pre-entry, entry, treatment, and treatment discontinuation evaluations).

Additionally, randomization of S.A. subjects may be necessary depending on the status of the study groups by the time Version 5.02 opens to accrual (See Section 8.12).

4.72 Enrollment Procedures for Step II

The South African Principal Investigator should send an e-mail to actg.teamp1020@fstrf.org with the study subject’s PID and SID for Step I, stating the study subject’s eligibility to continue receiving study treatment after Week 96 of the last subject enrolled into the respective study part of Step I.

South African subjects must meet eligibility criteria outlined in Sections 4.3 and 4.4 before registration into Step II is granted. Subjects registering to Step II will be assigned a new SID.

4.8 Co-enrollment Guidelines

Co-enrollment of subjects into other IMPAACT studies, require that all protocol chairs involved are informed of and agree that the inclusion/exclusion criteria of both studies are met simultaneously.
IMPAACT P1020A subjects are encouraged to participate in IMPAACT 219C and IMPAACT 1010.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

All subjects will remain on study until 96 weeks after the last subject is enrolled into each one of the two parts of Step I of the study. Step II will only be open to South African subjects who are virologically responding to treatment when the last enrollee into either part of Step I (Part A or Part B) has completed 96 weeks of treatment (end of Step I). Step II will continue in South Africa until BMS-232632 is approved and readily available by individual prescription as an off-study medication. Subjects in South Africa will remain in the study for as long as they are virologic successful as per protocol definition, or BMS-232632 is approved and readily available by individual prescription as an off-study medication. The follow-up period will be extended for groups 1, 2, 5 and 6 until the powder formulation is approved and locally available. Study visits will occur every 12 weeks and will include safety laboratory evaluations.

5.11 BMS-232632 powder formulation, and BMS-232632 powder formulation + ritonavir:

- Group 1: BMS-232632 at starting dose of 620 mg/m² PO QD failed under Version 3.0. This dosing approach will not re-open.

- Group 2: BMS-232632 at starting dose of 620 mg/m² PO QD failed under Version 3.0. This dosing approach will not re-open.

- Groups 5 and 6: BMS-232632 + ritonavir at starting doses of 310 mg/m² and 100 mg/m², respectively, PO QD in the morning.

Subjects in all groups also receive two new NRTIs or two NRTIs for which there is genotypic evidence of sensitivity. Concomitant NRTIs dose and dosing schedule will be as per each drug-insert-package information. If the subject has previously received treatment with ddC, ddI will not be considered a new NRTI for his/her new regimen under this protocol, and vice-versa. Abacavir sulfate (ABC, Ziagen®) and tenofovir disoproxil fumarate (TDF, Viread®) will be excluded as NRTI options for the subject’s regimen under IMPAACT P1020A.

As P1020A subjects age and become better able to swallow tablets and capsules, they may wish to switch from the powder to the capsule formulation of atazanavir. Additionally, some children require large
doses of atazanavir powder to achieve the P1020A protocol-defined area under the concentration time curve. Allowing these subjects to switch from the powder to the capsule formulation of atazanavir will facilitate study drug administration.

In comparing apparent oral clearance (as L/hr/kg) in age-matched subjects in Groups 6 and 7 receiving 310 mg/m², we found that apparent oral clearance in subjects on the capsule formulation is 0.6 times the clearance in subjects on the powder formulation. This suggests the powder is 40% less bioavailable than the capsules. As further evidence, group 6 (receiving atazanavir powder with a boosting dose of ritonavir) has passed our PK algorithm at 310 mg/m², while Group 7 (same age but taking capsules) has passed at a dose of 205 mg/m². To convert the dosage in subjects in Group 6 to the dosage in subjects in Group 7 would be a factor of 0.66.

Subjects greater than 2 years in Groups 1, 2, 5, and 6 receiving atazanavir powder may change to atazanavir capsules after completing the week 56 intensive pharmacokinetic study visit and having an atazanavir area under the concentration time curve (AUC) considered “passable” by our protocol criteria and not requiring a dosage adjustment. Subjects atazanavir powder dosages should be multiplied by 0.6 (and then rounded to the nearest 50 mg) to arrive at the new starting dosage for the atazanavir capsules. Refer to Table 11 for conversion.

Sites wishing to convert a subject from atazanavir powder to capsules should send an email to the 1020 protocol team in advance of the conversion to actg.teamp1020@fstrf.org, stating their intentions to change the formulation and include the PID number and proposed capsule dose. The protocol pharmacologist will verify the capsule dose and send an approval to the site.
### TABLE 11: Conversions for atazanavir powder dosage to atazanavir capsule dosage

<table>
<thead>
<tr>
<th>Current Powder Dose</th>
<th>Current Powder Dose times conversion factor of 0.6</th>
<th>Capsule dose to be administered based on converted dose rounded to the nearest 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>100</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>150</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>200</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>250</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>300</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>350</td>
<td>210</td>
<td>200</td>
</tr>
<tr>
<td>400</td>
<td>240</td>
<td>250</td>
</tr>
<tr>
<td>450</td>
<td>270</td>
<td>250</td>
</tr>
<tr>
<td>500</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>550</td>
<td>330</td>
<td>350</td>
</tr>
<tr>
<td>600</td>
<td>360</td>
<td>350</td>
</tr>
<tr>
<td>650</td>
<td>390</td>
<td>400</td>
</tr>
<tr>
<td>700</td>
<td>420</td>
<td>400</td>
</tr>
<tr>
<td>750</td>
<td>450</td>
<td>450</td>
</tr>
<tr>
<td>800</td>
<td>480</td>
<td>500</td>
</tr>
<tr>
<td>850</td>
<td>510</td>
<td>500</td>
</tr>
<tr>
<td>900</td>
<td>540</td>
<td>550</td>
</tr>
<tr>
<td>950</td>
<td>570</td>
<td>550</td>
</tr>
<tr>
<td>1000</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>1050</td>
<td>630</td>
<td>650</td>
</tr>
<tr>
<td>1100</td>
<td>660</td>
<td>650</td>
</tr>
<tr>
<td>1150</td>
<td>690</td>
<td>700</td>
</tr>
<tr>
<td>1200</td>
<td>720</td>
<td>700</td>
</tr>
</tbody>
</table>
Two weeks after changing from powder to capsules, a 24 hour intensive pharmacokinetic visit is required to evaluate this algorithm and to ensure the new capsule dosage is providing a similar exposure to the previous powder dosage. This dosage conversion should not be used outside of P1020A. Dose adjustments due to an increase in weight or toxicity will follow guidelines in Section 6.213.

5.12 BMS-232632 capsule formulation and BMS-232632 capsule formulation + ritonavir:

- Group 3: BMS-232632 at starting dose of 520 mg/m² PO QD in the morning (as established under Version 3.0). As per IMPAACT P1020A team’s decision the highest BMS-232632 starting dose of 620 mg/m² PO QD will not be tested if the 520 mg/m² fails for this group.

- Group 4: BMS-232632 at starting dose of 620 mg/m² PO QD in the morning (as established under Version 3.0).

- Groups 7 and 8: BMS-232632 + ritonavir at starting doses of 205mg/m² and 100 mg/m², respectively, PO QD in the morning.

Subjects in all groups also receive two new NRTIs or two NRTIs for which there is genotypic evidence of sensitivity. Concomitant NRTIs dose and dosing schedule will be as per each drug-insert-package information. If the subject has previously received treatment with ddC, ddl will not be considered a new NRTI for his/her new regimen under this protocol, and vice-versa. Abacavir sulfate (ABC, Ziagen®) and tenofovir disoproxil fumarate (TDF, Viread®) will be excluded as NRTI options for the subject’s regimen under IMPAACT P1020A.

Subjects will remain on the chosen NRTIs for the duration of the study, with the exception of NRTI-related toxicity. If a subject is experiencing toxicity believed to be related to one of the NRTIs, but not the study drug, and has completed at least 52 weeks on study, and is virologically suppressed, the site may contact the team about substituting an alternative NRTI.

5.13 Step II (continuation of study treatment after Step I has ended, i.e. the last subject enrolled has reached 96 weeks of treatment for each part of the study. Subjects must meet eligibility criteria outlined in Section 4.3 and 4.4).
IMPAACT Soweto Site Pharmacist must receive a new prescription bearing the new Step II SID number before dispensing additional BMS-232632 or BMS-232632 + ritonavir after Step I Part A or Step I Part B has ended.

- Study Groups 3 and 4: BMS-232632 capsule formulation PO QD in the morning at the same dose received at the end of Step I Part A + the two NRTIs received at the end of Step I Part A.

- Study Groups 5 and 6: BMS-232632 powder formulation will continue on the same dose received at the end of Step I Part B + ritonavir 100 mg/m² PO QD in the morning + the two NRTIs received at the end of Step I Part B. Subjects will be allowed to switch from powder to capsule formulation if treating physician deems it appropriate. A notification of this change in formulation should be sent to the team log-on at actg.teamp1020@fstrf.org.

- Study Groups 7 and 8: BMS-232632 capsule formulation at the same dose received at the end of Step I Part B + ritonavir 100 mg/m² PO QD in the morning + the two NRTIs received at the end of Step I Part B.

### TABLE 12. BMS-232632 Powder and Capsule Formulations Starting Dose of 310 mg/m²

<table>
<thead>
<tr>
<th>BSA in Meters Square</th>
<th>Dose of BMS-232632</th>
<th>Number of Scoops of BMS-232632 Powder</th>
<th>Number and Strength of BMS-232632 Capsules to Administer for Each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 - 0.26</td>
<td>50</td>
<td>1</td>
<td>1 x 50 mg</td>
</tr>
<tr>
<td>0.27 - 0.4</td>
<td>100</td>
<td>2</td>
<td>1 x 100 mg or 2 x 50 mg</td>
</tr>
<tr>
<td>0.41 - 0.56</td>
<td>150</td>
<td>3</td>
<td>3 x 50 mg</td>
</tr>
<tr>
<td>0.57 - 0.72</td>
<td>200</td>
<td>4</td>
<td>1 x 200 mg or 2 x 100 mg</td>
</tr>
<tr>
<td>0.73 - 0.88</td>
<td>250</td>
<td>5</td>
<td>5 x 50 mg</td>
</tr>
<tr>
<td>0.89 - 1.12</td>
<td>300</td>
<td>6</td>
<td>3 x 100 mg, 6 x 50 mg</td>
</tr>
<tr>
<td>1.13 - 1.45</td>
<td>400</td>
<td>8</td>
<td>2 x 200 mg, or 4 x 100 mg</td>
</tr>
<tr>
<td>1.46 - 1.77</td>
<td>500</td>
<td>10</td>
<td>5 x 100 mg</td>
</tr>
<tr>
<td>1.78 - 2.09</td>
<td>600</td>
<td>12</td>
<td>3 x 200 mg, or 6 x 100 mg</td>
</tr>
<tr>
<td>2.1 - 2.41</td>
<td>700</td>
<td>14</td>
<td>7 x 100</td>
</tr>
<tr>
<td>≥2.42</td>
<td>800*</td>
<td>16</td>
<td>4 x 200 mg, or 8 x 100 mg</td>
</tr>
</tbody>
</table>

*BMS-232 powder or capsule formulation dosing CAP at a 310 mg/m² dose is at 800 mg when prescribed alone or in combination with ritonavir.
### TABLE 13. BMS-232632 Powder and Capsule Formulations Starting Dose of 415 mg/m²

<table>
<thead>
<tr>
<th>BSA in Meters Square</th>
<th>Dose of BMS-232632 (mg)</th>
<th>Number of Scoops of BMS-232632 powder</th>
<th>Number and Strength of BMS-232632 Capsules to Administer for Each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.13 - 0.18</td>
<td>50</td>
<td>1</td>
<td>1 x 50 mg</td>
</tr>
<tr>
<td>0.19 - 0.3</td>
<td>100</td>
<td>2</td>
<td>1 x 100 mg or 2 x 50 mg</td>
</tr>
<tr>
<td>0.31 - 0.42</td>
<td>150</td>
<td>3</td>
<td>3 x 50 mg</td>
</tr>
<tr>
<td>0.43 - 0.54</td>
<td>200</td>
<td>4</td>
<td>1 x 200 mg, 2 x 100 mg</td>
</tr>
<tr>
<td>0.55 - 0.66</td>
<td>250</td>
<td>5</td>
<td>5 x 50 mg</td>
</tr>
<tr>
<td>0.67 - 0.84</td>
<td>300</td>
<td>6</td>
<td>3 x 100 mg, or 6 x 50 mg</td>
</tr>
<tr>
<td>0.85 - 1.08</td>
<td>400</td>
<td>8</td>
<td>2 x 200 mg, or 4 x 100 mg</td>
</tr>
<tr>
<td>1.09 - 1.32</td>
<td>500</td>
<td>10</td>
<td>5 x 100</td>
</tr>
<tr>
<td>1.33 - 1.56</td>
<td>600</td>
<td>12</td>
<td>3 x 200 mg, or 6 x 100 mg</td>
</tr>
<tr>
<td>1.57 - 1.72</td>
<td>700</td>
<td>14</td>
<td>7 x 100 mg</td>
</tr>
<tr>
<td>1.73 - 2.04</td>
<td>800</td>
<td>16</td>
<td>4 x 200 mg, or 8 x 100 mg</td>
</tr>
<tr>
<td>2.05 - 2.29</td>
<td>900</td>
<td>18</td>
<td>9 x 100 mg</td>
</tr>
<tr>
<td>≥2.3</td>
<td>1000*</td>
<td>20</td>
<td>5 x 200 mg</td>
</tr>
</tbody>
</table>

*BMS-232 powder or capsule formulation dosing CAP at a 415 mg/m² dose is at 1000 mg when prescribed alone or in combination with ritonavir.

### TABLE 14. BMS-232632 Powder and Capsule Formulations Starting Dose of 520 mg/m²

<table>
<thead>
<tr>
<th>BSA in Meters Square</th>
<th>Dose of BMS-232632 (mg)</th>
<th>Number of Scoops of BMS-232632 powder</th>
<th>Number and Strength of BMS-232632 Capsules to Administer for Each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17 - 0.24</td>
<td>100</td>
<td>2</td>
<td>1 x 100 mg or 2 x 50 mg</td>
</tr>
<tr>
<td>0.25 - 0.34</td>
<td>150</td>
<td>3</td>
<td>3 x 50 mg</td>
</tr>
<tr>
<td>0.35 - 0.43</td>
<td>200</td>
<td>4</td>
<td>1 x 200 mg, 2 x 100 mg</td>
</tr>
<tr>
<td>0.44 - 0.53</td>
<td>250</td>
<td>5</td>
<td>5 x 50 mg</td>
</tr>
<tr>
<td>0.54 - 0.67</td>
<td>300</td>
<td>6</td>
<td>3 x 100 mg, or 6 x 50 mg</td>
</tr>
<tr>
<td>0.68 - 0.86</td>
<td>400</td>
<td>8</td>
<td>2 x 200 mg, or 4 x 100 mg</td>
</tr>
<tr>
<td>0.87 - 1.05</td>
<td>500</td>
<td>10</td>
<td>5 x 100</td>
</tr>
<tr>
<td>1.05 - 1.25</td>
<td>600</td>
<td>12</td>
<td>3 x 200 mg, or 6 x 100 mg</td>
</tr>
<tr>
<td>1.26 - 1.44</td>
<td>700</td>
<td>14</td>
<td>7 x 100 mg</td>
</tr>
<tr>
<td>1.45 - 1.63</td>
<td>800</td>
<td>16</td>
<td>4 x 200 mg, or 8 x 100 mg</td>
</tr>
<tr>
<td>1.64 - 1.72</td>
<td>900</td>
<td>18</td>
<td>9 x 100 mg</td>
</tr>
<tr>
<td>≥1.73</td>
<td>1000*</td>
<td>20</td>
<td>5 x 200 mg</td>
</tr>
</tbody>
</table>

*BMS-232 powder or capsule formulation dosing CAP at a 520 mg/m² dose is at 1000 mg when prescribed alone or in combination with ritonavir.
### TABLE 15. BMS-232632 Powder and Capsule Formulations Starting Dose of 620 mg/m²

<table>
<thead>
<tr>
<th>BSA in Meters Square</th>
<th>Dose of BMS-232632 (mg)</th>
<th>Number of Scoops of BMS-232632 powder</th>
<th>Number and Strength of BMS-232632 Capsules to Administer for Each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 - 0.20</td>
<td>100</td>
<td>2</td>
<td>1 x 100 mg or 2 x 50 mg</td>
</tr>
<tr>
<td>0.21 - 0.28</td>
<td>150</td>
<td>3</td>
<td>3 x 50 mg</td>
</tr>
<tr>
<td>0.29 - 0.36</td>
<td>200</td>
<td>4</td>
<td>1 x 200 mg, 2 x 100 mg</td>
</tr>
<tr>
<td>0.37 - 0.44</td>
<td>250</td>
<td>5</td>
<td>5 x 50 mg</td>
</tr>
<tr>
<td>0.45 - 0.56</td>
<td>300</td>
<td>6</td>
<td>3 x 100 mg, 6 x 50 mg</td>
</tr>
<tr>
<td>0.57 - 0.72</td>
<td>400</td>
<td>8</td>
<td>2 x 200 mg, 4 x 100 mg</td>
</tr>
<tr>
<td>0.73 - 0.88</td>
<td>500</td>
<td>10</td>
<td>5 x 100 mg</td>
</tr>
<tr>
<td>0.89 - 1.04</td>
<td>600</td>
<td>12</td>
<td>3 x 200 mg, 6 x 100 mg</td>
</tr>
<tr>
<td>1.05 - 1.2</td>
<td>700</td>
<td>14</td>
<td>7 x 100 mg</td>
</tr>
<tr>
<td>1.21 - 1.37</td>
<td>800</td>
<td>16</td>
<td>4 x 200 mg, 8 x 100 mg</td>
</tr>
<tr>
<td>1.38 - 1.53</td>
<td>900</td>
<td>18</td>
<td>9 x 100 mg</td>
</tr>
<tr>
<td>&gt;1.54</td>
<td>1000*</td>
<td>20</td>
<td>5 x 200 mg</td>
</tr>
</tbody>
</table>

*BMS-232 powder or capsule formulation dosing CAP at a 620 mg/m² dose is at 1000 mg when prescribed alone or in combination with ritonavir.

### TABLE 16. BMS-232632 Powder and Capsule Formulations Dose Reduction to 205 mg/m²

<table>
<thead>
<tr>
<th>BSA in Meters Square</th>
<th>Dose of BMS-232632 (mg)</th>
<th>Number and Strength of BMS-232632 Capsules to Administer for Each Dose</th>
<th>Number and Strength of BMS-232632 Capsules to Administer for Each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 - 0.26</td>
<td></td>
<td>Must discontinue BMS-232632</td>
<td></td>
</tr>
<tr>
<td>0.24 - 4</td>
<td>50</td>
<td>1</td>
<td>1 x 50 mg</td>
</tr>
<tr>
<td>0.41 - 0.6</td>
<td>100</td>
<td>2</td>
<td>1 x 100 mg or 2 x 50 mg</td>
</tr>
<tr>
<td>0.61 - 0.85</td>
<td>150</td>
<td>3</td>
<td>3 x 50 mg</td>
</tr>
<tr>
<td>0.86 - 1.09</td>
<td>200</td>
<td>4</td>
<td>1 x 200 mg or 2 x 100 mg</td>
</tr>
<tr>
<td>1.1 - 1.34</td>
<td>250</td>
<td>5</td>
<td>5 x 50 mg</td>
</tr>
<tr>
<td>1.35 - 1.58</td>
<td>300</td>
<td>6</td>
<td>3 x 100 mg</td>
</tr>
<tr>
<td>1.59 - 1.82</td>
<td>350</td>
<td>7</td>
<td>7 x 50 mg</td>
</tr>
<tr>
<td>1.83 - 2.19</td>
<td>400</td>
<td>8</td>
<td>2 x 200 mg</td>
</tr>
<tr>
<td>≥2.2</td>
<td>500</td>
<td>10</td>
<td>5 x 100 mg</td>
</tr>
</tbody>
</table>

### TABLE 17. Ritonavir Dosing for Administration with BMS-232632 in Part B
### 5.14 BMS-232632 dosing

The variability of the AUC of BMS-232632 is reduced when given with meals. Administration of ddI concurrently with BMS-232632 decreased the CMAX of BMS-232632. Therefore, BMS-232632 should be administered around mealtime (QD, with food) and at least one hour before/after ddI administration. Additionally, subjects will be required to avoid consumption of GRAPEFRUIT JUICE for the duration of the study, as per dosing directions given by BMS. It is occasionally preferred by a subject, family, or care provider to have once daily doses administered in the evening rather than the morning for a number of reasons. However, it will not be permissible to administer BMS-232632 in the evening until intensive pharmacokinetic profiles have been completed and a maintenance dose has been determined.

### 5.15 Ritonavir dosing

Ritonavir should be taken at the same time as BMS-232632 with meals. The taste of the solution may be improved by mixing with chocolate milk, puddings, custards, or nutritional supplements within one hour of dosing.

### 5.16 Determination of body surface area (BSA)

To determine the correct dose of BMS-232632 and ritonavir, it is necessary to determine the subject’s BSA from his/her height and weight. Several methods for determining BSA are available and different institutions may routinely use one method over another. The different methods should ultimately provide approximately the same starting dose. Sites are encouraged to continue using the method for calculating BSA with which they are most comfortable. If BSA is not routinely calculated, the following formula is offered.

<table>
<thead>
<tr>
<th>BSA Range in m²</th>
<th>Ritonavir Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.66*</td>
<td>100 mg/m² administered as ritonavir solution</td>
</tr>
<tr>
<td>≥ 0.66</td>
<td>100 mg administered as one ritonavir 100 mg capsule* or 100 mg/m² of solution to a maximum of 1.25 mL of ritonavir solution</td>
</tr>
</tbody>
</table>

* For subjects whose BSA is < 0.66 m² the liquid formulation of ritonavir must be administered.

* Ritonavir CAP is 100 mg.
Formula for Calculating Body Surface Area (BSA):

\[ BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}} \]

5.2 Drug Formulation

5.21 BMS-232632 (atazanavir, ATV, Reyataz™)

BMS-232632 will be available in two formulations, capsules and dispersible oral powder.

BMS-232632 capsules are supplied as 50 mg, 100 mg or 200 mg strength (as free base equivalent) capsule formulations for oral administration containing white to pale yellow powder. These opaque, hard gelatin capsules contain BMS-232632 with lactose, crospovidone and magnesium stearate. Capsules are ready to administer, and are supplied in tightly closed high-density polyethylene bottles with child resistant closures. The BMS-232632 50 mg and 100 mg capsule formulation-strengths look identical and may NOT be used together to achieve any particular dose. The BMS-232632 200 mg capsules are blue. There is not a distinctive mark, or a symbol, or a number, or any kind of marking to differentiate the 50mg and 100mg capsules from each other once they are out of the bottle. Thus, it is required using only one capsule formulation-strength when prescribing. Capsules should be stored at 15° - 25°C (59° - 77°F) and storage in moist areas should be avoided.

The BMS-232632 dispersible powder for oral administration is a white to pale yellow powder. It contains BMS-232632 with sucrose, aspartame, and orange vanilla flavor. The powder is supplied in tightly closed induction-sealed high-density polyethylene bottles with child resistant closures. The bottles are labeled as 50 mg (as the free base)/1.5 g of powder. The 2.5 mL measuring scoops that will be provided for use with BMS-232632 powder for oral use, deliver 1.5 g of powder or 50 mg of BMS-232632 per scoop. Store at 15°-25°C (59°-77°F). Protect from moisture.

The dispersible powder for oral administration should be mixed with a small amount of applesauce, milk, yogurt, or baby formula. Once mixed with a food substance, the entire contents of the food and BMS-232632 must be consumed in order to obtain the full dose. The recommended storage of the product in these food items should not exceed three hours. Additionally, if prefer by study subject and/or treating physician, BMS-232632 powder for
oral administration can be mixed with water, but **ONLY** if dosing of this water-drug suspension is given with a light meal.

The variability of the AUC of BMS-233226 is reduced when given with meals. Administration of ddI concurrently with BMS-232632 decreased the CMAX of BMS-232632. Therefore, BMS-232632 should be administered around mealtime (QD, with food) and at least one hour before/after ddI administration. Additionally, subjects will be required to avoid consumption of GRAPEFRUIT JUICE for the duration of the study, as per dosing directions given by BMS.

It is occasionally preferred by a subject, family, or care provider to have once daily doses administered in the evening rather than the morning for a number of reasons. However, it will not be permissible to administer BMS-232632 in the evening until intensive pharmacokinetic profiles have been completed and a maintenance dose has been determined.

5.22 **Ritonavir (Norvir®, RTV)**

Ritonavir is supplied as soft gelatin white capsules imprinted with manufacturer, Abbott laboratories, logo containing 100 mg of ritonavir, and also as an orange-colored liquid in 240 mL amber-colored bottles containing 600 mg of ritonavir per every 7.5 mL dosage cup (80 mg/m²).

Ritonavir capsules should be kept in the refrigerator at 2 – 8°C (36-46°F). If capsules are not refrigerated, they should be used within 30 days, but always should be stored below 25° C (77°F) and protected from light.

Ritonavir oral solution should be kept at room temperature at 68°-77°F (20-25°C) and not refrigerated. Always shake solution well before use.

**Note:**

Home storage of ritonavir oral-solution: If the ritonavir oral solution is exposed to temperatures above 30° C (86°F) then a new supply of ritonavir oral solution should be dispensed every month. Ritonavir oral solution may be used for up to 3 months when stored at temperatures above 25°C and below 30°C (78° F to 85° F). New supplies of ritonavir oral solution should be dispensed every 3 months when stored at >25°C to < 30°C.

5.3 **Drug Supply, Distribution and Pharmacy**
5.31 Study medication

BMS-232632 and ritonavir will be provided by Bristol-Myers Squibb Pharmaceutical Research Institute for both U.S.A. and South African sites. The two NRTIs, for U.S.A. sites, will not be provided by the study and must be obtained by non-study individual prescriptions. And, in South Africa, they will be provided free of charge by non-study individual prescriptions through a program set up by BMS and the IMPAACT Soweto Site for IMPAACT P1020A subjects.

5.32 Study Supply Acquisition

BMS-232632 and ritonavir will be available through the NIAID Clinical Research Products Management Center (CRPMC). The IMPAACT pharmacist can obtain the study agents for this protocol by following the instructions in the manual "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks" in the section Study Product Control.

Obtaining ritonavir solution and ritonavir capsules through the NIAID CRPMC will be the normal and usual process. Upon occasion, the need may arise where the sites will be requested to purchase ritonavir solution or ritonavir capsules from commercial sources. When the site is required to purchase ritonavir solution or ritonavir capsules, the site will be reimbursed by Bristol-Myers Squibb (BMS). When it is determined that there is a need for the sites to purchase ritonavir solution or ritonavir capsules, this will be communicated to the sites by the protocol pharmacist or his/her designee. Only when permission has been given to the sites to purchase ritonavir solution or ritonavir capsules, will the sites be reimbursed for purchasing the ritonavir. The communication from the protocol pharmacist will include the form and instructions for reimbursement by BMS.

5.33 Study Agent Accountability

The IMPAACT pharmacist is required to maintain complete records of all study medication received from the NIAID CRPMC and subsequently dispensed. All unused study medication must be returned to the NIAID CRPMC after the study is completed or terminated. The procedures to be followed are given in the manual, "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks", in the section on Study Product Control. When the sites are required to
purchase ritonavir solution or ritonavir capsules, the site pharmacist must submit to the NIAID CRPMC the purchase details, including protocol number, date, quantity, lot number, and expiration date.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

Appendix II-A “DIVISION OF AIDS TOXICITY TABLE FOR GRADING SEVERITY OF PEDIATRIC (>3 MONTHS OF AGE) ADVERSE EXPERIENCES” must be used for grading these toxicities for subjects >3 months to \leq 21 years of age. The Data Management Center (DMC) will record all toxicity grades based on Appendix II-A "DIVISION OF AIDS TOXICITY TABLE FOR GRADING SEVERITY OF PEDIATRIC (>3 MONTHS OF AGE) ADVERSE EXPERIENCES" for all subjects in the study regardless of age (91 days to 21 years of age).

Whenever a toxicity grade includes the use of the “ULN”, as part of the calculation of the toxicity grade itself, sites must follow:

- “ULN” values reported by the laboratory report for the test, or
- “ULN” values routinely used/established by the site, or
- “ULN” values (and/or calculations) as per the Harriet Lane Handbook, or
- Specifically for indirect-bilirubin, the IMPAACT P1020A “ULN” reference value of 1.0 (IMPAACT P1020A Protocol Team based on published information).

Sites must be consistent with the way each toxicity is evaluated for all subjects in the study. Sites must provide documentation of calculated indirect-bilirubin and source of “ULN”, when your laboratory does not report them.

General toxicity management guidelines are provided in appendices II-A, II-B, and II-C; specific toxicities are addressed below. Alternate explanations for clinical or laboratory abnormalities must be sought prior to study drug discontinuation.

Abnormal clinical or laboratory observations \geq Grade 3 must be repeated within 72 hours for confirmation, continue the study drug, BMS-232632, pending receipt of the results (notify protocol team at actg.teamp1020@fstrf.org). However, the clinician has the option of immediately stopping the study drug and concomitant antiretrovirals if a repeat of confirmation of laboratory test cannot be performed within 72 hours, or if the clinician determines to be unsafe to continue study drugs while awaiting test results.
For ≥ Grade 4 toxicities stop study drugs and concomitant antiretrovirals and notify study chair, and copy protocol team at actg.teamp1020@fstrf.org, to determine course of action.

Grade 1 - No dose reduction; routine monitoring.
Grade 2 - No dose reduction; monitor closely with follow-up every 14 days; work-up to exclude other causes.
Grade 3* - For all confirmed Grade 3 toxicities other than bilirubin, neutropenia or anemia, discontinue the study drug and all the concomitant antiretrovirals until toxicity resolves to ≤ Grade 2. Restart all study medications at the same time once toxicity is ≤ Grade 2. If toxicity persists > 14 days or recurs on rechallenge, discontinue drug(s) permanently. Toxicity management for bilirubin will be as described in section 6.112.
Grade 4* - Notify protocol team at actg.teamp1020@fstrf.org. If clinically appropriate or due to study drug and/or concomitant medications, discontinue all drugs permanently.

*Note:

For all Grade 3 and 4 toxicities other than bilirubin, send an e-mail to actg.teamp1020@fstrf.org within 48 hours of the event. See bilirubin, toxicity management under sections 6.112.

For toxicities requiring dose modification of concomitant antiretrovirals, follow the insert package information package, e.g., zidovudine (ZDV), stavudine (d4T), zalcitabine (ddC), didanosine (ddI), lamivudine (3TC).

6.11 Criteria for subject management and dose modification

6.111 Neutropenia and anemia

The use of erythropoietin and/or G-CSF/GM-CSF is strongly encouraged. For a > Grade 3 anemia or neutropenia, stop all study medications and concomitant antiretrovirals and monitor laboratory values on a weekly basis. If levels return to < Grade 3 within 14 days, resume study medications at the indicated reduced dose. If levels remain < Grade 3 for at least fourteen days, resume full dose of medications. If after holding study medications there is no decrease to < Grade 3 values, or if after resuming study medications values return to ≥ Grade 3 contact study Chair. For neutropenia, only ZDV should be dose reduced and only two(2)
dose modification cycles are allowed. Following the second cycle, the full dosage of ZDV can no longer be resumed.

6.112 Liver Enzyme Elevation/Jaundice/Lactic Acidosis

BMS-232632 has been associated with increased plasma bilirubin levels, primarily through total bilirubin elevation. For purposes of IMPAACT P1020A, both the degree of bilirubin elevation value and the presence of clinical jaundice will be closely monitored.

The toxicity management for the elevation of the bilirubin level will be as follows:

- Subjects with total bilirubin levels ≤ 5.0 x ULN; dosing of BMS-232632 will be continued with close monitoring. Upon fractionation, the bilirubin should be predominantly indirect (70-80%). Other concurrently collected clinical chemistries predictive of liver function (e.g., ALT, AST, GGT, ALKP, and LDH) should be reviewed for evidence of other possible etiologies. Send e-mails to actg.teamp1020@fstrf.org notifying the protocol team and the Study Chair of the initial bilirubin level, and any subsequent laboratory values related with the monitoring of the bilirubin.

- Subjects with mild clinical jaundice should have their bilirubin level checked to determine proper course of action. Send an e-mail to actg.teamp1020@fstrf.org notifying the protocol team and the Study Chair of any worsening of jaundice symptoms in subjects previously observed to have mild levels of jaundice.

- Subjects with total bilirubin levels between 5.1 to 10 x ULN should have their bilirubin levels followed carefully. BMS-232632 should be withheld until the bilirubin level is ≤ 5.0 x ULN. BMS-232632 will be re-initiated at the first dose reduction. Send an e-mail to actg.teamp1020@fstrf.org notifying the protocol team and the Study Chair of the initial bilirubin level and the interruption of BMS-232632. The protocol team will discuss each subject case to determine the new dose for restarting the study drug.

- For subjects with confirmed total bilirubin levels > 10 x ULN, BMS-232632 will be PERMANENTLY discontinued. Send an
Lactic acidosis and a liver dysfunction syndrome have been associated with NRTI's mono-and combination therapies. In IMPAACT P1020A the possibility of the development of these conditions will be monitored. For subjects with ALT and AST values above 2.5 x ULN with no easily discernable etiology (e.g. acute hepatitis A, B, C, or chronic hepatitis B or C), a serum bicarbonate or lactate will be obtained. Send an e-mail to actg.teamp1020@fstrf.org notifying the protocol team and the Study Chair. The protocol team will work with the subject’s clinician to determine the best course of action for subjects in whom NRTI associated liver dysfunction syndrome and lactic acidosis are confirmed.

6.113 Cholesterol and triglycerides

Initiation of HAART therapy, with and without PIs has been associated with elevations in cholesterol and triglyceride levels. IMPAACT P1020A will follow Appendix II-B for toxicity grading of cholesterol and triglycerides for all subjects regardless of the subject’s age.

Lipid profiles are normally obtained in a non fasting-state, but:

- If non-fasting triglycerides are > 750 mg/dl (Grade 2 or higher), obtain a fasting-state lipid profile (triglycerides, cholesterol, HDL and LDL), as well as amylase and lipase.

- If non-fasting cholesterol >500 mg/dl (Grade 2 and higher), obtain a fasting-state level. Continue study drugs and notify the Study Chair at actg.teamp1020@fstrf.org.

- If non-fasting triglycerides and/or cholesterol are/is at any time ≥ Grade 3, notify Study Chair at actg.teamp1020@fstrf.org; and not only obtain a fasting-state lipid profile (triglycerides, cholesterol, HDL and LDL), as well as amylase and lipase, but continue obtaining all future lipid profiles on a fasting-state.

6.114 Hyperglycemia/glycosuria
If non-fasting blood glucose > 200 mg/dl or urinary glucose dipstick > 2+ positive, obtain fasting blood glucose and if ≥150 mg/dl, consider consulting an endocrinologist regarding possible new onset diabetes, and notify the Study Chair.

6.115 Rhythm disturbances and electrocardiogram changes:

Electrocardiogram changes and possible cardiac symptoms related to conduction abnormalities should be graded as per Appendix II-C. The following guidelines for toxicity management of the cardio-rhythm disturbances should be followed for all ECGs done while on study:

- at intensive PK days (Series of ECGs: arrival, 2-3 hours, and 4-6 hours post-administration of study drugs), and

- at anytime for symptomatology that the site deems possibly related to potential cardiac involvement (Cardiac signs and symptoms not associated with ECG changes should be graded as per Appendix II-A).

Two originals must be produced for all ECGs. One original must be reviewed by a pediatric cardiologist at the site, and the other original must be mailed to the central confirmatory site as per Appendix VI.

Upon reading of ECG, pediatric cardiologist at the site must notify the protocol team immediately at actg.teamp1020@fstrf.org, whenever one of the following cardio-rhythm disturbances is recorded. Sites must also contact the central confirmatory site, as per instructions in Appendix VI, to arrange an expedited 24-hour confirmation of abnormal findings.

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9 In order to expedite the reading of abnormal ECGs by the central confirmatory site, abnormal ECGs can be faxed, if the site does not have the capability of sending the information electronically via modem. Mailing one of the originals will still be required for all ECGs for archiving purposes. BMS will upgrade all sites to modem capacity; however, faxing (with FedEx shipment of paper-copy or original) will be acceptable until the site is ready to transmit ECGs electronically.
However, clinical management decisions will always be determined by the subject’s clinicians (e.g., cardiologist and/or primary care physician), and the protocol; the central ECG reading site will only supply confirmation of results.

6.114.1 PR-Intervals:

- Any subject $\geq$13 years of age with a prolonged PR-Interval $>0.250$ seconds (250 ms)

- Any subject $<$13 years of age with PR-Interval prolonged $>25\%$ above the 98th percentile for subject’s age (See Appendix VIII “Table to Determine the 98th Percentile for PR-intervals in Subjects $<$ 13 Years of Age”).

After notification to the team of the prolonged PR-Interval, arrange for a 24-hour ambulatory (Holter) monitoring within 72 hours of initial abnormal ECG. If Holter monitoring results are normal with the exception of the prolonged PR-Interval, or type I second-degree AV-block during sleep, subjects may continue study medications.

6.114.2 Cardiac-rhythm disturbances:

- A type I second-degree atrioventricular (AV) block (Mobitz type I heart-block) occurring during waking hours on any ECG, or Holter monitoring.

- A type II second-degree AV-block (Mobitz type II heart-block) at any time on any ECG, or Holter monitoring.

- A complete AV-block at any time on any ECG, or Holter monitoring.

Hold study medications, notify team and send one of the original print-outs for all ECGs. Confirmatory results must be received with in 24 hours.

- If confirmatory readings corroborate initial findings, notify subject that study medications will be
permanently discontinued. Subject will continue on-study, off-study-treatment until ECGs are back to normal.

- If confirmatory readings do not corroborate initial findings, contact protocol team immediately. The protocol team and the subject’s cardiologist will discuss the discrepancy and determine further course of action. REG REVIEW clinical management decisions will always be determined by subject’s main clinicians (e.g. cardiologist and/or primary care physician).

6.114.3 Heart Rate:

Low heart rate secondary to heart blocks, or prolongation of PR intervals on any ECG will cause permanent discontinuation of study drugs. Thus, if a subject heart rate is less than the 2\textsuperscript{nd} percentile for age of the of normal heart rate range, as per Appendix IX, stop all study medications and notify team.

6.114.4 QTc-Interval:

Corrected QTc-Interval > 0.470 seconds (470 msec). Hold study medications, notify team and send one of the original print-outs for confirmation. Confirmatory results must be received with in 24 hours.

If confirmatory readings confirm initial findings, notify subject that study medications will be permanently discontinued. Subject will continue on-study, off-study-treatment until ECGs are back to normal.

If confirmatory readings do not corroborate initial findings, contact protocol team immediately. The protocol team and the subject’s cardiologist will discuss the discrepancy and determine further course of action. REG REVIEW clinical management decision will always be determined by subject’s main clinicians (e.g. cardiologist and/or primary care physician).

6.115 Syncope or Palpitations (without clear evidence of non-cardiac etiology)
Study medications will be permanently discontinued to any subject developing syncope or palpitations (Grade 3 Toxicity—Appendix II-C) that can not be clearly ruled-out as unrelated to a cardiac etiology, or that the site deems possibly related to potential cardiac involvement. Subject will continue on-study, off-study-treatment, the subject will be followed with appropriate clinical and/or laboratory monitoring until resolved. Additionally, the subject will be asked to participate in the early discontinuation study visit and the two followup visits (See Appendix I-B).

6.116 Criteria for treatment interruption

Study medication and concomitant antiretroviral agents may be interrupted either for drug toxicity, as detailed previously, or for an intercurrent illness. Therapy or prophylaxis for opportunistic infections requiring use of concomitant medications not allowed in the protocol must be discussed with the Protocol Chair. Excluded medications include drugs, which could increase the toxicity or decrease the effectiveness of BMS-232632, or the concomitant antiretroviral agent(s), or medications, which may have an excessive or toxic effect when given with BMS-232632, or the concomitant antiretroviral agents.

6.12 Procedures for modification

Causes of toxicities other than the study medications, e.g., infection, other concomitant medications, lactose intolerance, etc., should be excluded before dose adjustment of study medications. Symptomatic therapy for toxicities, such as analgesics, antiemetics, antidiarrheal agents, or other necessary therapy, is permitted, but must be recorded in the case report forms (CRF).

IF IT BECOMES NECESSARY TO INTERRUPT THE STUDY MEDICATIONS FOR TOXICITY ≥ GRADE 3 (EXCEPT FOR HYPERBILIRUBINEMIA, SEE BELOW), BMS-232632, AND THE CONCOMITANT ANTIRETROVIRAL AGENT(S) MUST BE STOPPED AND RESTARTED AT THE SAME TIME (ON THE SAME DAY), WHETHER AT FULL OR ADJUSTED DOSE. SUBJECTS SHOULD NOT RECEIVE MONOTHERAPY AT ANY TIME. SEQUENTIAL RESTARTING OF STUDY MEDICATIONS IS NOT ALLOWED.

FOR TOXICITY MANAGEMENT OF HYPERBILIRUBIN IN BLOOD, FOLLOW INSTRUCTIONS UNDER SECTION 6.112; IN THIS CASE, HOLD BMS-232632 UNTIL BILIRUBIN LEVELS ARE ≤ 5.0X ULN,
BUT CONTINUE DOSING CONCOMITANT ANTIRETROVIRALS. RE-
START BMS-232632 AT FIRST DOSE REDUCTION AS SOON AS 
BILIRUBIN LEVELS ≤ 5.0X ULN (WHICH GENERALLY OCCURS 
WITHIN THREE DAYS OF DOSE INTERRUPTION).

Concomitant antiretroviral agents must be dose-adjusted according to the 
current package inserts. Dose adjustment for all toxicities other than those 
described specifically in Section 6.11 may be managed according to the 
general toxicity management guidelines in Appendices II-A to II-C. If there 
are recurrent toxicities, the investigator should contact the Protocol Chair for 
further individual subject management.

6.2 Study Management Plan

6.2.1 ART Naive and Experienced Subjects

For subjects with extensive NRTI treatment experience, genotypic testing 
will be performed using the plasma samples collected at Screening Visit. 
For subjects with treatment experience with more than one PI, phenotypic 
testing will be performed using the plasma samples collected at Screening 
Visit. These subjects must remain on their current ARV at the time of 
resistance testing. Genotypic sensitivity will be determined as outlined in 
Appendix VII “Guide to Antiretroviral Resistance Mutations” (see also 
Appendix III-A “Virology Collection and Shipping Instructions”). 
Phenotypic sensitivity to BMS-232632 will be defined as a resistance index 
ratio of less than 10.

Subjects will receive BMS-232632 or BMS-232632 + ritonavir and two 
NRTIs. Intensive pharmacokinetics studies will be performed on Day 7. 
Dose adjustments will be done to subjects with area-under-the-curve (AUC) 
values outside of the target value (See Section 6.213). Repeat PK studies 
will be performed to all subjects whose starting doses needed to be adjusted, 
within 14 days of dose adjustments.

6.2.11 Starting dose of BMS-232632 and BMS-232632 + ritonavir

The initial starting dose of BMS-232632 will correspond to a target 
AUC of 45,000 ng.h/mL. An AUC value of 45,000 ng.h/mL was 
selected as it would cover the approximately 2-fold higher rate of 
hepatic clearance observed in young children versus adults taking 
protease inhibitors. Ritonavir dose will be 100 mg/m² for subjects 
with BSA <1 m² and 100 mg for BSA ≥ 1 m².
Using the tables of standard ages (9 through 16), weights and body surface areas in children, the BMS-232632 allometrically scaled doses will be equivalent to:

- Group 1: closed
- Group 2: closed
- Group 3: closed
- Group 4: closed
- Group 5: closed
- Group 5A: 310 mg/m$^2$
- Group 6: closed
- Group 7: closed
- Group 8: closed

6.212 Adjustments of the BMS-232632 strata starting doses (Diagram 1)

The IMPAACT P1020A Team considers that it is worthwhile to pursue optimal dosing of BMS-232632 capsules alone, without ritonavir boost, in the pediatric population.

For the powder formulation of BMS-232632 administered alone, the protocol team has concluded that it is not practicable to try to establish dosing that would obtain adequate AUC levels. The early experience in IMPAACT P1020A suggest that the dose needed to achieve AUC and pharmacokinetics targets (when used without ritonavir boosting) would require a large amount of powder, difficult to disperse in liquid. Thus, the team decided to close Groups 1 and 2 permanently, and pursue dosing with the powder formulation of BMS-232632 only used in combination with ritonavir.

- Part A:

  There will be no further starting dose adjustments for Groups 3 and 4. If either of the two current doses, BMS-232632 520 mg/m$^2$ and 620 mg/m$^2$, fails the PK and/or safety criteria, accrual will be suspended for that study group.

- Part B:

  The starting dose will be adjusted based on the tolerability and BMS-232632 plasma concentrations of the first five subjects receiving that dose in each stratum (see Section 8.3 for Safety
and PK criteria as they were applied for Part A). An initial sample of 5 subjects in each stratum will be treated for one week and evaluated for pharmacokinetics at Day 7 and for toxicity at Week 4.

A dose is considered “tolerated” if no more than 1 of the 5 subjects experienced Grade 3 toxicity or greater (bilirubin toxicity management will be unique for IMPAACT P1020A, please refer to 6.112 and 8.3.1). If any of these 5 subjects have life-threatening toxicities attributable to the study treatment, further accrual into the particular study group will be suspended, pending a thorough investigation by the Protocol Team.

The above initial BMS-232632 starting dose of 310 mg/m² a set of five subjects in each one of the four study groups of Part B, and it will be acceptable if the following criteria are all met (each group is managed independently):

- the dose is tolerated, no more than one subject has a ≥ Grade 3 toxicity, other than bilirubin (See Section 8.31).
- no AUC is below 15,000 ng.h/mL,
- at least 4 of the 5 subjects reach an AUC of > 30,000 ng.h/mL, and
- at least 4 of the 5 subjects have a trough (C_MIN) concentration ≥ 60 ng/mL.

If the five subjects accrued into a given study group of Part B fails (each group is managed independently) the above criteria under a higher starting BMS-232632 dose of 415 mg/m² in combination with 100 mg/m² ritonavir, the BMS-232632 dose will be adjusted to 520 mg/m² in combination with 100 mg/m².

- If the median AUC is < 19,300 ng.h/mL the study group will be suspended, and the protocol team will determine if higher daily doses or alternative regimens are warranted. Dose adjustment will be done only by study amendment.
- If no tolerated dose achieving at least an AUC of 30,000 ng.h/mL in 4 of 5 subjects can be identified, accrual into this group will be suspended and alternative dosing regimens will be considered by the study team (amendment to the protocol).
These same criteria will be applied for 520 mg/m$^2$ BMS-232632 and the dose re-adjusted to 620 mg/m$^2$ (See Dosing Tables 12 to 17).

Any change in a group initial starting dose of BMS-232632 in combination with ritonavir will be communicated to the sites by the Protocol Team.

Enrollment of subjects will be ongoing and subjects who began on a given starting dose will continue on that dose until individual subject dose adjustments are needed according to their individual pharmacokinetic evaluations (see section 6.213).

**Note:**

If the median BMS-232632 AUC of the first five subjects in a particular study group of Part B receiving the BMS-232632 starting dose of 310 mg/m$^2$ in combination with 100 mg/m$^2$ ritonavir exceeds 60,000 ng.h/mL, the BMS-232632 dose will be reduced to 205 mg/m$^2$ (See Table 15).
Diagram 1: Adjustments of the BMS-232632 Group Starting Dose For Part B

Study Groups 5, 5A, 6, 7, and 8
BMS-232632 + ritonavir Starting Dose (target AUC of 45,000 ng.h/mL)
(Each Study Group Is Managed Independently)

Accrue 5 subjects per Group to establish BMS-232632 starting dose of 310 mg/m²
(Data will not be pooled across countries)

Criteria to accept BMS-232632 starting dose:
- Dose is tolerated, meaning no more than one of this 5 first subjects has a ≥ Grade 3 toxicity (other than bilirubin, please see Section 8.31).
- No AUC is below 15,000 ng.h/mL.
- Four of the five subjects have AUC levels ≥ 30,000 ng.h/ml.
- At least 4 of the 5 subjects have trough (C_{MIN}) concentration of ≥ 60 ng/ml.

Accepted Dose
(Based on PK and safety criteria)*

Accrue five more subjects in using this starting dose.

Re-evaluate dose using PK criteria but with a N_{total}=10
(see Section 8.32)
(Data will not be pooled across countries, except for Group 5A)

Dose Not accepted

If a tolerated starting dose, which gives at least an AUC level of 30,000 ng.h/mL in 4 of the 5 subjects, can not be identified, the study group will be suspended and the protocol team will consider a new dosing algorithm.

Dose failed the above criteria

Accrue 5 new subjects at new BMS-232632 starting dose of 415 mg/m²

BMS-232632 (Re-start Chart)
This same algorithm will be used to evaluate 520 mg/m² and 620mg/m² BMS-232632 starting doses. If 620 mg/m² fails, an amendment will be needed.

BMS-232632
Dose passed/found (full accrual)
*For Group 5A only: A minimum of 5 subjects will be enrolled in group 5A, at the starting dose of 310mg/m². The protocol team may elect to enroll an additional number of subjects at that dose. If the dose fails safety or PK criteria for these first 5 subjects, the starting dose may be adjusted, and an additional number of subjects enrolled. Unlike other groups, however, a full ten subjects will not need to be enrolled for the confirmation of the dose in this subset of group 5.

6.213 Adjustment of BMS-232632 doses in individual subjects (Diagram 2)

The use of ritonavir in Groups 5-8 (including Group 5A) makes it conceivable that a group may fail the AUC criterion but pass the protocol Cmin criterion. The Cmin used for pharmacokinetic evaluations (as defined in clarification memo #3) is the 24-hour post-observed dose concentration. Since C24 reflects a concentration following an observed dose of study medication, it minimizes the effect of poor adherence. If the C24 level is not available or unevaluable, the C-predose value will be used. This scenario of meeting the Cmin criteria, but failing the AUC criteria may arise because of ritonavir’s potent inhibition of atazanavir elimination. In such a scenario, further evaluation of the dose can be warranted because of the relationship between atazanavir Cmin and virologic response.

For these dose groups, the team will use Cmin to meet pharmacokinetic criteria for passing a dose, and to evaluate that group’s present dose of atazanavir in an additional 10 children. The following criteria must be met: in the first 10 children for the dose to pass no child may have a Cmin of less than 60 ng/mL, and no more than two of ten children may have a Cmin of less than 120 ng/mL. If the protocol-defined safety criteria are met, an additional 10 children may then be studied at the same dose.

For group 5A, to fulfill dosing criteria, a minimum of 5 subjects will need to meet safety, Cmin and AUC criteria. The protocol team may decide to allow additional subjects to enroll into group 5A depending on the results of the first 5 enrolled.

For each subject in the study, a 24-hour pharmacokinetic profile (samples obtained at 0, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose)
will be performed at Week 1 and Week 56\(^{10}\) (See Appendix V “Pharmacology Specimen Collection, Processing, and Storage”). For subjects requiring dose adjustments, repeat 24-hour pharmacokinetic studies will be performed two weeks after initiation of new dose, e.g., Week 3 (and 7, 11 etc., as needed), the BMS-232632 dose will be adjusted as required. Individual dose adjustments will be as follows:

- If subject's current dose is well tolerated (no toxicity ≥ Grade 3) but the AUC is < 30,000 ng.h/mL, then a new dose will be determined by prorating the current dose to attain an AUC of approximately 45,000 ng.h/mL.

- If subject's current dose is not well tolerated (toxicity > Grade 3) then the dose will be prorated to achieve a lower AUC according to the following AUC ranges:
  - AUC > 60,000 ng.h/mL, a revised dose will be calculated to provide an AUC of 45,000 ng.h/mL.
  - AUC between 45,000 and 60,000 ng.h/mL, the new dose will correspond to an AUC of 30,000 ng.h/mL.
  - AUC between 30,000 and 45,000 ng.h/mL, the dose will be revised to provide an AUC of 25,000 ng.h/mL.
  - AUC between 25,000 and 30,000 ng.h/mL, the dose will be revised to provide an AUC of 20,000 ng.h/mL.

- If a subject has not achieved an AUC of greater than 25,000 ng.h/mL, yet is suffering Grade 3 or greater toxicity, that subject will be discontinued from the protocol.

- If a subject's AUC exceeds 90,000 ng.h/mL, even if no toxicity is observed, for safety reasons, the BMS-232632 may be reduced to attain an AUC level less than 60,000 ng.h/mL.

All subject’s individual dose adjustments will have repeat 24-hour pharmacokinetic evaluations performed two weeks after initiation of the new dose. For further dose changes follow the algorithm previously described.

\(^{10}\)Intensive pharmacokinetics at week 56 will be done as per week 1 PK; however, dose adjustments, if needed, will be for individuals only. No group-dose adjustments will be done based on week 56 PK data.
Increases of 25% in subject's body weight will trigger a BMS-232632 dose increase as follows:

- If NO PK directed dose change was made at Week 1, i.e., the starting BMS-232632 dose from dosing tables in Section 5.0 provide and adequate AUC, then the dose corresponding to the 25% weight increase from the appropriate table can be used. If the Week 56 intensive PK AUC remained adequate, a 25% weight increase from the weight at Week 56 will trigger a dose increase based on the corresponding weight from the appropriate BMS-232632 dosing table in Section 5.0.

- If a PK directed dose change was made at any time, a dose increase is triggered when the subject's weight has increased by 25% from the weight at the most recent AUC. Contact the protocol team at actg.teamp1020@fstrf.org for an individualized dosing recommendation based on the subject's pharmacokinetic parameters.

There will be no 24-hour pharmacokinetic studies for dose adjustments due to increase in body weight.

It is acknowledged that, in some pediatric subjects a total daily dose of 400 mg of BMS-232632 (the current targeted adult dose) may not be sufficient to achieve the target AUC in this protocol. Therefore, on a subject by subject basis, assuming acceptable tolerance of the subject’s current dosing regimen, doses greater than 400 mg/day will be permitted. The daily dose of BMS-232632 will not be increased by an amount > 250 mg at one time in an individual subject.
Diagram 2: Adjustment of BMS-232632 doses in individual subjects
(Revisions as per Version 4.0)

Child's current BMS-232632 dose (alone or in combination with ritonavir)

Tolerated (toxicity <Grade 3) but AUC < 30,000 ng.h/mL

- Prorate current dose to attain an AUC = 45,000 ng.h/mL

Tolerated (toxicity <Grade 3) but AUC > 90,000 ng.h/mL

- Prorate current dose to attain an AUC < 60,000 ng.h/mL

Not Tolerated (Toxicity ≥ Grade 3, other than bilirubin, please see Section 8.31.)*

*Bilirubin toxicity management will be unique for this protocol. Please refer to section 6.112.

- AUC > 60,000 ng.h/mL
  - Prorate current dose to attain an AUC = 45,000 ng.h/mL

- AUC 45,000 - 60,000 ng.h/mL
  - Prorate current dose to attain an AUC = 45,000 ng.h/mL

- AUC 30,000 - 45,000 ng.h/mL
  - Prorate current dose to attain an AUC = 30,000 ng.h/mL

- AUC = 25,000 - 30,000 ng.h/mL
  - Prorate current dose to attain an AUC = 25,000 ng.h/mL

- AUC = 20,000 - 25,000 ng.h/mL
  - Prorate current dose to attain an AUC = 20,000 ng.h/mL

- Discontinue any child that does not achieve an AUC ≥ 25,000 ng/hr/mL and exhibits ≥ Grade 3 toxicity or (due to BMS-232632).

- AUC = 20,000 - 25,000 ng.h/mL
  - Prorate current dose to attain an AUC = 20,000 ng.h/mL
6.214 Adjustment of the BMS-232632 AUC target (Diagram 3)

Section 6.212 describes in detail how the BMS-232632 starting dose in combination with ritonavir will be adjusted in each one of the four study groups of Part B. However, the initial AUC target of 45,000 ng.h/mL may produce an unexpectedly high rate of intolerance. This section will describe how to modify the BMS-232632 dose early for any group if a high rate of toxicity/intolerance is documented.

The tolerability of the initial AUC target 45,000 ng.h/mL will be evaluated by assessing the first 10 subjects of the combined (U.S.A. and S.A.) accrual into each of the Groups 5, 6, 7, and 8. If any of these 10 subjects, during the first four weeks of treatment, has life-threatening toxicities attributable to the study treatment, further accrual to the study will be suspended. A thorough investigation by the protocol team will be conducted to determine if it is safe to proceed with this AUC target or if the dosing regimen or pharmacokinetic targets should be modified. If five or more subjects, of these first 10, have clinically significant toxicity ≥Grade 3 (other than bilirubin, please see Section 8.31), then the starting dose of BMS-232632 will be reduced to correspond to a new target AUC of 30,000 ng.h/mL.

Diagram 3: Adjustment of BMS-232632 Target AUC

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**Evaluation of tolerability of initial BMS-232632 Target AUC**

- The first 10 subjects of the combined accrual into Groups 5, 6, 7, and 8
  - One child has a life-threatening toxicity due to study treatment
    - Suspend Study
    - IMPAACT P1020A Team Evaluation
      - Proceed with AUC at 45,000 ng.h/ml if safety is established

  - Five or more of these 10 subjects exhibit ≥Grade 3 toxicities (other than bilirubin, please see Section 8.31).
    - Decrease Target AUC for the whole study to 30,000
    - Modify target AUC as per IMPAACT P1020A team
6.3 Population PK

Random pharmacokinetic sampling will be performed at subject’s treatment-weeks 12, 24, 36, 72, 96, and every 24 weeks after Week 96 of subject's treatment until study end. One 1.5 mL sample of blood will be collected for these random drug level determinations and the time from last study-drug dose will be recorded. These samples are to be shipped as soon as possible to the drug analysis laboratory (See Appendix V “Pharmacology Specimen Collection, Processing, and Storage”).

6.4 Treatment Discontinuation

6.41 Step I

Any study subject who discontinues the study, for any reason, before the last accrued subject’s Week 96 of treatment into the respective part of the Step I will be asked to come to the clinic for an early discontinuation study visit (See Appendix I-B). There will be two more followup study visits four and eight weeks after the early discontinuation visit. The laboratory assays to be done at these two followup visits will be the same as per the early discontinuation study visit, with the exception of no random PK sampling since the subject will not be on study medications. Additionally, South African subjects who discontinue the study “early” will be offered free of charge alternative antiretroviral treatment (subject’s physician decision). Arrangements for the treatment will be made between BMS and the site in South Africa.

In the U.S.A., once the last accrued subject has reached 96 weeks of treatment into a given part of Step I, subjects remaining in this study part will complete the End of Study Visit. There will be two more followup study visits four and eight weeks after the End of Study Visit. The laboratory assays to be done at these two followup visits will be the same as per the End of Study Visit, with the exception of no random PK sampling since the subject will not be on study medications.

In South Africa, once the last accrued subject has reached 96 weeks of treatment into a given part of Step I, subjects will be offered to continue study treatment by enrolling into Step II.

6.42 Step II:

IMPAACT P1020A study treatment will be discontinued on individual basis when subject’s virologic failure is determined and/or toxicity/tolerability deems it appropriate. Subjects will be offered free of charge alternative
antiretroviral treatment (subject’s physician decision) by BMS. Arrangements for the treatment will be made between BMS and the site in South Africa.

6.43 Criteria for Treatment Discontinuation for Step I and Step II:

6.431 The subject meets one of the following treatment failure criteria.

- Less than a $1 \log_{10}$ drop from baseline in plasma HIV RNA level by Week 16, confirmed by a second plasma HIV RNA level obtained within 30 days.

- A plasma HIV RNA level $> 10,000$ copies/mL on two successive determinations in a subject who had previously achieved a plasma HIV RNA level $< 400$ copies/mL, confirmed by a second plasma HIV RNA level obtained within 30 days.

If a subject meets one of these criteria, the site investigator should contact the Protocol Chair and copy the study team at actg.teamp1020@fstrf.org. If in the Protocol Chair, the site investigator, and the parents decide that it is in the best interest of the subject to stay on his/her current treatment, he/she will be allowed to continue on study, on study treatment.

6.432 The subject or legal guardian refuses further treatment and/or follow-up evaluations.

6.433 The investigator determines that further participation would be detrimental to the subject’s health or well being.

6.434 The subject fails to comply with the study requirements so as to cause harm to self or seriously interfere with the validity of the study results.

6.435 The subject requires treatment with medications, which are disallowed while on this study.

6.436 The subject meets a drug-toxicity as defined in Section 6.1. If early discontinuation is due to toxicity or occurs while the subject is experiencing ≥ Grade 3 toxicity, the subject will be followed with appropriate clinical and/or laboratory monitoring until
resolved to ≤ Grade 2 or baseline values for the specific toxicity. Additionally, after toxicity has resolved to Grade 2 or baseline value, the subject will be asked to participate in the early discontinuation study visit and the two followup visits as described above (See Appendix I-B).

6.437 The subject becomes pregnant.

7.0 SERIOUS ADVERSE EXPERIENCE REPORTING

IMPAACT P1020A follows the intensive reporting requirements defined in the current U.S.A. Division of AIDS Serious Adverse Experience Reporting Manual. Additionally, Principal Investigators in South Africa will follow The Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants, Section 4.19 Adverse Drug Reaction Reporting (on file).

DAIDS Serious Adverse Experience (SAE) forms should be submitted to the Regulatory Compliance Center AER Office as described in the most recent SAE Reporting Manual. Appropriate CRFs must also be completed with the event information and entered into the ACTG database.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

During the initial design of IMPAACT P1020A, the judgment of the protocol team was that each of the four strata, defined with respect to age and BMS-232632 treatment formulation, should accrue at least 10 study subjects treated at the BMS-232632 dose that satisfied both safety and PK criteria (see Sections 8.31 and 8.32), i.e. 10 evaluable study subjects in each one of the four study groups 1, 2, 3, 4 of Part A.

However, during these initial discussions of the design of the study, the pharmaceutical sponsor, Bristol Myers Squibb, indicated that for its own regulatory purposes, a sample size of at least 70 study subjects receiving BMS-232632 was more appropriate.

Thus, the protocol team decided on the original sample size for the study of 72 study subjects, 18 study subjects per study group or stratum (Versions 1.0, 2.0, and 3.0).
8.11 Version 4.0

As a result of this protocol amendment (Version 4.0), the study design was modified to include four additional study groups: 5, 6, 7 and 8 of Part B, which follow the same stratification conditions as the original four groups. However, these groups receive ritonavir as a boosting agent for BMS-232632. Thus, the new study design maintains four strata defined with respect to age and BMS-232632 treatment formulation, but includes eight study groups, four for Part A receiving BMS-232632 and two NRTIs and four for Part B receiving BMS-232632 + ritonavir and two NRTIs. The four study groups in Part B will accrue at least 40 study subjects in the U.S.A., 10 evaluable study subjects in each study group of the four study strata.

8.12 Version 5.0

Version 5.0 will include South African (S.A.) sites to obtain S.A. data in study groups 3, 4, 5, 6, 7, 8 and to test whether there are significant differences in drug effects between the 2 countries with respect to rates of adverse events, PK parameters and virologic outcomes. These comparisons will provide information needed to examine the extent to which data gathered in one of the countries can be used to make dosing decisions in the other. As a result, the study design has been modified to further stratify study groups 3, 4, 5, 6, 7, 8, by country, i.e., U.S.A. versus S.A., such that 10 evaluable study subjects will be accrued in parallel to each study group-country cohort.

Note that Groups 1 and 2 under Part A failed to reach the specified PK targets; thus, these groups will remain closed, will not accrue into S.A. cohorts and will not be included in U.S.A. versus S.A. comparisons.

Data within a given study group will be combined across countries for applying the dose-finding algorithm (see Section 8.3), whose aim is to limit exposure to sub-therapeutic and/or toxic doses and to establish REG REVIEW starting doses, which satisfy safety and PK criteria.

By the time Version 5.0 opens to accrual, it is possible that Groups 3 and/or 4 will still be open under the following scenarios:

8.121 Scenario 1:
The dose has been established for Group 3 and/or 4, based on the USA data. Therefore, Group 3 and/or 4 will continue accruing for n=10 additional subjects from South Africa. In parallel, Groups 7 and/or 8 will open for dose-finding, accruing from both U.S.A. and S.A. sites. In consequence, S.A. subjects will be randomized to either Group 3 or 7 and/or Group 4 or 8.

8.122 Scenario 2:

The dose has not been established for either Group 3 or 4, or both; therefore, Group 3 and/or 4 will be open to both U.S.A. and S.A. subjects to evaluate the safety and PK for the specific group dose. If the group dose passes the safety and PK criteria, then full accrual of 10 subjects from each country will occur, and in parallel, enrollment to Groups 7 and/or 8 will begin. In consequence, subjects within each country will be randomized to either Group 3 or 7 and/or Group 4 or 8.

Note:

If the dose for Group 3 fails the safety and PK criteria; then, Group 7 will be the only group accruing subjects in this age population, randomization will not be possible. The same will be true for Group 8 if Group 4 fails the safety and PK criteria.

8.13 For Part A (BMS-232632 and two NRTIs):

Versions 1.0, 2.0, and 3.0 of the study set the total enrollment into the original four study groups as approximately 72 study subjects, 18 in each of the four study groups. Study subjects were stratified into groups representing study subject populations, which required different dose levels. The dose finding algorithm was applied independently to study group. Because of dose escalation or de-escalation within a given study group, the sample taking the final dose, which satisfied both safety and pharmacokinetic criteria, required to consist of at least 10 evaluable study subjects.

Version 5.0 is designed to enroll at least 20 study subjects to Groups 3 and 4, allocating 10 to each country, such that the sample taking the final dose, which satisfies both safety and pharmacokinetic criteria, is required to consist of 10 evaluable study subjects from each country-study group cohort (see Section 8.3).
It is possible that Groups 3 and 4 will have failed on the basis of data from the U.S.A., before Version 5.0 has been approved and accrual in S.A. has begun. This could occur if the safety criteria are failed, and there are no doses which meet both safety and PK criteria. In this case, study Groups 3 and 4 would not open in S.A.

8.14 For the Part B [BMS-232632 + ritonavir and two NRTIs]

Protocol Version 4.0 is designed to enroll approximately 40 study subjects into four study groups, 10 in each group of the four age/formulation strata. Study subjects will be stratified into groups representing study subject populations, which may require different dose levels. The dose finding algorithm (Section 8.3) will be applied independently to each study group. The sample taking the REG REVIEW dose, which satisfies both safety and pharmacokinetic criteria, will be required to consist of 10 evaluable study subjects. Because of dose escalation within a study group, it is possible, although unlikely, that more than 10 study subjects would be accrued to a given study group.

Version 5.0 is designed to enroll approximately 80 evaluable study subjects, i.e., 20 per study group, characterized by age and treatment formulation. These study groups 5, 6, 7, 8 are further stratified by country such that 10 study subjects are allocated into each country (U.S.A. versus S.A.). The dose finding algorithm (Section 8.3) will be applied independently to each study group. Note that for each study group, the data will be pooled across countries to establish final doses satisfying safety and PK targets. Because of dose escalation within a study group, it is possible, although unlikely, that more than 20 study subjects would be accrued to a given age/treatment formulation study group.

8.15 Rationale for Adding Group 5A

The FDA has requested enrollment of at least 4-5 additional infants between 3-6 months of age to further define the pharmacokinetics, dosing, safety and efficacy of atazanavir in this age group. For Version 6.0, a dosing subset of Group 5 (Group 5A) will open to infants 3-6 months of age. Inclusion and exclusion criteria remain as per previous versions of the protocol. The IMPAACT P1020A dosing strategy and pharmacokinetic and safety algorithm will apply to Group 5A infants. A minimum of five infants will be enrolled at the 310 mg/m² starting dose. The protocol team will apply the safety and pharmacokinetic algorithm designed for the first 5 infants, and then determine if
additional dose adjustments are necessary. If the five infants meet safety and pharmacokinetic criteria at the initial 310 mg/m² starting dose, the dose will be accepted for this age cohort and Group 5A will close to enrollment. However, if the pharmacokinetics in these first five infants is highly variable, the team may allow the enrollment of additional infants at the same dose to further define the pharmacokinetics in this 3-6 month age group. Alternatively, if these first five infants have consistently high or low exposures then the starting dose will be adjusted, and an additional minimum of five infants may be enrolled at the new dose.

8.2 Endpoints and Response Variables

8.21 Endpoints for analytic purposes only; see section 6.4 for study subject management:

- Grade 3 or 4 toxicity attributed to study treatment and as defined in Appendices II-A, II-B and II-C
- Failure to achieve a 1 Log(10) reduction in RNA at Week 16
- Plasma HIV RNA level that is increased by \( \geq 1 \) log from baseline at any time, confirmed by a second specimen.
- Plasma HIV RNA level confirmed to be > 10,000 copies/mL at study Week 24.
- Plasma HIV RNA level confirmed to rebound at or after study Week 24 by > 1 log from the lowest HIV RNA level achieved, provided the lowest level was > 1,000. If the lowest level was < 1,000 copies/mL, then a confirmed plasma HIV RNA rebound to > 10,000 copies/mL.

8.22 Endpoints defining increasing levels of virologic success

- 1 Log(10) drop from baseline RNA at week 16
- RNA < 400 copies/mL (Standard Assay)
- RNA < 50 copies/mL (Ultra-Sensitive Assay)

8.23 Primary response variables:

- Safety data: Grade 3 or 4 toxicities
- Pharmacokinetic parameters, as specified in Sections 6.2 and 9.0.

8.24 Secondary Response Variables
8.3 Dose Finding

Algorithm for Evaluating Toxicity and Pharmacokinetics on the first five study subjects within a study group:

8.31 Safety:

Evaluations of the safety status of the first 5 study subjects treated at a given dose will be performed at Week 4. These evaluations will be performed for each study group, allowing for study group specific adjustments in the doses. These toxicity assessments will make use of the following algorithm:

- An initial sample of 5 study subjects from a given study group will be treated at a given dose of BMS-232632.
- The dose will be considered safe for that study group, and full accrual to that cohort will proceed if the following conditions are met:
  
  \[ \Rightarrow \text{none of these 5 study subjects experience life threatening toxicities attributable to study treatment,} \]
  
  \[ \Rightarrow \text{fewer than 2 of these 5 study subjects experience non-life-threatening grade 3 or 4 toxicity, apart from bilirubin, attributable to the study treatment, and} \]
  
  \[ \Rightarrow \text{fewer than 3 of these 5 study subjects have bilirubin levels higher than } 5.1 \times \text{ULN.} \]

- If any of these 5 study subjects have life-threatening toxicities attributable to the study treatment, further accrual of that study group to the treatment regimen will be suspended, pending a thorough investigation by the Protocol Team. The Team will decide whether it is safe to proceed, and will make any necessary adjustments to the dosing regimen and/or pharmacokinetic targets.
• If 2 or more of these 5 study subjects experience non-life-threatening grade 3 or 4 toxicities, apart from bilirubin, attributable to the study treatment, a new cohort of 5 study subjects will be tested at a reduced dose, and this new cohort will evaluated for safety as specified in above.

• If 3 or more of these 5 study subjects have bilirubin levels higher than 5.1 x ULN, a new cohort of 5 study subjects will be tested at a reduced dose, and this new cohort will evaluated for safety as specified in above.

Given the small sample size, the information available for safety decisions will be imperfect. Two types of sampling errors are possible:

• At a dose level whose true rate of toxicity is unacceptable, the sample data may pass the safety criteria and
• At a dose level whose true rate of toxicity is warranted by the potential benefits of the medication, the sample data may fail the safety criteria.

8.32 Pharmacokinetics (PK):

In addition to being examined for toxicities, the first 5 study subjects in each study group will be evaluated in respect to pharmacokinetic levels at the Day 7 visit. If any of the first 5 study subjects falls below an AUC of 15,000 or if more than one of the first 5 study subjects falls below an AUC of 30,000, the next 5 study subjects would be treated at a higher starting dose, provided that the current starting dose has passed the safety criteria. Succeeding cohorts of 5 study subjects will be evaluated in an attempt to find a dose which passes both the AUC and safety criteria. When 5 study subjects within a given study group have been treated at a given starting dose and have passed the AUC and safety criteria, AUC will be evaluated on the first 10 study subjects to be treated at this dose. (This evaluation will include the 5 initial study subjects who have taken this dose, plus the next 5 study subjects in this study group.) In this case failure would be defined as any study subject’s falling below an AUC of 15,000 or more than 2 of the 10 falling below 30,000. If AUC failure should occur at this point, the dose finding algorithm would be repeated, starting with a new cohort of 5 study subjects and proceeding as described in Section 8.31 and the current paragraph.

The following table presents the probability that the sample will fail the AUC criteria, under various assumptions concerning the true failure rates that would occur in large populations treated at a given dose. The table shows these probabilities for evaluations of the first 5 study subjects and the first 10.
TABLE 18. Probability of Failing AUC Criteria
Under Potential Rates of True Failure

<table>
<thead>
<tr>
<th>True Rate of AUC Failure:</th>
<th>Probability of Failing AUC Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30,000</td>
<td>&lt;15,000</td>
</tr>
<tr>
<td>≥15,000</td>
<td>N=5</td>
</tr>
<tr>
<td>0.50</td>
<td>0.00</td>
</tr>
<tr>
<td>0.40</td>
<td>0.00</td>
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<tr>
<td>0.30</td>
<td>0.00</td>
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<td>0.20</td>
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<td>0.10</td>
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<td>0.05</td>
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</table>

This table indicates that doses whose true failure rates are upwards of 40% are likely to fail the AUC criteria after the first 5 study subjects have been accrued. Those whose true failure rates are between 30% and 40% are also likely to fail at this point, provided that a significant percentage of the true failure rate represents AUC’s below 15,000. Doses whose true failure rates are less than 20% have a low probability of failing after the first 5 study subjects have been accrued, especially if a relatively small percentage of the true failure rate consisted of AUC’s below 15,000. The rate of AUC failure increases to a moderate extent at doses whose true rate of AUC < 15,000 is zero, but increases considerably under conditions where half of the AUC failure rate consists of AUC < 15,000.

In addition to the AUC criteria discussed above, Section 6.212 requires that 80% study subjects have trough levels ≥60 ng/mL. It is expected that all study subjects will meet this requirement. If this is true, then the overall probability of meeting the pharmacokinetic criteria will be equivalent to that of meeting the AUC criteria, presented in Table 18. If this is not true, then the probabilities of meeting the PK criteria will be somewhat lower than those presented in Table 18.

8.4 Analysis

8.41 Primary analyses
The primary analyses will consist of tabulating success rates in meeting the safety and PK criteria, bounded by 90% confidence intervals. This will provide 95% confidence that the true success rates in the population represented by the samples are no worse than the lower limits of the confidence intervals. These analyses will be performed on PK data from week 1 and for safety data at weeks 4, 48 and 96. Study subjects included in these analyses will be limited to those from study groups taking the final starting doses, which have passed safety and PK criteria.

Logistic regression models will be used to test whether the probability of meeting safety or PK criteria vary significantly as a function of country, study group or the interaction between country and study group. If no such effects are found, the confidence intervals around the overall rates of meeting safety and/or PK criteria will be reported, with a sample size of approximately 120 study subjects. Table 19A shows how the width of these confidence intervals will vary with the observed rate of success.

If significant effects of country, study group or their interaction are observed in the logistic analysis of either the safety or PK data, the overall success rates for those data will not provide an appropriate summary of the results. In this case, the success rates will be broken down by the factors whose effects have been found to be significant. Potential scenarios include the following:

If a success rate varies significantly by country, but there is no country by study group interaction, the success rates for each country (with sample sizes of approximately 60 study subjects) will be bounded by 90% confidence intervals. Table 19B presents confidence intervals for sample sizes of 60 study subjects, across a range of potential results.

If a success rate varies significantly by study group, but there is no country by study group interaction, the success rates for each study group (with sample sizes of approximately 20 study subjects) will be bounded by 90% confidence intervals. Table 19C presents confidence intervals for sample sizes of 20 study subjects, across a range of potential results.

If there is a significant country by study group interaction, the success rates for each study group within each country (with sample sizes of approximately 10 study subjects) will be bounded by 90% confidence intervals. Table 19D presents confidence intervals for sample sizes of 10 study subjects, across a range of potential results.
The confidence intervals presented in Table 19A-19D indicate the precision with which samples of 120, 60, 20 and 10 evaluable study subjects, respectively, will estimate rates of success, with respect to meeting safety or PK criteria. The lower limits of the intervals indicate the threshold above which the true success rate falls, with 95% probability, given the sample data. For example, for n=120, if the proportion of study subjects meeting the safety criteria were no less than 0.8 (96/120), we could be 95% certain that the true rate of success within the population represented by this sample was no less than 0.73.
TABLES 19A to 19D. 90% Confidence Intervals around Potential Success Rates for Safety and PK Criteria

**TABLE 19A**

<table>
<thead>
<tr>
<th>Sample Rate</th>
<th>90% Confidence Limits (N=120)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 (0/120)</td>
<td>0.00</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>0.20 (24/120)</td>
<td>0.14</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>0.40 (48/120)</td>
<td>0.32</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>0.60 (72/120)</td>
<td>0.52</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>0.80 (96/120)</td>
<td>0.73</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>1.00 (120/120)</td>
<td>0.98</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 19B**

<table>
<thead>
<tr>
<th>Sample Rate</th>
<th>90% Confidence Limits (N=60)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 (0/60)</td>
<td>0.00</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>0.20 (12/60)</td>
<td>0.12</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>0.40 (24/60)</td>
<td>0.29</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>0.60 (36/60)</td>
<td>0.48</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>0.80 (48/60)</td>
<td>0.70</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>1.00 (60/60)</td>
<td>0.95</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 19C**

<table>
<thead>
<tr>
<th>Sample Rate</th>
<th>90% Confidence Limits (N=20)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 (0/20)</td>
<td>0.00</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>0.20 (4/20)</td>
<td>0.07</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>0.40 (8/20)</td>
<td>0.22</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>0.60 (12/20)</td>
<td>0.39</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>0.80 (16/20)</td>
<td>0.60</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>1.00 (20/20)</td>
<td>0.86</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 19D.

<table>
<thead>
<tr>
<th>Sample Rate</th>
<th>90% Confidence Limits (N=10)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 (0/10)</td>
<td></td>
<td>0.00</td>
<td>0.26</td>
</tr>
<tr>
<td>0.20 (2/10)</td>
<td></td>
<td>0.04</td>
<td>0.51</td>
</tr>
<tr>
<td>0.40 (4/10)</td>
<td></td>
<td>0.15</td>
<td>0.70</td>
</tr>
<tr>
<td>0.60 (6/10)</td>
<td></td>
<td>0.30</td>
<td>0.85</td>
</tr>
<tr>
<td>0.80 (8/10)</td>
<td></td>
<td>0.49</td>
<td>0.96</td>
</tr>
<tr>
<td>1.00 (10/10)</td>
<td></td>
<td>0.74</td>
<td>1.00</td>
</tr>
</tbody>
</table>

8.42 Secondary analyses

Study subjects included in the analyses described below will be limited to those from study groups taking the final starting doses, which have passed safety and PK criteria.

A key secondary analysis will be aimed at estimating success rates in meeting the criterion of a 1-log reduction in viral load at Week 16. As with the safety and PK analyses, the extent to which the data can be pooled across countries and study groups will be tested by means of a logistic regression analysis (see Section 8.41). The results of this analysis will determine whether the overall success rate represents a valid summary of the data, or whether the results need to be broken down by country (N=60), study group (N=20) or study group within country (N=10). The confidence intervals presented in Tables 19A-19D indicate the precision with which samples of 120, 60, 20 and 10 evaluable study subjects, respectively, will estimate the rate of success in achieving a 1-log reduction in viral load. The lower limits of the intervals indicate the threshold above which the true success rate falls, with 95% probability, given the sample data. For example, if the proportion of study subjects achieving a 1-log reduction in viral load within a given study group were no less than 0.80 (16/20) in a sample of 20 evaluable study subjects, we could be 95% certain that the true rate of success within the population represented by this sample was no less than 0.60.

Further secondary analyses will include the following and will be broken down by country and study group:

- Kaplan-Meier estimates of the median time to undetectable plasma HIV RNA levels, or to a 1 log drop in RNA.
- Among those who achieve undetectable viral load, Kaplan-Meier estimates of the time to return to detectable viral load.
Among those who achieve at least a 1-log reduction in viral load, Kaplan-Meier estimates of the time to return to baseline levels.

Change from baseline to Weeks 20 and 48 in CD4 and CD8 counts and percent, along with 90% confidence limits.

Correlations between self reported adherence, PK values, and changes from baseline RNA at Weeks 12, 24, 48 and 96.

Data from Adherence Module 1 will be used to quantify number of missed doses, or fraction of doses taken (i.e., number of doses taken/number of doses prescribed x 100 for percent of doses taken). This continuous factor will be correlated with pharmacokinetic values to determine the association between reported adherence and objective endpoints. These data will also be transformed into a categorical factor with 3 levels [i.e., complete adherence (CA), partial adherence (PA) and non-adherence (NA)] to describe adherence levels for the sample as a whole (For U.S.A. data only).

Qualitative data from Module 2 will be coded and analyzed to provide information about specific barriers to adherence with each study drug (For U.S.A. data only).

8.5 Monitoring

The safety and tolerability of the study treatments will be monitored by means of adverse event reports (AER) and toxicity reports presenting laboratory and clinical data. It is required that these data be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available. The toxicity reports will be discussed by the protocol team on conference calls twice a month (or as often as needed by IMPAACT P1020A protocol team decision).

The dose-finding algorithm (see Section 8.31) is designed to detect toxicity failures from the first 5 study subjects per study group, during the first 4 weeks after treatment has started. However, further safety data from those study subjects will be closely evaluated after that time interval, as will data from the remaining study subjects who are accrued. The extent to which adverse events are over-represented in particular study groups will also be monitored. If the protocol team observes any pattern which suggests that study subject safety may be jeopardized, further accrual will be stopped, pending a thorough investigation, and the study will not resume unless the team determines that it is safe to do so.

Periodically, analyses summarizing toxicity patterns will be distributed to the protocol team. Since Phase I studies are not routinely reviewed by the Data and
Safety Monitoring Board, it is the responsibility of the Principal Investigator, the Medical Officer and the protocol team to interpret the toxicity data and make any decisions needed to protect study subjects from undue risk.

9.0 CLINICAL PHARMACOLOGY PLAN

The Clinical Pharmacology studies in IMPAACT P1020A have been designed to determine the steady-state pharmacokinetic profile and dosing schedule of orally administered BMS-232632 capsules and liquid formulation, alone or in combination with ritonavir, in HIV-infected infants, young children, and adolescents receiving 2 NRTIs.

9.1 Intensive Pharmacokinetics

An intensive pharmacokinetic study will be conducted in all children in to address the first pharmacological objective. The primary parameters will be AUC 0-24, and CMIN (trough concentration); CL/F, T-half, CMAX, and Tmax will be secondary parameters. Concentration-time data will be graphically inspected, and standard non-compartmental techniques will be used to assess pharmacokinetic parameters. The AUC 0-24 will be determined using the trapezoidal rule; CMIN will be directly observed. CL/F will be calculated as dose/AUC 0-24. The elimination half-life is a secondary parameter and will be determined using regression analysis when possible. CMAX will be taken as the maximum observed concentration, and Tmax is the time at which CMAX occurs. If more than one Tmax occurs in a given profile, the median of these values will be taken. Pharmacokinetic parameters for BMS-232632 will be summarized and descriptive statistics calculated.

9.2 BMS-232632 Dose Adjustment

Doses of BMS-232632 will be adjusted to attain the target AUC of > 30,000 ng.h/mL. If the pharmacokinetics of BMS-232632 deviate substantially from expected values and AUCs are lower than adult values, it will be determined early and appropriate dosage requirements can be determined. It is not unreasonable to suspect that infants, older children, and the adolescent groups may each have different dosage requirements. This protocol will determine appropriate doses for each of these strata. In addition, the pharmacokinetic characteristics BMS-232632 following capsule administration may be different from those following powder formulation administration. The protocol will also identify these differences if they exist. Most children under 2 years of age are expected to be administered the powder formulation, and most adolescents (over the age of 13 years) are expected to be administered capsules. Children in the age range 2 to 13 may be on either formulation. Hence, the pharmacokinetic profiles and dosing requirements will be explored in 4 strata.
9.3 Population PK

Population PK data, including randomly obtained serum drug concentrations will be correlated with self-reported adherence and viral load response.

9.4 Intensive PK guidelines (Morning dosing schedule)

The following guidelines apply to any intensive PK study done based on a morning dosing schedule for BMS-232632 (See section 9.5 for the specific changes to these procedures, for the Week 56 PK study based on an evening dosing schedule for BMS-23-2632).

The important points to consider for these intensive PK studies based on a morning dosing schedule for BMS-232632 are:

- Clinic personnel should inform the subject that he/she will stay at the clinic for at least 12 hours, and in some clinics overnight.

- In preparation for these tests, clinic personnel should ensure that the subject:
  
  ⇒ is scheduled for an early morning appointment,
  
  ⇒ is aware that study drug doses should routinely be taken in the morning after breakfast,
  
  ⇒ does not take study drug doses at home on the day of the intensive PK study, and
  
  ⇒ will bring his/her study drugs to the clinic on the day of the intensive PK study.

- Once the subject has arrived to the clinic, he/she should be offered a breakfast appropriate for age. This breakfast should contain the recommended amounts of protein, fat and carbohydrate, as well as approximately 1/3 of the daily calories.

- Clinic personnel must verify and record, prior to administration of the study-drug doses on the day of the PK study, the time of administration of the last BMS-232632 dose taken on the previous day.

- Clinic personnel should collect the first blood-sample for the 0 time-point, 15 to 30 minutes after the subject has had breakfast.

- Within 30 minutes of collection of the time 0 blood-sample, clinic personnel should give, observe, and record the administration of the study drug doses.

- Clinic personnel should collect blood samples post-dose administration at 1, 2, 3, 4, 6, 8, 12 hours and the following day at 24 hours.
• Sites should maintain a record of the meal given on the day of the PK study. This is a special team’s request that is not required by the protocol document, or any of the protocol CRFs.

• Clinic personnel should remind the subject, whether he/she stays overnight at the clinic or goes home after the 12-hour blood sample, that no study-drug doses should be taken on the evening of the PK study.

• The following day, clinic personnel must find out before collecting the 24-hour blood sample, if study-drug doses were taken/given by mistake on the previous day, other than the observed dose in the morning for the PK study.

• The time-frame for the 24-hour intensive PK study at Week 1 is from Day 6 to Day 10. As a rule, for any intensive PK study the subject must have been taking the study drugs for at least six consecutive days prior to PK testing.

9.5 Intensive PK Guidelines (Evening dosing schedule)

The following guidelines apply to the Week 56 intensive PK study based on an evening dosing schedule for BMS-232632. There are two options for completing these PK studies, maintaining the evening dosing schedule for BMS-232632 through the PK study, or switching to morning dosing schedule for BMS-2232632 three days prior to the PK study. The modifications to the procedures previously described in 9.4 are:

9.51 Maintaining evening dosing schedule for BMS-232632:

• Clinic personnel must schedule subject's arrival to the clinic on the late afternoon.

• Once the subject has checked in, he/she should be offered a supper appropriate for age. This supper should contain the recommended amounts of protein, fat and carbohydrate, as well as approximately 1/3 of the daily calories.

• Clinic personnel should collect the first blood-sample for the 0 time-point after the subject has had supper, and within 30 minutes of administration of study drug-doses, which should be given at subject’s regular dosing hours.

• Proceed with previous guidelines for morning dosing of BMS-232632, described for Week 1 PK study.

• The subject will remain the clinic until the 24-hour blood sample is collected on the following day.
9.52 Switching to morning dosing schedule for BMS-232632 three days prior to Week 56 PK study:

- Three days prior to PK test, the subject should be administered study drug-doses at his/her regular evening dosing schedule.
- Two days prior to PK test, the subject should receive his/her study drug-doses in the morning; at least 10 hours post administration of the regular evening doses on previous day. No more doses will be given on the evening of this Day –2.
- A day prior to PK test, the subject will receive his/her study drug doses in the morning at a similar time as per previous day. No more doses will be given on the evening of this Day –1.
- On the day of the PK study, the subject will come into the clinic early in the morning as per previous guidelines for morning dosing schedule of BMS-232632.
- Proceed with previous guidelines for morning dosing of BMS-232632, described for Week 1 PK study.
- The subject will go home after the 24-hour blood sample is collected. No more morning dosing will be given on this day; he/she will resume his/her evening dosing schedule on that evening after returning home.

9.6 Random Concentration and Adherence Evaluations

The random concentrations obtained at Weeks 12, 24, and 36 will be analyzed and made available to the protocol pharmacologist for assessment of possible non-adherence.

Non-adherence will be evaluated as likely when any of the following occur:

- Any random concentration is determined to be non-detectable.
- Two random concentrations are < 50 ng/mL.
- Any one concentration is less than 20% and another is more than 500% of the expected concentrations based on the AUC of an observed BMS-232632 dose.

If non-adherence is considered likely, the protocol pharmacologist will notify the study team and contact the site and request that the study subject/family be queried regarding adherence issues.

10.0 HUMAN STUDY PARTICIPANTS
The Division of AIDS has concluded that this protocol does NOT meet U.S.A. Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs for the recruitment of prisoners.

10.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Appendix X) and any subsequent modifications will be reviewed and approved by the Institutional Review Board (IRB) or Ethics Committee responsible for oversight of the study. Written informed consent will be obtained in accordance with the relevant laws of the country or state.

The study subject’s assent must also be obtained if he or she is able to understand the nature, significance and risks associated with the study (assent form/procedure must follow the relevant national, or state, or local IRB or Ethics Committee guidelines). The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

A copy of the consent form will be given to the study subject (or parent, or legal guardian, or caretaker).

10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only.

Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the U. S. Food and Drug Administration (FDA), by Bristol-Myers Squibb (BMS) (pharmaceutical sponsor), by the U.S.A. National Institute of Allergy and Infectious Diseases (NIAID), and by the South African Medicines Control Council (MCC).

10.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, BMS, or the U.S.A. FDA. Additionally, the study can be discontinued by the MCC in South Africa.

10.4 Regulatory Authorities

At all clinical sites regardless of their location, i.e. U.S.A. or South Africa, the protocol will be carried out under the provisions of Good Clinical Practice
Guidelines and regulated by the U.S.A. FDA IND # 60,878. The trial will also be regulated and conducted as per the South African Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants (in particular Section 9.0) (on file).

Additionally, in South Africa IMPAACT P1020A will be conducted in full concordance with the principles of the Declaration of Helsinki, October 2000 and the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, May 1997.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by Pediatric ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control.

The International Air Transportation Association (IATA) regulations for the shipment of HIV containing specimens were updated in March 2003. Please refer to the each individual carrier guidelines (e.g., FedEx, Airborne) and the ACTG Website for specific instructions and shipping guidelines for any IMPAACT P1020A specimens.
13.0 REFERENCES


11. Personal data assessment of Tammy Meyers, M.D. Chris Hani Baragwanath Hospital, Pediatrics Department. IMPAACT Soweto Site Principal Investigator. PO Bertsham, Johannesburg 2013, South Africa.


25. BMS Data provided to the IMPAACT P1020A Protocol Team in March 2003—Data on file at BMS, Wallingford, CT.

26. Personal communications between BMS Representative, Steven Schnittman, M.D., Wallingford, CT, and IMPAACT P1020A Study Chair, Richard Rutstein, M.D., Philadelphia, PA.


34. Baxter JD MD, Wnetworth DN, Neaton JD, Merigan and the CPCRA 046 Team for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). A pilot study of the short-term effects of antiretroviral management based on plasma genotypic


# APPENDIX I-A
## SCHEDULE OF EVALUATIONS (SCREENING TO WEEK 96)

<table>
<thead>
<tr>
<th>EVENTS</th>
<th>SUBJECT'S WEEK OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Evaluations</strong></td>
<td></td>
</tr>
<tr>
<td>Signed Consent</td>
<td>X</td>
</tr>
<tr>
<td>History &amp; Physical(1)</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test(2)</td>
<td>X</td>
</tr>
<tr>
<td>Hematologies (3)(purple top)</td>
<td>1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL</td>
</tr>
<tr>
<td>Chemistries(4)(red top)</td>
<td>1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL</td>
</tr>
<tr>
<td>Liver Function Tests(5)(no extra draw)</td>
<td>X</td>
</tr>
<tr>
<td>Lipid Profile (6)(red Top)</td>
<td>2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL 2.0mL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
</tr>
<tr>
<td>Adherence Modules (ONLY U.S.A. SITES)</td>
<td>X</td>
</tr>
<tr>
<td>ECG(21, 22, 23, 24)</td>
<td>X</td>
</tr>
<tr>
<td><strong>Virology(7)</strong></td>
<td></td>
</tr>
<tr>
<td>HIV RNA(8,9)(purple top)</td>
<td>3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL</td>
</tr>
<tr>
<td>Genotypic(9, 10) Resistance (purple top)</td>
<td>3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL 3.0mL</td>
</tr>
<tr>
<td>Qualitative Microculture (purple top) (ONLY U.S.A. SITES)</td>
<td>5.0mL</td>
</tr>
<tr>
<td>Viable PBMC for storage (11) and plasma for phenotypic and genotypic resistance(9, 10) and storage (purple top)</td>
<td>3.0mL 3.0mL 3.0mL 3.0mL</td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets (purple top)(12)</td>
<td>1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL 1.0mL</td>
</tr>
<tr>
<td>Special Immunology (13)</td>
<td>1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL</td>
</tr>
<tr>
<td><strong>Pharmacology(14)</strong></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetics (purple top)(15)</td>
<td>13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15) 13.5mL(15)</td>
</tr>
<tr>
<td>Random PK samples (purple top)(16)</td>
<td>1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL 1.5mL</td>
</tr>
<tr>
<td>Max. Blood (mL)</td>
<td>14.5 5.0 13.0 20.0 8.5 8.5 10.0 12.0 5.5 12.0 4.5 10.0 6.0 8.5 4.5 13.0 26.0 8.5 13.5 8.5 7.5 14.5</td>
</tr>
</tbody>
</table>
APPENDIX I-A (Cont.)

(1) Physical exam (height, weight, vital signs, symptoms, HIV Assessment)

(2) Can be either a urine or HCG blood test, must be performed on all females of childbearing potential within 72 hours of enrollment. If blood test is performed, collect 1.0 mL in a red–top tube.

(3) Hematology (complete blood count, cell differential, platelet count)

(4) Chemistries [electrolytes (sodium, chloride, potassium, and HCO₃), glucose, bun, creatinine, amylase, and lipase].

(5) Liver Function tests (total bilirubin, indirect bilirubin, direct bilirubin, AST, ALT, GGT, albumin). If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented in source document.

(6) Lipid Profile (triglycerides and cholesterol), this test will be performed in a non-fasting state. However, if results are ≥ Grade 2, a complete fasting-state lipid profile (triglycerides, cholesterol, HDL and LDL) as well as amylase and lipase must be drawn. Fasting intervals will be (1) for children ≤ 2 years of age, 4 hours, and (2) for children > 2 years, overnight.

(7) See Appendix III for virology collection and shipping instructions for these samples.

(8) Screening RNA value may have been obtained up to 2 months prior to study entry by an ACTG certified lab using Roche Amplicor PCR. Baseline RNA level will be the average the day (-5 to -1) and Entry Zero hour value. See Appendix III for details.

(9) Plasma for phenotypic and genotypic resistance will be collected from all subjects; however, only samples from subjects who are ART-experienced at Screening Visit will be processed real time for phenotypic and/or genotypic testing. All other samples should be sent to the protocol virologist lab for storing and will be tested at the end of study for data analysis purposes (samples may be used for either or both phenotypic and genotypic testing).

(10) Sites must send an e-mail to the protocol team at actg.teamp1020@fstrf.org detailing the candidate’s antiretroviral history, date of birth, along with the PID#. This e-mail is to request permission to schedule the Screening Visit and to determine if genotypic or/and phenotypic testing is/are needed at subject’s Screening Visit. Sites must wait for a team notification of approval before screening any subjects for IMPAACT P1020A. Real-time phenotypic testing at Screening Visit will be for subjects with prior experience with more than one PI. Real-time genotypic testing for subjects with prior NRTI experience. Resistance results will be available to the site within two-week time. Please follow Appendix VII to determine subject’s future ART treatment using the guide to antiretroviral resistance mutations.

(11) Viable PBMC for storage is to be used to obtain viral stocks for further phenotypic studies of viral resistance as described in Virology Appendix III. Plasma for storage will be used for future phenotypic and genotypic studies.

(12) See Appendix IV-A for immunology collection and shipping instructions.

(13) See Appendix IV-B for special immunology specimen processing, storage, and shipping instructions.

(14) See Appendix V for pharmacology specimen collection, processing and storage guidelines.
(15) All subjects in the study will be asked to be at the clinic for at least 12 hours following a breakfast appropriate for age and their study drug doses. Samples will be taken at 0, 1, 2, 3, 4, 6, 8, 12 hours and the following day at 24 hours post-dosing. Pharmacokinetic studies will be done for all subjects in the study at 7 days and 56 weeks post-study drug initiation; and for subjects requiring individual dose adjustments, two weeks after the new dose initiation. Intensive pharmacokinetics at Week 56 will be done as per Week 1 PK; however, dose adjustments, if needed, will be for individuals only. No group-dose adjustments will be done based on Week 56 PK data.

(16) Random PK samples will be taken at these visits. Time from last study-drug dose will be recorded. The random concentrations obtained at Weeks 12, 24, and 36 will be used for assessment of possible non-adherence.

(17) For subjects requiring dose adjustments, repeat 24-hour intensive PK will be performed two weeks after initiation of new dose.

(18) Screening viral load determination should confirm VL ≥ 5,000 copies/mL.

(19) The time frame from Screening Visit to Entry Visit will be –2 weeks when no resistant testing is required. When phenotypic and/or genotypic testing is required the time-frame will be -1 to -6 weeks.

(20) The time frame for the 24-hour Intensive PK will be from Day 6 to Day 10; however, the subject must have been taken the study drug for at least 6 consecutive days prior to PK testing.

(21) ECGs will be required at Screening visit, every time a 24-hour Intensive PK is performed, and at anytime for symptomatology that the site deems possible related to potential cardiac involvement.

(22) ECGs on intensive PK day will be done at subject’s arrival prior to dosing with study medications, at 2 to 3 hours post-administration of study medication, and at 4 to 6 hours post-administration of study medication.

(23) On study, Holter testing (24-hour monitoring) will be required from subjects ≥13 years of age found to have Prolonged PR-Interval >0.250 seconds (250 ms), and on subjects <13 years of age found to have PR-Interval outside the 98th percentile (See Appendix VIII).

(24) Study candidates with a history of undefined syncope will require a complete cardiac conduction evaluation at screening [e.g. ECG, 24-hour monitoring (Holter), and exercise test (if age appropriate)]. This evaluation must rule-out any cardiac conduction abnormalities (e.g. exclusion criteria 4.210 to 4.214).

(25) Due to the long window of time allowed/needed, up to six weeks when genotypic and/or phenotypic testing is required, between the Screening Visit and the Entry Visit, the protocol DOES NOT ALLOW any ≥ Grade 2 laboratory or clinical toxicity at Entry. Hematology, chemistries, liver function tests, lipid profile, and urinalysis MUST be checked at Entry and test results MUST be received before enrollment of any subject into the study. No subject should receive study medications before getting confirmation of no ≥ Grade 2 toxicities at Entry.
<table>
<thead>
<tr>
<th>For insufficient blood draws of NAÏVE subjects at SCREENING visit, priorities are as follows:</th>
<th>For insufficient blood draws of ART-EXPERIENCED subjects at SCREENING and ENTRY visits, priorities are as follows:</th>
<th>For insufficient blood draws of any subject at any other study visit but the Screening Visit, priorities are as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) RNA</td>
<td>(1) RNA</td>
<td>(1) RNA</td>
</tr>
<tr>
<td>(2) Hematology</td>
<td>(2) Phenotypic and genotypic resistance testing</td>
<td>(2) Pharmacology</td>
</tr>
<tr>
<td>(3) Lymphocyte subset</td>
<td>(3) Qualitative microculture</td>
<td>(3) Hematology</td>
</tr>
<tr>
<td>(4) Liver function tests</td>
<td>(4) Hematology</td>
<td>(4) Liver function tests</td>
</tr>
<tr>
<td>(5) Chemistries</td>
<td>(5) Lymphocyte subset</td>
<td>(5) Lymphocyte subset</td>
</tr>
<tr>
<td>(6) Lipid profile</td>
<td>(6) Liver function tests</td>
<td>(6) Chemistries</td>
</tr>
<tr>
<td></td>
<td>(7) Chemistries</td>
<td>(7) Lipid profile</td>
</tr>
<tr>
<td></td>
<td>(8) Lipid profile</td>
<td>(8) Phenotypic and genotypic resistance testing</td>
</tr>
</tbody>
</table>
# APPENDIX I-B

## SCHEDULE OF EVALUATIONS FOR STEP I (Week 104 to Week 272)

<table>
<thead>
<tr>
<th>EVENTS</th>
<th>SUBJECT’S WEEK OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>104</td>
</tr>
<tr>
<td>Early (13) Discontinuation or End of Step I</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Evaluations</td>
<td></td>
</tr>
<tr>
<td>History &amp; Physical(1)</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test(2)</td>
<td>X</td>
</tr>
<tr>
<td>Hematology (3) (purple top)</td>
<td>1.5mL</td>
</tr>
<tr>
<td>Chemistries(4) (red top)</td>
<td>1.0mL</td>
</tr>
<tr>
<td>Liver Function Tests(5) (no extra draw)</td>
<td>X</td>
</tr>
<tr>
<td>Lipid Profile (red top)</td>
<td>2.0mL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
</tr>
<tr>
<td>Adherence Modules (ONLY U.S.A. SITES)</td>
<td>X</td>
</tr>
<tr>
<td>Virology(7)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA (purple top)</td>
<td>3.0mL</td>
</tr>
<tr>
<td>Genotypic Resistance (purple top)</td>
<td></td>
</tr>
<tr>
<td>Qualitative Microculture (purple Top) (ONLY U.S.A. SITES)</td>
<td></td>
</tr>
<tr>
<td>Viable PBMC for storage and plasma for phenotypic and genotypic resistance and storage (purple top)(9)</td>
<td>3.0mL</td>
</tr>
<tr>
<td>Immunology</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets (purple top)(9)</td>
<td>1.0mL</td>
</tr>
<tr>
<td>Special Immunology (10)</td>
<td>1.5mL</td>
</tr>
<tr>
<td>Pharmacology(11, 12)</td>
<td></td>
</tr>
<tr>
<td>Random PK samples (purple top)</td>
<td>1.5mL</td>
</tr>
<tr>
<td>Max. Blood (mL)</td>
<td>4.5</td>
</tr>
</tbody>
</table>
APPENDIX I-B (Cont.)

(1) Physical exam (height, weight, vital signs, symptoms, HIV Assessment)
(2) Can be either a urine or HCG blood test, must be performed on all females of childbearing potential. If blood test is performed, collect 1.0 mL in a red-top tube.
(3) Hematology (complete blood count, cell differential, platelet count)
(4) Chemistries [electrolytes (sodium, chloride, potassium, and HCO$_3$) glucose, bun, creatinine, amylase].
(5) Liver Function tests (indirect bilirubin, direct bilirubin, AST, ALT, GGT, albumin). If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented in source document.
(6) Lipid Profile (triglycerides and cholesterol), this test will be performed in a non-fasting state. However, if results are $\geq$ Grade 2, a complete fasting-state lipid profile (triglycerides, cholesterol, HDL and LDL) as well as amylase and lipase must be drawn. Fasting intervals will be (1) for children $\leq$ 2 years of age, 4 hours, and (2) for children $>$ 2 years, overnight.
(7) See Appendix III for virology collection and shipping instructions for all these samples.
(8) Viable PBMC for storage is to be used to obtain viral stocks for further phenotypic studies of viral resistance as described in Virology Appendix III. Plasma for storage will be used for future phenotypic and genotypic studies.
(9) See Appendix IV-A for immunology collection and shipping instructions.
(10) See Appendix IV-B for special immunology specimen processing, storage, and shipping instructions.
(11) See Appendix V for pharmacology specimen collection, processing and storage guidelines.
(12) Random PK samples will be taken at these visits. Time from last study-drug dose will be recorded.
(13) Any study subject who discontinues the study, for any reason, before the last accrued subject’s Week 96 of treatment, will be asked to come to the clinic for an early discontinuation study visit. Furthermore, there will be two more follow-up study visits four and eight weeks after the early discontinuation visit. The laboratory assays to be done at these two follow-up visits will be the same as per the early discontinuation study visit, with the exception of no random PK sampling since the subject will not be on study medications. If early termination is due to toxicity or occurs while the subject is experiencing a $\geq$ Grade 3 toxicity, the subject must be followed with appropriate clinical and/or laboratory monitoring until resolved to $\leq$ Grade 2 or baseline values, before completing the early termination study visit and the two followup study visits.
(14) Once the last accrued subject has reached 96 weeks of treatment, all U.S.A. subjects remaining in the study will complete the End of Step I Study Visit. Additionally, there will be two more follow-up study visits four and eight weeks after the End of the Step I Study Visit. U.S.A. subjects will go off-study at the end of Step I. Appendix I-C should be followed for Step I evaluations beyond week 272. US subjects and South African subjects on powder formulation will continue on-study under Step II. Appendix I-D should be followed for Step II evaluations.
Blood Draw Priorities
(1) RNA
(2) Pharmacology
(3) Hematology
(4) Liver function tests
(5) Lymphocyte subset
(6) Chemistries
(7) Lipid profile
(8) Phenotypic and genotypic resistance testing
### APPENDIX I-C

#### SCHEDULE OF EVALUATIONS FOR STEP I (Week 280 to End of Study)

<table>
<thead>
<tr>
<th>EVENTS</th>
<th>SUBJECT'S WEEK OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>280</td>
</tr>
<tr>
<td>Early (13) Discontinuation or End of Step I (1)</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Evaluations</td>
<td></td>
</tr>
<tr>
<td>History &amp; Physical (1)</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test (2)</td>
<td>X</td>
</tr>
<tr>
<td>Hematology (3) (purple top)</td>
<td></td>
</tr>
<tr>
<td>Chemistries (4) (red top)</td>
<td></td>
</tr>
<tr>
<td>Liver Function Tests (5) (no extra draw)</td>
<td></td>
</tr>
<tr>
<td>Lipid Profile (6) (red top)</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
</tr>
<tr>
<td>Adherence Modules (ONLY U.S.A. SITES)</td>
<td>X</td>
</tr>
<tr>
<td>Virology (7)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA (purple top)</td>
<td></td>
</tr>
<tr>
<td>Genotypic Resistance (purple top)</td>
<td></td>
</tr>
<tr>
<td>Qualitative Microculture (purple Top) (ONLY U.S.A. SITES)</td>
<td></td>
</tr>
<tr>
<td>Viable PBMC for storage and plasma for phenotypic and genotypic resistance and storage (purple top) (8)</td>
<td></td>
</tr>
<tr>
<td>Immunology</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets (purple top) (9)</td>
<td></td>
</tr>
<tr>
<td>Special Immunology (10)</td>
<td></td>
</tr>
<tr>
<td>Pharmacology (11, 12)</td>
<td></td>
</tr>
<tr>
<td>Random PK samples (purple top)</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX I-C (Cont.)

(1) Physical exam (height, weight, vital signs, symptoms, HIV Assessment)
(2) Can be either a urine or HCG blood test, must be performed on all females of childbearing potential. If blood test is performed, collect 1.0 mL in a red–top tube.
(3) Hematology (complete blood count, cell differential, platelet count)
(4) Chemistries [electrolytes (sodium, chloride, potassium, and HCO₃) glucose, bun, creatinine, amylase].
(5) Liver Function tests (indirect bilirubin, direct bilirubin, AST, ALT, GGT, albumin). If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented in source document.
(6) Lipid Profile (triglycerides and cholesterol), this test will be performed in a non-fasting state. However, if results are ≥ Grade 2, a complete fasting-state lipid profile (triglycerides, cholesterol, HDL and LDL) as well as amylase and lipase must be drawn. Fasting intervals will be (1) for children ≤ 2 years of age, 4 hours, and (2) for children > 2 years, overnight.
(7) See Appendix III-A for virology collection and shipping instructions for all these samples.
(8) Viable PBMC for storage is to be used to obtain viral stocks for further phenotypic studies of viral resistance as described in Virology Appendix III-A. Plasma for storage will be used for future phenotypic and genotypic studies.
(9) See Appendix IV-A for immunology collection and shipping instructions.
(10) See Appendix IV-B for special immunology specimen processing, storage, and shipping instructions.
(11) See Appendix V for pharmacology specimen collection, processing and storage guidelines.
(12) Random PK samples will be taken at these visits. Time from last study-drug dose will be recorded.
(13) Any study subject who discontinues the study, for any reason, before the last accrued subject’s Week 96 of treatment, will be asked to come to the clinic for an early discontinuation study visit. Furthermore, there will be two more follow-up study visits four and eight weeks after the early discontinuation visit. The laboratory assays to be done at these two follow-up visits will be the same as per the early discontinuation study visit, with the exception of no random PK sampling since the subject will not be on study medications. If early termination is due to toxicity or occurs while the subject is experiencing a ≥ Grade 3 toxicity, the subject must be followed with appropriate clinical and/or laboratory monitoring until resolved to ≤ Grade 2 or baseline values, before completing the early termination study visit and the two followup study visits.
(14) Once the last accrued subject has reached 96 weeks of treatment, all U.S.A. subjects remaining in the study will complete the End of Step I Study Visit. Additionally, there will be two more follow-up study visits four and eight weeks after the End of the Step I Study Visit. U.S.A. subjects will go off-study at the end of Step I. US subjects and South African subjects on powder formulation will continue on-study under Step II. Appendix I-D should be followed for Step II evaluations.
Blood Draw Priorities

(1) RNA
(2) Pharmacology
(3) Hematology
(4) Liver function tests
(5) Lymphocyte subset
(6) Chemistries
(7) Lipid profile
(8) Phenotypic and genotypic resistance testing
### APPENDIX I-D

**SCHEDULE OF EVALUATIONS FOR SUBJECTS IN THE US ON POWDER WHO HAVE REACHED WEEK 96; STARTING January 31, 2009**

**SCHEDULE OF EVALUATIONS FOR ALL SOUTH AFRICAN SUBJECTS WHO HAVE REACHED WEEK 96; STARTING January 31, 2009 (STEP II)**

<table>
<thead>
<tr>
<th>EVENTS</th>
<th>SUBJECT’S WEEKS OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>q12 weeks(^{(11)})</td>
</tr>
<tr>
<td><strong>Clinical Evaluations</strong></td>
<td></td>
</tr>
<tr>
<td>History &amp; Physical(^{(1)})</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test(^{(2)})</td>
<td>X</td>
</tr>
<tr>
<td>Hematology (^{(3)}) (purple top)</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>Chemistries(^{(4)}) (red top)</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Liver Function Tests(^{(5)}) (no extra draw)</td>
<td>X</td>
</tr>
<tr>
<td>Lipid Profile (^{(6)}) (red top)</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
</tr>
<tr>
<td><strong>Virology(^{(7)})</strong></td>
<td></td>
</tr>
<tr>
<td>HIV RNA (purple top)</td>
<td>3.0 mL</td>
</tr>
<tr>
<td>Genotypic Resistance (purple top)</td>
<td></td>
</tr>
<tr>
<td>Viable PBMC for storage and plasma for phenotypic and genotypic resistance and storage (purple top)(^{(8)})</td>
<td></td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets (purple top)(^{(9)})</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Max. Blood (mL)</td>
<td>8.5 mL</td>
</tr>
</tbody>
</table>
APPENDIX I-D (Cont.)

(1)  Physical exam (height, weight, vital signs, symptoms, HIV Assessment)

(2)  Can be either a urine or HCG blood test, must be performed on all females of childbearing potential. If blood test is performed, collect 1.0 mL in a red–top tube.

(3)  Hematology (complete blood count, cell differential, platelet count)

(4)  Chemistries [electrolytes (sodium, chloride, potassium, and HCO₃) glucose, bun, creatinine, amylase].

(5)  Liver Function tests (indirect bilirubin, direct bilirubin, AST, ALT, GGT, albumin). If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented in source document.

(6)  Lipid Profile (triglycerides and cholesterol), this test will be performed in a non-fasting state. However, if results are ≥ Grade 2, a complete fasting-state lipid profile (triglycerides, cholesterol, HDL and LDL) as well as amylase and lipase must be drawn. Fasting intervals will be (1) for children ≤ 2 years of age, 4 hours, and (2) for children > 2 years, overnight.

(7)  See Appendix III-A for virology collection and shipping instructions for all these samples.

(8)  Viable PBMC for storage is to be used to obtain viral stocks for further phenotypic studies of viral resistance as described in Virology Appendix III-A. Plasma for storage will be used for future phenotypic and genotypic studies.

(9)  See Appendix IV-A for immunology collection and shipping instructions.

(10)  This visit will be scheduled when BMS-232632 has been approved in South Africa and it is available for distribution off-study through BMS and the IMPAACT Site.

(11)  Starting at week 280, study visits should continue to occur every 12 weeks for the duration of the study.

(12)  Applies to all subjects on powder after week 96 starting 1/31/09 until BMS 232632 is locally available to both US and SA sites. Also applies to South African subjects in the event that study drug capsules are not available locally by 01/31/09.

Blood Draw Priorities

(1)  RNA

(2)  Pharmacology

(3)  Hematology

(4)  Liver function tests

(5)  Lymphocyte subset

(6)  Chemistries

(7)  Lipid profile

(8)  Phenotypic and genotypic resistance testing
APPENDIX II-A

DIVISION OF AIDS

TOXICITY TABLE FOR GRADING SEVERITY OF
PEDIATRIC (> 3 MONTHS OF AGE) ADVERSE EXPERIENCES APRIL, 1994

THE IMPAACT P1020A PROTOCOL TEAM ADDED THE UNITS FOR
LABORATORY TEST RESULTS TO FACILITATE THE TABLE’S USE IN SOUTH AFRICA

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMATOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3 mo. - &lt; 2 y.o.</td>
<td>9.0-9.9</td>
<td>7.0-8.9</td>
<td>&lt;7.0</td>
<td>Cardiac Failure 2ndary to anemia</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10-10.9</td>
<td>7.0-9.9</td>
<td>&lt;7.0</td>
<td>Cardiac Failure 2ndary to anemia</td>
</tr>
<tr>
<td>&gt; = 2 y.o.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abs Neutrophil CT/µL</td>
<td>750-1200</td>
<td>400-749</td>
<td>250-399</td>
<td>&lt;250</td>
</tr>
<tr>
<td>Platelets/µL</td>
<td>50,000-75,000</td>
<td>25,000-49,999</td>
<td>&lt;25,000 or bleeding</td>
<td></td>
</tr>
<tr>
<td>PT (seconds)</td>
<td>1.1-1.25xN</td>
<td>1.26-1.5xN</td>
<td>1.51-3.0xN</td>
<td>&gt;3xN</td>
</tr>
<tr>
<td>PTT (seconds)</td>
<td>1.1-1.66xN</td>
<td>1.67-2.33xN</td>
<td>2.34-3.0xN</td>
<td>&gt;3xN</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.1-1.9xN</td>
<td>2.0-2.9xN</td>
<td>3.0-7.5xN</td>
<td>&gt;7.5xN</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>1.1-4.9xN U/L</td>
<td>5.0-9.9xN U/L</td>
<td>10.0-15.0xN U/L</td>
<td>&gt;15.0xN U/L</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1.1-4.9xN U/L</td>
<td>5.0-9.9xN U/L</td>
<td>10.0-15.0xN U/L</td>
<td>&gt;15.0xN U/L</td>
</tr>
<tr>
<td>GGT</td>
<td>1.1-4.9xN U/L</td>
<td>5.0-9.9xN U/L</td>
<td>10.0-15.0xN U/L</td>
<td>&gt;15.0xN U/L</td>
</tr>
<tr>
<td>Pancreatic Amylase</td>
<td>1.1-1.4xN U/L</td>
<td>1.5-1.9xN U/L</td>
<td>2.0-3.0xN U/L</td>
<td>&gt;3.0xN U/L</td>
</tr>
<tr>
<td>Total Amylase + Lipase*</td>
<td>1.1-1.4xN U/L</td>
<td>1.5-2.4xN U/L</td>
<td>2.5-5.0xN U/L</td>
<td>&gt;5.0xN U/L</td>
</tr>
<tr>
<td>Uric Acid (mg/dL)</td>
<td>7.5-9.9</td>
<td>10-12.4</td>
<td>12.5-15.0</td>
<td>&gt;15.0 or Gout</td>
</tr>
<tr>
<td>CPK See Neuromuscular Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Mild</td>
<td>Moderate-No Rx Needed</td>
<td>Moderate-Rx Needed</td>
<td>Severe-Hospital and Rx</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Soft stools</td>
<td>Liquid stools</td>
<td>Liquid Stools &amp; Mild Dehydration Bloody stools</td>
<td>Dehydration requiring IV therapy or Hypotensive Shock</td>
</tr>
<tr>
<td>Constipation</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Distention and Vomiting</td>
</tr>
<tr>
<td>Nausea</td>
<td>Mild</td>
<td>Moderate-Decreased po intake</td>
<td>Severe-Little po intake</td>
<td>Unable to ingest food or fluid for &gt;24 hours</td>
</tr>
<tr>
<td>Vomiting</td>
<td>&lt;1 episode/day</td>
<td>1-3 episodes/day or duration &gt;3d</td>
<td>&gt;3 episodes/day or duration &gt;7d</td>
<td>Intractable Vomiting</td>
</tr>
</tbody>
</table>

Comments:

*Both amylase and lipase must be elevated to the same grade or higher (i.e. if total amylase is Grade 4, but lipase is only Grade 1, the Toxicity Grade is 1. In pediatric HIV subjects, the most common source of serum amylase is the salivary glands. Salivary amylase elevations are generally not clinically significant. When amylase is released from damaged pancreatic cells, it can be a marker of pancreatitis. In most cases of clinical pancreatitis, lipase will also be elevated. However, lipase is also a non-specific marker. Combined elevation of amylase and lipase (each >5 x normal) often indicates pancreatic disease and requires evaluation. However, in the absence of pancreatic disease, drug can be resumed even at Grade 3 and 4 toxicities.
## APPENDIX II-A (Cont.)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RENAL AND ELECTROLYTES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CREATININE (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Month-2 Years</td>
<td>0.6-0.8</td>
<td>0.9-1.1</td>
<td>1.2-1.5</td>
<td>&gt;1.5</td>
</tr>
<tr>
<td>2 Years-Adolescent</td>
<td>0.7-1.0</td>
<td>1.1-1.6</td>
<td>1.7-2.0</td>
<td>&gt;2.0</td>
</tr>
<tr>
<td>Adolescents</td>
<td>1.0-1.7</td>
<td>1.8-2.4</td>
<td>2.5-3.5</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Creatinine Clearance (cc/min/1.73 m²)</td>
<td>60-75</td>
<td>50-59</td>
<td>35-49</td>
<td>&lt;35</td>
</tr>
<tr>
<td><strong>ELECTROLYTES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Sodium (mmo/L)</td>
<td>145-149</td>
<td>150-155</td>
<td>&gt;155 or mental status changes</td>
<td></td>
</tr>
<tr>
<td>Low Sodium (mmo/L)</td>
<td>130-135</td>
<td>129-124</td>
<td>&lt;124 or mental status changes</td>
<td></td>
</tr>
<tr>
<td>High Potassium (mmo/L)</td>
<td>5.0-5.9</td>
<td>6.0-6.4</td>
<td>6.5-7.0</td>
<td>&gt;7.0 or Cardiac arrhythmias</td>
</tr>
<tr>
<td>Low Potassium (mmo/L)</td>
<td>3.0-3.5</td>
<td>2.5-2.9</td>
<td>2.0-2.4</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>High Calcium (mg/dL)</td>
<td>10.5-11.2</td>
<td>11.3-11.9</td>
<td>12.0-12.9</td>
<td>&gt;=13.0</td>
</tr>
<tr>
<td>Low Calcium (mg/dL)</td>
<td>7.8-8.4</td>
<td>7.0-7.7</td>
<td>6.0-6.9</td>
<td>&lt;6.0</td>
</tr>
<tr>
<td>Low Magnesium (mg/dL)</td>
<td>1.2-1.4</td>
<td>0.9-1.1</td>
<td>0.6-0.8</td>
<td>&lt;0.6 or Cardiac arrhythmias</td>
</tr>
<tr>
<td>Hypoglycemia (mg/dL)</td>
<td>55-65</td>
<td>40-54</td>
<td>30-39</td>
<td>&lt;30 or Mental status changes</td>
</tr>
<tr>
<td>Hyperglycemia (mg/dL)</td>
<td>116-159</td>
<td>160-249</td>
<td>250-400</td>
<td>&gt;400 or Ketoacidosis</td>
</tr>
<tr>
<td>Proteinuria (mg/dL)</td>
<td>Tr-1+ &lt;150 mg/day</td>
<td>2+ 150-499 mg/day</td>
<td>3+ 500-1000 mg/day</td>
<td>4+, or nephrotic syndrome &gt;1000 mg/day</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Microscopic &lt;25 cells/hpf</td>
<td>Microscopic &gt;=25 cells/hpf</td>
<td>Gross</td>
<td>Obstruction or Transfusion requirement</td>
</tr>
</tbody>
</table>

**Comments**
Calcium values are corrected for albumin concentration. CrCl values do not apply to infants <2 months old.

<table>
<thead>
<tr>
<th>OTHER</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>Pruritis without Rash</td>
<td>Pruritic Rash</td>
<td>Mild Urticaria</td>
<td>Severe Urticaria Anaphylaxis, Angioedema</td>
</tr>
<tr>
<td>Drug Fever (Rectal)</td>
<td>38.5-40 °C</td>
<td>&gt;40 °C</td>
<td>Sustained Fever: &gt;40 °C, &gt;5 days</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Diffuse maculo-papular rash, dry desquamation</td>
<td>Vesiculation, ulcers</td>
<td>Exfoliative dermatitis, Stevens-Johnson or Erythema multiforme, Moist desquamation</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Mild discomfort</td>
<td>Painful, difficulty swallowing, but able to eat and drink</td>
<td>Painful: unable to swallow solids</td>
<td>Painful: requires IV fluids</td>
</tr>
</tbody>
</table>
### APPENDIX II-A (Cont.)

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>None</td>
<td>1 Uncomplicated Sz +/- Temp Elevation</td>
<td>1 Sz/Month for &gt;=2 Consecutive Months Or 3 Sz over 6 Months; No Temp Elevation</td>
<td>&gt;=1 Sz/Month; No Temp Elevation; No Decrease in Sz Frequency Despite dose reduction</td>
</tr>
</tbody>
</table>

Seizures are a ubiquitous symptom of numerous systemic or CNS disturbances; alternative explanations should be vigorously sought and eliminated. Status epilepticus represents a severe end of the seizure spectrum, but should be considered as a single seizure event. The need for chronic or acute anticonvulsant medication should be made on a clinical basis. Seizures as a manifestation of drug toxicity are usually primarily generalized. Focal (partial onset) seizures are suggestive of focal central nervous system pathology and should be appropriately investigated, although they may be a manifestation of drug toxicity. Beware of focal seizures which secondarily generalize; these should be approached diagnostically as partial onset seizures. Children with underlying epileptic conditions who experience persistent breakthrough seizures despite maximal anticonvulsant therapy coincident with beginning the trial medication should be considered Grade 4.

### Headache

<table>
<thead>
<tr>
<th></th>
<th>&lt;=1/Month</th>
<th>&gt;1/Month</th>
<th>&gt;2/Month</th>
<th>&gt;4/Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=2 Hrs duration</td>
<td>Mild</td>
<td>Moderate to Severe</td>
<td>Responds to non-narcotic analgesia or prophylaxis</td>
<td>Does not respond to prophylaxis</td>
</tr>
</tbody>
</table>

Headache is a non-specific symptom, but may be a symptom of CNS/intracranial pathology. Appropriate diagnostic measures should be pursued. Duration refers to the waxing and peak phases, not to the resolution/waning phases of the headache. Mild refers to a grade of headache pain which does not affect function or activity. Moderate to severe refers to a grade of headache which affects function or activity.

### Mental Status And Behavior

<table>
<thead>
<tr>
<th></th>
<th>Changes which do not Affect Function</th>
<th>Changes requiring pharmacologic or other therapy; or mild lethargy, sedation or somnolence which resolves with rest</th>
<th>Changes not improved by drugs or other therapies; or onset of confusion, memory impairment, lethargy, sedation, or somnolence which does not respond to rest</th>
<th>Onset of delirium, obtundation, coma, or psychosis, or Grade 3 toxicity which does not respond to dose reduction</th>
</tr>
</thead>
</table>

Behavior refers to the development of attention deficits with or without hyperactivity, depression, mania, agitation, sleep disorders, phobias, obsessive-compulsive behaviors, or anxiety. Mental status refers to the level of consciousness, memory function, language and analytical operations, and non-dominant hemisphere functioning. Alternative explanations should be sought.

### Balance & Posture

|                        | None | None | Ataxia, dizziness, vertigo, tremor, impaired postural balance | Onset of movement disorder; or Grade 3 toxicity which does not respond to dosage adjustment |

"Ataxia" can be mistakenly diagnosed in the face of central weakness or peripheral neuropathy, which should not be considered a drug toxicity of this category. Movement disorders refer to tardive or other dyskinesias, dystonias, chorea, or ballismus. Alternative explanations should be sought.
### APPENDIX II A (Cont.)

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>None</td>
<td>Blurriness, diplopia, or horizontal nystagmus of &lt; 1 hour duration, with spontaneous resolution</td>
<td>&gt;= 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 Sx lasting 1 hour with spontaneous resolution by 4 hours or vertical nystagmus</td>
<td>Decrease in visual acuity, visual field deficit, or oculogyric crisis, or Grade 3 Sx which persist after dose reduction</td>
</tr>
</tbody>
</table>

Many of the symptoms in this category can be the result of CNS pathology, or alternatively can be an external (i.e., non-CNS) neuro-ophthalmologic disorder. Appropriate diagnostic investigations should be pursued.

**Myelopathy**

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>Myelopathic/spinal cord symptoms, such as: Pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction</th>
</tr>
</thead>
</table>

HIV can cause spinal cord syndromes rarely in children. Other infectious agents can cause myelopathies as well. Alternative explanations should be sought.

### PERIPHERAL NERVOUS SYSTEM

**Neuropathy/ Lower Motor Neuronopathy**

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild transient Paresthesia only</th>
<th>Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss</th>
<th>Onset of significant weakness, decrease or loss of DTRs, sensory loss in “stocking glove” distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness. Grade 3 symptoms which do not resolve after dose reduction</th>
</tr>
</thead>
</table>

Infectious agents other than HIV can precipitate a neuropathy and should be considered, especially CMV. Neuropathies which do not resolve after dose reduction or discontinuation should be pursued for alternative infectious or non-infectious etiologies, since drug-related neuropathies will usually resolve after dose reduction or drug discontinuation. It should be borne in mind that many subjects will worsen for up to one month after drug discontinuation prior to improvement ("coasting"). Abnormalities should be confirmed by nerve conduction studies (NCS) +/- electromyographic studies (EMG).

**Myopathy or Neuromuscular Junction Impairment**

<table>
<thead>
<tr>
<th></th>
<th>Normal or mild (&lt;2 x N) CPK elevation</th>
<th>Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (&lt;2 x N)</th>
<th>Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK &gt;2 x N; Consider confirmatory EMG and/or muscle bx</th>
<th>Onset of myasthenia-like symptoms (fatiguable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms (confirm with EMG); or Grade 3 symptoms which do not resolve on dose adjustment; confirm with muscle bx</th>
</tr>
</thead>
</table>

HIV can produce a myopathy, and should be differentiated. Drug-induced myopathy can be accompanied by normal CPK levels. On occasion, neuropathic or central weakness can mimic myopathic weakness.
# APPENDIX II A (Cont.)

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms not otherwise specified in this table</td>
<td>No therapy; monitor condition</td>
<td>May require minimal intervention and monitoring</td>
<td>Requires medical care and possible hospitalization</td>
<td>Requires active medical intervention, hospitalization, or hospice care</td>
</tr>
<tr>
<td>Laboratory values not otherwise specified in this table</td>
<td>Abnormal, but requiring no immediate intervention; follow</td>
<td>Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not sufficient severity to warrant immediate changes in the study drug</td>
<td>Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug</td>
<td>Life-threatening severity. Requires immediate evaluation, treatment, and usually hospitalization. Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism than the study drug</td>
</tr>
</tbody>
</table>
APPENDIX II-B

SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY
OF TRIGLYCERIDES AND CHOLESTEROL

(IMPAACT P1020A will follow this appendix for toxicity grading of cholesterol and triglycerides for all subjects regardless of the subject’s age)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Triglycerides</th>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1:</td>
<td>136 – 749 mg/dL</td>
<td>171 – 499 mg/dL</td>
</tr>
<tr>
<td>Grade 2:</td>
<td>750 – 1199 mg/dL</td>
<td>500 – 749 mg/dL</td>
</tr>
<tr>
<td>Grade 3:</td>
<td>≥ 1200 mg/dL</td>
<td>≥ 750 mg/dL</td>
</tr>
</tbody>
</table>
# APPENDIX II-C

**SUPPLEMENTAL TOXICITY TABLE FOR GRADING ELECTROCARDIOGRAM CHANGES AND POSSIBLE SYMPTOMS RELATED TO CARDIAC CONDUCTION ABNORMALITIES**

<table>
<thead>
<tr>
<th>Cardiac Conduction</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;13 years of age:</td>
<td>&lt;13 years of age:</td>
<td>One of the following:</td>
<td>A complete AV-block at any time.</td>
</tr>
<tr>
<td>PR-interval</td>
<td>A PR-Interval prolonged ≤ 25% above the 98th percentile for subjects age (Use Appendix VIII to determine 98th percentile)</td>
<td>A PR-Interval prolonged &gt; 25% above the 98th percentile for subject’s age (Use Appendix VIII to determine 98th percentile)</td>
<td>A type I second-degree atrioventricular (AV) block occurring during waking hours (Mobitz type I heart-block, or Wenckebach),</td>
<td></td>
</tr>
<tr>
<td>QTcB-interval</td>
<td>≥13 years of age: PR-Interval &gt; 200 msec</td>
<td>≥13 years of age: PR-Interval &gt; 250 msec</td>
<td>A corrected QTcB-Interval &gt; 470 msec.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ventricular pause &gt;3 seconds.</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Subjects having a low HR defined as &lt; 2nd percentile for age with no symptoms or heart block. In addition: PR interval must be ≤25% above the 98th percentile for age and QTcB interval ≤ 470 msec. (Use Appendix IX to determine 2nd – 98th percentile)</td>
<td>Subjects having a low HR defined as &lt; 2nd percentile for age with symptoms and associated with first- or second-degree heart block, which may include PR prolongation &gt;25% above the 98th percentile for age, and QTcB &gt;470 msec. (Use Appendix IX to determine 2nd – 98th percentile)</td>
<td>Any of the following clinical symptoms: Syncope (without clear evidence of non-cardiac etiology) Palpitations (without clear evidence of non-cardiac etiology)</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX III-A

VIROLOGY COLLECTION AND SHIPPING INSTRUCTIONS FOR U.S.A. AND SOUTH AFRICAN SITES

ASSAYS:
QUANTITATIVE PLASMA HIV-1 RNA PCR (Roche Amplicor Assay) and
PLASMA FOR GENOTYPIC RESISTANCE

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Plasma            | Minimum of 3 mL blood collected by venipuncture At Screening Visit, collect two 3.0 mL blood tubes. One tube will be used solely for genotypic testing. | Tripottasium EDTA Vacutainer® tube (purple-top tube) | • Gently invert tubes several times to mix. Do not shake.  
• Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, specimen type.  
• Specimen should be kept at room temperature (18°-24°C) and processed within 4-6 hours of collection. |

SPECIMEN PROCESSING:
• Centrifuge blood at 400 x g for 10 minutes at 18°-24°C.
• Transfer plasma to a centrifuge tube; recentrifuge at 800 x g for 10 minutes to completely remove platelets and cell debris.
• If plasma is not to be tested within 30 minutes of separation, aliquot plasma into sterile, labeled cryovials (label with same information as blood tubes) and store at -60°to-80°C or below for batch testing.
• PBMC are separated from red blood cells and neutrophils by density centrifugation on Ficoll-Hypaque and frozen in standard aliquots.

ALIQUOTS: At least 2-3 Aliquots of .6 mL

DESIGNATED LABORATORY/CONTACT PERSON:
• For U.S.A. sites, all HIV RNA assays and genotypic resistance assays at Screening Visit or any other visit will be done at Children’s Hospital of Los Angeles (U.S.A. LDMS 130).
• For Soweto site:
  • all HIV RNA assays should be shipped to Contract Laboratory Service in Johannesburg (LDMS 350), and
  • genotypic resistance assays at Screening Visit or any other visit should be shipped to Children’s Hospital of Los Angeles (U.S.A. LDMS 130).

SHIPPING: Real time or batched as outlined in attached table
(1) RNA assays and genotypic assays at screening will be sent at time of draw or sent with the next shipment outlined in the Virology table
(2) All sites must provide the name, phone number, fax number and e-mail address of the persons responsible for on-site storage and shipping of samples (See page 5 of this appendix).
(3) Two aliquots of plasma are to be sent to the laboratory as outlined above for real time testing. The remaining aliquots should be sent at a later date as outlined below. This is to prevent loss of all samples from a particular time point in the event of courier mishap.
APPENDIX III-A (Cont.)

### ASSAY:
Viable PBMC for Storage, Plasma for phenotypic resistance, Plasma for storage

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PBMC</td>
<td>Minimum 3 mL blood collected by venipuncture</td>
<td>Tripottasium EDTA Vacutainer® tube (purple-top tube)</td>
<td>• Gently invert tubes several times to mix. Do not shake.</td>
</tr>
<tr>
<td>• Plasma for phenotypic assay and for storage</td>
<td></td>
<td></td>
<td>• Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and type of specimen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Specimen should be kept at room temperature (18°-24°C) and processed within 1 hour of collection.</td>
</tr>
</tbody>
</table>

### SPECIMEN PROCESSING:
- Centrifuge tubes at 400 x g for 15 minutes. Transfer plasma to a centrifuge tube; recentrifuge at 800 x g 10 minutes to completely remove platelets and cell debris. Transfer plasma to sterile, labeled cryovials (labeled with same information as above), and store at –60° –80°C.
- This assay requires the separation of PBMC from red blood cells and neutrophils by density centrifugation on Ficoll-Hypaque and should be performed by a Certified Virology Laboratory using the method described in the DAIDS Virology Manual for HIV Laboratories for processing PBMCs for HIV microculture.

### ALIQUOTS:
- 0.6 mL aliquots of plasma (at least 2-3 aliquots) and 1.0 mL aliquots of 2-5 million cells/mL, at least 4 aliquots.

### DESIGNATED LABORATORY/CONTACT PERSON:
- Plasma from Screening Visits should be sent to ViroLogic Inc. (Attn. Liza Santos, see end of this appendix)
- Plasma for storage from all other study visits should be sent to Children’s Hospital of Los Angeles (U.S.A. LDMS 130).

### SHIPPING:
- Send minimum two 0.6 plasma samples per subject from Screening Visits to ViroLogic Inc.
- Send plasma for storage monthly from all other study visits to Children’s Hospital of Los Angeles (U.S.A. LDMS 130). Contact the receiving laboratory via fax (see Appendix III-C) prior to shipping any samples. They will act as the repository for the study.
- Each site will store viable PBMC until contacted by the IMPAACT P1020A Team with instructions for when and where to ship these samples.
APPENDIX III-A (Cont.)

ASSAY:
QUALITATIVE MICROCULTURE (ONLY FOR U.S.A. SITES)

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| PBMC              | Minimum: 5 mL blood collected by venipuncture | Tripottasium EDTA Vacutainer® tube (purple-top tube) | • Gently invert tubes several times to mix. Do not shake.  
• Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, specimen type.  
• Specimen should be kept at room temperature (18°C-24°C) and processed within 30 hours of collection. Specimens can be shipped overnight at room temperature |

SPECIMEN PROCESSING:

DESIGNATED LABORATORY/CONTACT PERSON:
Each site should have cultures performed in their designated IMPAACT approved lab.

SHIPPING: Each site will store viral isolates on site until contacted by the team with instructions for when to ship viral isolate PBMC Children’s Hospital of Los Angeles, (U.S.A. LDMS 130).

OTHER INSTRUCTIONS:
Qualitative HIV microculture should be obtained at:
(1) Entry  
(2) 56 weeks  
(3) Early study termination or end of study

HIV co-culture should be done in real time. At least $2 \times 10^6$ cells should be used to set up each culture as described in the virology manual and summarized below. Sites which do not have HIV culture capability will ship whole blood collected in a purple top tube at ambient temperature (or with cold packs NOT touching specimen if ambient temperature is expected to exceed 65°C), by overnight courier to the ACTG certified virology lab.

THIS SPECIMEN MUST BE SET UP IN CO-CULTURE WITHIN 30 HOURS OF BEING DRAWN. Please record the time the blood was drawn and send this information to the laboratory performing the culture.
APPENDIX III-B

PLASMA FOR HIV-1 RNA PCR, GENOTYPIC ASSAY AND STORAGE FOR U.S.A. AND SOUTH AFRICA SITES

<table>
<thead>
<tr>
<th>TIMEPOINT</th>
<th>SEND AT TIME OF DRAW</th>
<th>SEND WITH NEXT SHIPMENT</th>
</tr>
</thead>
</table>
| Screening Visit (Week –4 to –2) | • For U.S.A. sites, two aliquots of plasma for HIV-1 RNA PCR and genotypic assays to the Children's Hospital of Los Angeles (U.S.A. LDMS 130).  
• For Soweto site, two aliquots of plasma for HIV-1 RNA PCR to Contract Laboratory Service in Johannesburg (LDMS 350).  
• For Soweto site, two aliquots of plasma for genotypic assays to Children's Hospital of Los Angeles (U.S.A. LDMS 130).  
• For subjects who need real time phenotypic assays, two aliquots of plasma for phenotypic assays to Virologic Inc.  
• For subjects who are banking samples for phenotypic analysis specimens, two aliquots of plasma to Children's Hospital of Los Angeles (U.S.A. LDMS 130). | All remaining samples will be sent with entry shipment. |
| Pre-Entry (Day –5 to Day –1) | • For U.S.A. sites, two aliquots of plasma for HIV-1 RNA PCR to the Children's Hospital of Los Angeles (U.S.A. LDMS 130).  
• For Soweto site, two aliquots of plasma for HIV-1 RNA PCR to Contract Laboratory Services in Johannesburg (LDMS 350).  
• For Soweto site, two aliquots of plasma to Children's Hospital of Los Angeles (U.S.A. LDMS 130). | Store all aliquots at site to be sent with Day 0 real time samples |
| Entry (Day 0) and Weeks 1, 4, 8, 12, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, every 16 weeks (after Week 96 of subject’s treatment and until the End of Study, and/or early study discontinuation visit), and at both of the two followup visits after the End of Study visit and/or early discontinuation study visit. | • For U.S.A. sites, two aliquots of plasma to the Children’s Hospital of Los Angeles (U.S.A. LDMS 130).  
• For Soweto site, two aliquots of plasma for HIV-1 RNA PCR to Contract Laboratory Services in Johannesburg (LDMS 350).  
• For Soweto site, two aliquots of plasma to Children's Hospital of Los Angeles (U.S.A. LDMS 130). | Remaining aliquots |
APPENDIX III-C

GENERAL INSTRUCTIONS FOR VIROLOGY SPECIMEN PROCESSING, SHIPPING AND PAPERWORK FOR U.S.A. AND SOUTH AFRICA SITES

General Instructions:

All specimens should be packaged according to the ACTG Virology Manual with strict attention to Federal and carrier specific regulation for the shipment of hazardous biological material. Include sufficient dry ice to keep the specimens frozen.

For shipments greater than 15 vials, the samples should be placed in the Nalgene cryovial box in the order of the shipping manifest (if an LDMS program is available). If less than 15 vials are to be sent they can be placed in plastic baggies inside the orange topped shipping canister. The orange topped container is placed in the cardboard box, which is placed inside the polystyrene insulated box and the box filled with sufficient solid carbon dioxide (dry ice) to last 48 hours. Likewise the Nalgene cryovial box should be wrapped in absorbent material and placed inside a heavy duty plastic bag, sealed and placed in the polystyrene insulated box filled as above with dry ice. The outer box is sealed with packing tape and marked with the appropriate stickers, which will be provided.

Paperwork for Lab Specimens sent to Children’s Hospital of Los Angeles:

If the site has the LDMS, an ACTG Virology shipment notice, a shipping diskette and shipping manifest should accompany the shipment. Please fax the ACTG Shipping Notice prior to sending the shipment. THIS WILL ENSURE THAT YOUR SPECIMENS WILL MAKE THE WEEKLY RUN.

If the site does not have the LDMS, an ACTG Virology Shipment notice, a duplicate F3006 Virology Tracking From and a list of specimens being sent (box map) should be included with the shipment.

Plasma samples from HIV-1 RNA PCR (all study visits as per Appendix I), Genotypic Assay (Screening Visit), and Storage samples (as per Appendix I) with appropriate paperwork should be sent as follows:

Children’s Hospital of Los Angeles
IMPAACT Virus Lab 130
ATTN: Don Decker/Grace Aldrovandi
Smith Research Tower Room 901
4650 Sunset Boulevard
Los Angeles, CA 90027
U.S.A.
Phone: 323-361-8502  FAX: 323-361-8599
e-mail: viruslab130@dom.geomed.uab.edu or viruslab130@chla.usc.edu
Shipments may be made Monday through Thursday only by overnight courier service using the before 10:30 am option. DO NOT SHIP SAMPLES WHEN THEY WOULD BE RECEIVED ON A HOLIDAY. HOLIDAYS INCLUDE: New Year’s Day, M.L. King’s Birthday, Good Friday, Memorial Day, July 4, Labor Day, Thanksgiving and the day after Thanksgiving, and several days around Christmas. Prior to shipment, please fax the ACTG Virology Shipping Notice to Don Decker at 323-361-8599 (a copy should also be included with all shipments in addition to the other paperwork). This is a Federal regulation. At the time of shipment, please contact the laboratory by phone to advise that a shipment has been sent and provide the airway bill number. Any questions relating to specimen handling shipment or identification should be directed to Don Decker at 323-361-8502.

Paperwork for Phenotypic Specimens sent to ViroLogic, Inc.:  

Complete a ViroLogic Test Requisition Form for each specimen. Include the top copy of this form with the shipment to ViroLogic. Keep the remaining two copies for your records.

The plasma specimens for phenotyping and test requisition form should be sent to:

Attention: Carmeliza (Liza) Santos  
ViroLogic, Inc.  
345 Oyster Point Blvd.  
South San Francisco, CA  94080  
U.S.A.  
Phone: (650) 866-7482  
FAX: (650) 624-4457 fax  
E-mail: csantos@virologic.com

Prior to shipment please fax a copy of the completed ViroLogic Test Requisition Form and the courier airbill to ViroLogic Receiving at 650-615-0177 OR you may email receiving@virologic.com the following information:
- number of specimens
- protocol name
- courier service name and airbill number
- date specimen(s) shipped
- contact name and phone number.

Shipments should only be made Monday through Wednesday. U.S.A. sites should use the overnight courier service using the before 10:30 am option. IMPAACT Soweto Site must use World Carrier. DO NOT ship on a Thursday, Friday, Saturday, Sunday, or the day before a U.S.A. Federal Holiday. Keep samples frozen and ship them on the next regular U.S.A. working day. To determine the U.S.A. Federal Holidays go to http://www.opm.gov/fedhol/.
# IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS FOR U.S.A. AND SOUTH AFRICAN SITES

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte subsets:</td>
<td>1.0 mL blood collected by venipuncture</td>
<td>Tripotassium EDTA Vacutainer® tubes (purple top)</td>
<td>• Gently invert tubes several times to mix. Do not shake.</td>
</tr>
<tr>
<td>Isotype controls</td>
<td></td>
<td></td>
<td>• Specimen should be identified as to subject ID#, study ID#, visit ID#, date and time of collection.</td>
</tr>
<tr>
<td>CD3/CD45/CD4, CD3/CD45/CD8,</td>
<td></td>
<td></td>
<td>• Specimen must be processed within 24-30 hours of collection.</td>
</tr>
<tr>
<td>CD45/CD3/CD19</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SHIPPING AT U.S.A. Sites: real-time at room temperature to a local IQA/CLIA-certified lab.

SHIPPING AT IMPAACT SOWETO SITE: real time to Contract Laboratory Services (LDMS 350).

Attention: Wendy Stevens, M.D.
University of Witwatersrand
School of Pathology
Department of Molecular Medicine and Hematology
7 York Road
Parktown
Johannesburg
South Africa
Phone: 271 148 98505
Fax: 271 148 45812
E-mail: wendy@dlatech.co.za
### APPENDIX IV-B
SPECIAL IMMUNOLOGY SPECIMEN PROCESSING STORAGE AND SHIPPING INSTRUCTIONS FOR U.S.A. AND SOUTH AFRICAN SITES

**ASSAY:** ADVANCED FLOW CYTOMETRY (Immunophenotyping)

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Whole Blood       | 1.5 mL blood collected by venipuncture | Tripotassium EDTA Vacutainer7 tube (purple top) | ☑️ Gently invert tube several times to mix. Do not shake.  
☑️ Specimen should be identified as to subject ID#, study ID#, visit ID#, date and time of collection.  
☑️ Specimen should be kept at room temperature (18°C-22°C) and shipped real time, priority overnight to the CHOP IMPAACT Immunology Core Lab (LDMS Lab #208).  
Analysis is optimally performed within 24 to 30 hours of specimen draw |

**SPECIMEN PROCESSING FOR U.S.A. SITES:**

Further specimen processing (e.g. lysing of the whole blood and immunofluorescent staining) must be done by the CHOP IMPAACT Immunology Core Laboratory using the ACTG Immunology Consensus Method for Flow Cytometry.

**SPECIMEN PROCESSING FOR IMPAACT SOWETO SITE:**

Further specimen processing (e.g. lysing of the whole blood and immunofluorescent staining) must be done Contract Laboratory Services (LDMS 350)
### APPENDIX IV-B (Cont.)

<table>
<thead>
<tr>
<th>DESIGNATED LABORATORY/CONTACT PERSON FOR U.S.A. SITES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s Hospital of Philadelphia</td>
</tr>
<tr>
<td>(LDMS Lab #208)</td>
</tr>
<tr>
<td>Attn: Eric Riedel/Don Campbell</td>
</tr>
<tr>
<td>Abramson Pediatric Research Center</td>
</tr>
<tr>
<td>Room 1207H</td>
</tr>
<tr>
<td>34th Street and Civic Center Boulevard</td>
</tr>
<tr>
<td>Philadelphia, PA 19104</td>
</tr>
<tr>
<td>Phone: 215-590-3402</td>
</tr>
<tr>
<td>Fax: 215-590-7671</td>
</tr>
<tr>
<td><a href="mailto:riedel@email.chop.edu">riedel@email.chop.edu</a></td>
</tr>
<tr>
<td><a href="mailto:campbelld@email.chop.edu">campbelld@email.chop.edu</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SHIPPING FOR U.S.A. SITES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-time, at room temperature by priority overnight express mail to the assigned core laboratory</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SHIPPING FOR IMPAACT SOWETO SITE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-time, at room temperature to Contract Laboratory Services (LDMS 350).</td>
</tr>
<tr>
<td>Attention: Wendy Stevens, M.D. University of Witwatersrand, School of Pathology</td>
</tr>
<tr>
<td>Department of Molecular Medicine and Haematology</td>
</tr>
<tr>
<td>7 York Road, Parktown, Johannesburg, South Africa</td>
</tr>
<tr>
<td>Phone: 271 148 98505, Fax: 271 148 45812, and E-mail: <a href="mailto:wendy@dlatech.co.za">wendy@dlatech.co.za</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER INSTRUCTIONS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>For U.S.A. sites, a fax must go to the CHOP (215-590-7671) IMPAACT Immunology core lab each time a sample is sent. The fax must include the PID# of the subject whose samples are being shipped, and the Federal Express/Airborne tracking number of the shipment. Send the fax on the day the sample is drawn. DO NOT send specimens on Fridays or the day before a legal holiday. The labs listed above are only for the special immunology studies. DO NOT send routine labs (standard phenotyping, CBC, chemistries) to these laboratories.</td>
</tr>
</tbody>
</table>
APPENDIX V

PHARMACOLOGY SPECIMEN COLLECTION, PROCESSING AND STORAGE GUIDELINES FOR U.S.A. AND SOUTH AFRICAN SITES

1. **Intensive Pharmacokinetic Studies:**

   These studies will be performed on all subjects in the study. If the BMS-232632 dose is adjusted as a result of the first 24-hour intensive pharmacokinetic study (Week 1 PK), a new 24-hour PK will be performed two weeks after the new dose has been initiated, only for subjects whose BMS-232632 dose was adjusted.

   **Intensive Pharmacokinetic Study Sample Collection at Week 1 and Week 56**: 
   - Blood samples for evaluation of steady-state concentrations of BMS-232632 will be obtained as described below during the Day 7 study visit following an observed administration of the morning doses of the combination antiviral drug regimen.

   - Blood samples collected for pharmacokinetic studies should be drawn in a purple-top tube. 1.5 milliliters of whole blood is to be collected at each of the following time points: 0, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose administration.

2. **Random Pharmacokinetic Samples:**

   All subjects will participate in a population pharmacokinetics studies (i.e., sparse sampling). A 1.5 milliliter blood sample for evaluation of steady-state concentrations of BMS-232632 will be obtained in a purple-top tube at study visits 12, 24, 36, 72 and 96 (and every 24 weeks thereafter until the end of the study), and should be collected at least 3 hours after dose of BMS-232632 has been taken. The random concentrations obtained at Weeks 12, 24, and 36 will be used for assessment of possible non-adherence.

3. **Processing and storage of samples:**

   Each blood sample should be processed, and the plasma separated by centrifugation within 30 minutes of the time of collection.

   - Centrifuge the blood sample at 2500 rpm for 10 minutes to obtain the plasma and whatever BMS needs.
   - Transfer the plasma-matrix to a labeled polypropylene-cryotube that has a screw top. The plasma should be kept in an ice bath until it is frozen.

---

11 Intensive PKs at Week 56 are done as per Week 1 PKs. However, dose adjustments, if needed, are for individuals only. No group-dose adjustments are done based on Week 56 PK data.
APPENDIX V (Cont.)

- Freeze the cryovials in the upright position and maintain frozen at -20C to -70C until shipment.

4. **Labeling of Samples:**

Whenever possible, and as long as ALL the following information is include, use LDMS Computer Generated Labels. If not available, using a waterproof pen and a non removable label, label each cryovial with the subject's ID number, study number, and study week number and date and time of collection.

A pharmacokinetic case record form should be completed and a copy sent with each shipment. Example:

PID#:
Study Wk#:
Date:
Time Drawn:
Time of Dose:

5. **Shipment of All PK Samples:**

- Place frozen cryovials in a zip lock bag in an ISS-1 SAF-T-PAK with sufficient dry ice to ensure that samples are frozen upon arrival (for 48 hours).
- Pack, seal, and label the shipping carton according to the ACTG guidelines for shipping etiologic agents.
- Include a copy of the appropriate CRF detailing the timing of dose and collection of the samples.
- Ship all samples on the NEXT U.S.A. working day after collection to:
  
  **Laboratory Contact**
  Lane R. Bushman
  (303) 315-1670
  (303) 315-1721 (Fax)
  E-mail: lane.bushman@uchsc.edu
Shipping Address (Fed-Ex):
Lane R. Bushman
Antiviral Pharmacology Laboratory (DMC Lab 90)
BRB-Room 344
University of Colorado Health Sciences Center
4200 East Ninth Avenue
Denver, CO 80262
Phone: (303) 315-1670
Fax: (303) 315-1721
E-mail: lane.bushman@uchsc.edu

U.S. Mail Address:
Lane R. Bushman
School of Pharmacy (DMC Lab 190)
BRB Room 344
Campus Box C-238
4200 East Ninth Avenue
Denver, CO 80262

- DO NOT ship on a Thursday, Friday, Saturday, Sunday, or the day before a U.S.A. Federal Holiday. Keep samples frozen and ship them on the next regular U.S.A. working day. To determine the U.S.A. Federal Holidays go to [http://www.opm.gov/fedhol/](http://www.opm.gov/fedhol/).
- Fax a copy of the appropriate CRFs to the University of Minnesota Pharmacology Laboratory at 612-625-3927 (Attention Richard Brundage).
APPENDIX VI
CONFIRMATORY ELECTROCARDIOGRAMS (ECGS), INSTRUCTIONS AND CONTACT INFORMATION

eResearchTechnology will be providing confirmatory analysis of ECGs for the study. The following personnel at this company are available to assist you in specific matters. Please remember always to notify the protocol team at actg.teamp1020@fstrf.org of any abnormal findings even before contacting the confirmatory ECG reading center.

CONTACT LIST
To facilitate a quick response to your inquiry it is IMPORTANT that you have the following information available:

4 Bristol-Myers Squibb
4 IMPAACT P1020A
4 Principal Investigator Name

For questions regarding ECG protocol procedures contact:
Kimberly Kitecy, Project Manager 215-282-5564

For questions regarding Technical Support or the ordering of any materials, equipment or supplies, contact:
The Site Support Dept. during our normal business hours of 9:00 am to 6:00 pm (EST) at 215-282-5565
For emergency technical/equipment issues outside normal business hours, call 267-253-6459

For questions regarding ECG results contact:
Linda Brokaw, Manager, Diagnostic Services 215-282-5357

For Alert ECGs contact our Modem Specialist at:
Patricia Itri,, ECG Modem Specialist 215-282-5346

For questions regarding missing ECG reports, contact:
eRT Site Support 215-972-0420 x2201
1. Type of Tracing: 12 Lead ECG with Lead II rhythm strip

2. ECG Recorder Type:

IMPAACT Sites may initially use their own ECG equipment and supplies. Abnormal ECGs can be faxed, if the site does not have the capacity of sending the information electronically via modem. Mailing one of the originals will be required for all ECGs for archiving purposes. Any site participating in IMPAACT P1020A will eventually have to transmit all the ECGs via modem using the MAC®1200. BMS will upgrade all sites to modem capacity. Faxing (with FedEx shipment of paper-copy or original) will be acceptable only until the site is ready to transmit ECGs electronically via MAC®1200.

Bristol-Myers Squibb will provide free of charge the ECG machines (MAC®1200) with modem capacity for all sites. These machines will be loaned to the sites until the end of the study. Please contact eRT Site Support Department at the number given on the first page of this appendix, to request the MACT®1200. eRT will send the MAC®1200 machines to the every site, upon request. The ECG Investigator Manual for the MAC®1200, specifically developed for IMPAACT P1020A will be sent with the machines.

Sites will need to be trained and certified in using and transmitting IMPAACT 1020A ECGs with the MAC®1200. eRT will provide this training by conference call once the site has receive the new machines. Sites will receive the MAC®1200 specifically programmed for IMPAACT P1020A. Part of the programming is to assign a "cart" and "site number" within MAC®1200 that would correspond to a location in the MUSE database. The direct number to the MUSE is also programmed within the unit to allow sites transmission of ECGs without problems.

If a site decides to use its own MAC®1200, eRT will provide the necessary programming to the site. However, once the unit is programmed for IMPAACT P1020A, it would be advisable that the unit be used only for IMPAACT P1020A subjects. The reason for this requirement is to prevent the transmission of non-IMPAACT P1020A ECGs to eRT by mistake.

3. Return of ECG equipment

When a site is ready to return a machine, please let us know which site is ready and we will issue them an Equipment Return memo along with a preprinted airbill. The site will then have to box up the machine and patient cable with sufficient packing material and send to eRT. Once received at eRT, we will then return the unit back into
inventory and stop billing BMS for rental. The sites can also pack up their machines and patient cables and send to us if they do not wish to wait for the Equipment Return memo or air bill. All sites, except for those in S. Africa, would return the boxes to the following address:

eResearchTechnology
30 South 17th Street
Philadelphia, PA 19103
Phone: 215.972.0420

Sites in South Africa should contact the protocol team at actg.teamp1020@fstrf.org for information and instructions regarding how the ECG equipment should be returned.

Please contact the protocol team at actg.teamp1020@fstrf.org if you have any questions.

4. Original ECGs Delivery to eRT:

Initially, sites that do not have fax or modem must send original EGCs via Federal Express Standard Overnight.

Sites using their own modem or after installing the MAC®1200 can send the original ECGs via regular mail. Please follow instructions in your MAC®1200 manual.

5. ECG Report Flow:

a. ECG with abnormal (grade 2,3,4) findings, as read by site’s pediatric cardiologist: The site will contact the protocol team and eRT upon reading of ECG. If the MAC®1200 is not available yet, the site must send the original ECG for confirmatory reading via fax. A paper-copy of the tracing should also be sent via FedEx overnight. After receiving and installing the MAC®1200, sites must send these ECGs via modem upon completion of tests.

Once the ECGs are received at eRT, an ECG analyst collects interval duration measurements from the Lead II rhythm strips using a Sigma Scan digitizing tablet. The eRT cardiologist then completes the ECG evaluation.

b. ECG without abnormal findings as read by site’s pediatric cardiologist: All 12 Lead ECGs with Lead II rhythm strip are sent to eRT via modem. If the MAC®1200 is not available yet, the site must send the original ECG for confirmatory reading via FedEx overnight. After receiving and installing the MAC®1200, sites must send these ECGs via modem upon completion of tests.
Once the ECGs are received at eRT, an ECG analyst collects interval duration measurements from the Lead II rhythm strips using a Sigma Scan digitizing tablet. The eRT cardiologist then completes the ECG evaluation.

6. Preliminary Feedback:

   a. ECG with abnormal findings as read by site’s pediatric cardiologist: Upon completion of the eRT cardiologist’s evaluation, ECG results are faxed to the site in the form of a worksheet within 24 hours post receipt of ECG from site. If eRT reading of ECG does not confirm abnormal findings established by pediatric cardiologist at the site, the site’s principal investigator must contact the protocol team at actg.teamp1020@fstrf.org. A conference call will be scheduled to discuss the discrepancy and decide a course of action.

   b. ECG without abnormal findings as read by site’s pediatric cardiologist: Upon completion of the eRT cardiologist’s evaluation, ECG results are faxed to the site in the form of a worksheet within 48 to 72 hours post receipt of ECG from site. If eRT reading of ECG does not confirm the reading by pediatric cardiologist at the site, the site’s principal investigator must contact the protocol team at actg.teamp1020@fstrf.org. A conference call will be scheduled to discuss the discrepancy and decide a course of action.

   c. Investigator must contact the protocol team at actg.teamp1020@fstrf.org. A conference call will be scheduled to discuss the discrepancy and decide a course of action.

Note:
eRT cardiologist’s hours are Monday-Friday 8:30 AM - 5:00 PM. If ECGs are sent on Friday for Saturday delivery, and preliminary results are required before Monday, you must contact the project manager to arrange for a weekend evaluation.

7. ECG Results Reporting:

   a. ECG Overview:

<table>
<thead>
<tr>
<th>Interval Measurements</th>
<th>Tracing Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-R Interval</td>
<td>Rhythm</td>
</tr>
<tr>
<td>PR</td>
<td>Conduction</td>
</tr>
<tr>
<td>QRS</td>
<td>Morphology</td>
</tr>
<tr>
<td>QT</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>QTc-Bazett’s Formula</td>
<td>ST Segments</td>
</tr>
<tr>
<td>QTc-Fridericia’s Formula</td>
<td>T Waves</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>U Waves</td>
</tr>
</tbody>
</table>

   b. Hard Copy Report Delivery Time: One original hard copy report is sent to the investigator within 7-10 days via two-day Federal Express.
8. ECG Label Completion Guide:

- Place one completed ECG label on each 12 Lead ECG that you are sending to eRT for analysis. Verify that the ECG label has the correct protocol number and site number. Use one label per subject, per visit. These ECGs will be used for archiving purposes.

- If there are multiple tracing pages, write the PID number on each page.

- When using the MAC®1200 enter PID#, visit, and ECG identifiers into the computer. Once the appropriate information is entered, it will appear on the ECG print-out.

- Consult the Visit Schedule to guarantee that the proper terminology is used to describe each visit.

- Misidentified ECGs will delay processing and reporting.

---

Notes:

To avoid any confusion that may delay reports, the following instructions explain the correct completion of an ECG label.

- Complete the PID Number in the “Sub #” field.

- Complete the subject’s Date of Birth using the DD/MMM/YYYY format.

- Complete the date of the ECG recording, using the DD/MMM/YYYY format.

- Complete the time that the tracing was recorded using a 24-hour clock (e.g. an ECG that was recorded at 2:15 PM would be written as 14:15).

- Sites must receive an approval notification for using the MAC®1200 by eRT, before sending any IMPAACT P1020A ECGs.
APPENDIX VII

GUIDE TO ANTIRETROVIRAL RESISTANCE MUTATIONS

This table gives an overview of the mutations associated with resistance to antiretrovirals, and only intends to help in the interpretation of the genotypic analysis results. Final decisions on subject eligibility based on resistance assay results will be made by the IMPAACT 1020 Protocol Team. If you have any questions regarding the interpretation of the genotypic assays when deciding on your subject’s future treatment, please contact the protocol team at actg.teamp1020@fsrif.org. The protocol chair and/or protocol virologist will answer your query.

Mutations Conferring Resistance to Antiretroviral Drugs
[Source: The Genotypic Antiretroviral Resistance Testing (GART) Table][12]
(Original table was modified by the IMPAACT 1020 Protocol Team to suit the specific needs of the protocol)

<table>
<thead>
<tr>
<th>Reverse Transcriptase Mutation</th>
<th>Expected Drug Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>75T</td>
<td>stavudine</td>
</tr>
<tr>
<td>215F/Y ± (41L, 67N, 70R, 210W, 219E/Q)</td>
<td>zidovudine</td>
</tr>
<tr>
<td>74V or 65R or 69D</td>
<td>didanosine, zalcitabine</td>
</tr>
<tr>
<td>184V</td>
<td>lamivudine; possible: didanosine, zalcitabine</td>
</tr>
<tr>
<td>M184V+(K65R or L74V)</td>
<td>possible: abacavir</td>
</tr>
<tr>
<td>RT44D and V118I</td>
<td>possible: lamivudine</td>
</tr>
<tr>
<td>215 F/Y + [74V or 65R or 69D]</td>
<td>zidovudine, didanosine, zalcitabine</td>
</tr>
<tr>
<td>151 M ± (62V, 75I, 77L, 116Y)</td>
<td>zidovudine, didanosine, zalcitabine, stavudine; possible: lamivudine</td>
</tr>
<tr>
<td>69SS</td>
<td>every nucleoside reverse transcriptase</td>
</tr>
<tr>
<td>E44D, V118I</td>
<td>inhibitor: lamivudine</td>
</tr>
</tbody>
</table>

---

APPENDIX VIII

TABLE TO DETERMINE 98TH PERCENTILE FOR PR-INTERVALS IN SUBJECTS <13 YEARS OF AGE

This table should be used when evaluating ECGs for subjects <13 years of age. This table is to be followed in conjunction with exclusion criterion 4.213, toxicity management section 6.115.1, and Appendix II-C. If you have any questions regarding the implementation of this table, please contact the protocol team at actg.teamp1020@fstrf.org.

98th Percentile for PR-Interval in Lead II


<table>
<thead>
<tr>
<th>Subject’s Age</th>
<th>PR-Interval (milliseconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 to &lt;6 months</td>
<td>150</td>
</tr>
<tr>
<td>≥6 to &lt;12 months</td>
<td>160</td>
</tr>
<tr>
<td>≥1 to &lt;3 years</td>
<td>150</td>
</tr>
<tr>
<td>≥3 to &lt;5 years</td>
<td>160</td>
</tr>
<tr>
<td>≥5 to &lt;8 years</td>
<td>160</td>
</tr>
<tr>
<td>≥8 to &lt;12 years</td>
<td>170</td>
</tr>
<tr>
<td>≥12 to &lt;13 years</td>
<td>180</td>
</tr>
</tbody>
</table>
APPENDIX IX

TABLE TO DETERMINE THE LOWER LEVEL OF NORMAL HEART RATE BY AGE

This table should be used when evaluating heart rates on ECGs performed for Screening and for on-study visits. This table is to be followed in conjunction with exclusion criterion 4.214, or toxicity management section 6.115.3. If you have any questions regarding the implementation of this table, please contact the protocol team at actg.teamp1020@fstrf.org.

Normal Heart Rate Ranges by Age

[Source: Van Hare GF, Dubin AM. The Normal Electrocardiogram in Moss and Adams, Heart Disease in Infants, Children and Adolescents. Allen HD, Gutgesell HP, Clark EB, Driscoll DJ EDS., 6th Edition. Lippincott Williams and Wilkins, Philadelphia, 2001; p430. (Original table labeled as Table 23B.2. Normal ECG Standards for Children by Age, was modified by the IMPAACT P1020A Protocol Team to suit the specific needs of the protocol)]

<table>
<thead>
<tr>
<th>Subject’s Age</th>
<th>≥3 to &lt;6 Months</th>
<th>≥6 to &lt;12 Months</th>
<th>≥1 to &lt;3 Years</th>
<th>≥3 to &lt;5 Years</th>
<th>≥5 to &lt;8 Years</th>
<th>≥8 to &lt;12 Years</th>
<th>≥12 to &lt;16 Years</th>
<th>≥16 to ≤21 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Heart Rate Range (bpm)</td>
<td>105-185</td>
<td>108-169</td>
<td>89-152</td>
<td>73-137</td>
<td>65-133</td>
<td>62-130</td>
<td>60-120</td>
<td>50-100*</td>
</tr>
<tr>
<td>Mean (bpm)</td>
<td>141</td>
<td>131</td>
<td>119</td>
<td>109</td>
<td>100</td>
<td>91</td>
<td>80</td>
<td>--</td>
</tr>
</tbody>
</table>

*Range values are 2nd to 98th percentiles.
*Normal heart rate range values for adults, reported by the American Heart Association.
APPENDIX X

DIVISION OF AIDS
International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)
SAMPLE INFORMED CONSENT

For protocol: IMPAACT P1020A

“Phase I/II, Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, atazanavir, ATV, Reyataz™) in Combination Regimens in Antiretroviral Therapy (ART)-Naïve and -Experienced HIV-Infected Infants, Children, and Adolescents”, VERSION 6.0

SHORT TITLE FOR THE STUDY: IMPAACT P1020A. “A PK and Safety Study of BMS-232632 in ART-Naïve and ART-Experienced HIV-infected Subjects 91 days to 21 Years of Age.”

INTRODUCTION

You/your child/your baby are/is being asked to take part in this research study because you/your child/your baby are/is infected with HIV. This study is sponsored by the U.S.A. National Institutes of Health (NIH) and it is being conducted in the United States of America and South Africa. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your child/baby to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You will be given time to think about participating in this study before signing this consent form. You are free to ask questions about this study at any time. If you agree to allow your child/baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

BMS-232632, also known as atazanavir, ATV, or Reyataz™, is a new anti-HIV drug, which has been approved by the U.S.A. Food and Drug Administration for treatment of HIV-infected adults. However, it is not approved for infants, children, or adolescents. This drug has not been approved by the Medicines Control Council (MCC) of South Africa.
BMS-232632 is in the class of drugs called protease-inhibitors. The study will evaluate if the capsule or the powder forms of BMS-232632, given alone or in combination with ritonavir (Norvir®) and two other drugs that also fight HIV, given to children or adolescents, is safe and decreases the amount of HIV in the blood. The study will also evaluate for how long this decrease might last. Ritonavir is another drug to fight HIV, which boosts up the capacity of BMS-232632 to fight HIV, when given in small amounts in combination with BMS-232632.

The specific purposes of this study are:

(1) To find out if BMS-232632 alone or in combination with ritonavir is a safe and effective treatment for HIV infection in children between the ages of 91 days and 21 years when given with two other drugs that also fight HIV (FDA approved drugs).

(2) To see if this is the correct dose of BMS-232632 alone or in combination with ritonavir to give safe and effective levels in blood.

BMS-232632 alone or in combination with ritonavir and the other two anti-HIV drugs will be given depending on your/your child's/your baby's history of previous drugs used to fight HIV. The study will enroll about 152 subjects who have never taken medications to fight HIV as well as subjects who have received anti-HIV drugs previously.

Subjects will receive BMS-232632 alone or in combination with ritonavir, as well as two of the following anti-HIV FDA approved drugs:

(1) Zidovudine (AZT, ZDV)
(2) Stavudine (d4T)
(3) Lamivudine (3TC)
(4) Didanosine (ddI)
(5) Zalcitabine (ddC)

Subjects may be randomized (assigned by a flip of a coin) to receive BMS-232632 alone or in combination with ritonavir depending on the results of blood tests from other subjects in this study.

This is an open-label study, meaning that you/your child baby will know what drugs and doses you/your child/your baby are/is given in the study. This study will provide free of charge the study drug, BMS-232632, and ritonavir. The other two anti-HIV drugs will be given by prescription.
WHAT DOES MY CHILD HAVE TO DO IF MY CHILD IS IN THIS STUDY?

Your baby is being asked to participate in Version 6.0 of this study. In this version, children who are 90 to 180 days old will receive BMS-232632. Your baby will remain on the study until BMS-232632 is approved and available in your local area. The study staff will inform you when it becomes available.

Children who are already enrolled in the study will be allowed to remain in the study until BMS-232632 is approved and available in both the United States and South Africa.

If your child is 2 years old and taking the powder form of the study drug, your child will be allowed to switch to the capsule form of the study drug. Your child will be allowed to take the capsule after they have completed week 56 PK test. This test will check to the amount of medicine that is in your child’s blood.

SCREENING VISIT

You/your child/your baby will have tests to find out if you/your child/your baby can enter the study. A complete medical history and physical exam will be done at this visit. About 3.0 teaspoons of blood will be drawn and a urine sample will be collected. If you/your child are/is a girl old enough to become pregnant, a second urine sample or a second blood sample will be collected for a pregnancy test at this visit. The amount of blood for this pregnancy test will be much less than 1.0 teaspoon.

If you/your child/your baby have/has previous treatment with anti-HIV drugs, blood will be collected to determine what kind of resistance (HIV drugs are no longer effective) to any of those previous drugs the HIV virus is already showing. This test will help the study team determine the best anti-HIV drugs to be used in your/your child’s/your baby’s new drug regimen.

On this visit, you/your child/your baby will have an electrocardiogram (ECG) done. Heartbeats (contractions of the heart) occur due to electrical current (electrical impulses), that are generated within the heart. The ECG measures the heartbeats (rhythms) and electrical impulses. During the test, you/your child/your baby will be asked to lie down. The person giving the test will place special stickers (electrodes) on your/your child’s/your baby’s arms, legs and chest. The electrodes are attached to a testing machine, which measures and records the electrical activity from the heart beats.
APPENDIX X (Cont.)

The ECG can easily detect any changes in the normal way of the heart beats (abnormalities of the electrical impulses that cause the heart to contract). This ECG will be used to determine if any of these possible abnormalities are present in you/your child’s/your baby’s heart. The pediatric cardiologist (a children’s doctor specialized in heart problems) at the site will discuss with you/your child the results of this test. The doctor will tell you/your child if any found abnormalities of your heart exclude you/your child/your baby from participation in the study.

If you/your child/your baby have/has had fainting spells (blacking-out or passing-out) that have not been completely and medically explained, you/your child/your baby will require a 24-hour continued ECG (this test is called Holter monitoring) at this visit. The results of this special ECG must show no serious electrical problems with the heart or heart-related reasons to your/your child’s/your baby’s fainting spells to allow your/your child’s/your baby’s participation in the study.

PRE-ENTRY VISIT

You/your child/your baby will need to come for a Pre-Entry Visit scheduled one to five days before starting study treatment. About 1.0 teaspoon of blood will be drawn.

ENTRY VISIT

You/your child/your baby will need to come to for an Entry Visit, which will be on the day that the BMS-232632 or BMS-232632 + ritonavir and the other two anti-HIV drugs are started (study treatment). In this visit, about 3.0 teaspoons of blood will be drawn for laboratory tests to determine if study medications may be started. These tests include determination of viral load (amount of HIV in bloodstream), the number of cells in blood that fight HIV (known as CD4+ cells counts), and to tell apart the specific kind of HIV virus circulating in the blood (qualitative microculture). Additionally, a complete medical history and physical exam will be performed at this visit.

In this version, the study will begin by enrolling five subjects. These initial subjects may establish the dose or BMS-232632 alone or in combination with ritonavir for each group. However, a second set of five subjects may be needed.

ON STUDY VISITS

At each one of these visits, a complete medical history and a physical examination will be performed, a urine sample will be collected and about 2.0 teaspoons of blood will be drawn for
APPENDIX X (Cont.)

laboratory tests. The blood tests will evaluate your/your child’s/your baby’s HIV viral load, CD4+ cell counts and the increase of the HIV in resisting the anti-HIV drugs used in the study. Additionally, if you/your child are/is a girl of childbearing age, a urine or blood pregnancy test will be done. The amount of blood for this pregnancy test will be much less than 1.0 teaspoon.

At Weeks 56, 96 visits and the last study visit (study-end or early termination), about 1.0 teaspoon of blood will be drawn to determine the changes of the HIV virus circulating in blood (as explained before this test is called qualitative microculture). After 1 week of receiving study treatment, and again after 56 weeks, about 3.0 teaspoons of blood will be drawn to determine how well the study medications are absorbed in your/your child's/your baby’s bloodstream (PK testing). For these blood tests, you/your child/your baby will stay in the clinic for up to 12 hours or overnight if the site requires. On the test-day you/your child/your baby will be asked to wait and take the study medications after you/your child/your baby come(s) to the clinic. Once you/your child/your baby have/has arrived to the clinic:

- you/your child/your baby will be offered a breakfast appropriate for age,
- blood will be collected when you/your child/your baby arrive(s) and at 1, 2, 3, 4, 6, 8, 12 and 24 hours after taking the study drugs.

If you/your child/your baby do not/does not stay overnight, you/your child/your baby will need to come on the following day for a final blood sample.

Also, if you/your child/your baby are/is regularly taking the study drugs at night, and do not switch to a morning dosing three days before the Week 56 visit, the PK testing will start in the late afternoon. Once you/your child/your baby have/has arrived to the clinic, you/your child/your baby will be offered a supper appropriate for age. Then, blood samples will be taken as previously explained.

For these PK tests, a heparin lock (a small needle that allows blood to be drawn over the course of a day without re-puncturing the vein) may be placed in one of your/your child's/your baby’s veins. This will be done to decrease the number of needle sticks.

Additionally, if the blood level of BMS-232632 is too low or too high, the dose may be changed and the PK testing will be repeated two weeks after changing the BMS-232632 dose to make sure that the new-dose is right.
APPENDIX X (Cont.)

If your child is 2 years old and taking the powder form of the study drug, your child will be allowed to switch to the capsule form of the study drug if he/she chooses. Your child will be allowed to take the capsule after they have completed the week 56 PK test.

On the PK test days, three ECGs will be done. The first one will be done when you/your child/your baby arrive(s) at the clinic and before receiving any study drugs, a second one two-to-three hours after receiving the study drugs, and a REG REVIEW one four-to-six hours after receiving the study drugs. These ECGs will be done to determine if the study drugs are causing changes to the way your/your child’s/your baby’s heart beats. The pediatric cardiologist at the site will discuss with you/your child the results of these tests, and will tell you/your child if they will exclude you/your child/your baby from continue taking the study treatment drugs.

If the ECG results are only slightly abnormal as determined by the pediatric cardiologist, you/your child/your baby will have to have a 24-hour ECG, the Holter monitoring. The pediatric cardiologist at the site will use the Holter monitoring results to determine if you/your child/your baby can continue taking the study treatment drugs. The results of the Holter monitoring will be discussed with you/your child.

Additionally, at Weeks 12, 24, 48, 72, 96, and every 24 weeks after Week 96 of treatment until the study-end, much less than 1.0 teaspoon of blood will be drawn. These blood tests will re-check the amount of BMS-232632 in the bloodstream.

Domestic Sites:

You/your child/your baby will have a study visit every 4 weeks until Week 48 of treatment. After Week 48, the study visits will be every 8 weeks until the end of the study for subjects in the United States of America. A notification from your/your child’s/your baby’s clinician will inform you when the study will end.

If your child is already enrolled in the study and taking the powder form of the drug, your child will be allowed to remain in the study until BMS-232632 is approved and available in both the United States and South Africa. Once your child has been on the study for about 6 months (Week 280), your child will have a study visits every 12 weeks until the end of the study.

We hope that medicines are taken as per doctor's orders, but we understand that this is not always possible. We need to understand the effect on your/your child’s/your baby’s virus of not being able to take the medicines every time, so you/your child/your baby will be asked several questions at some study visits. There will be two sets of questions given to you, (1) to determine
APPENDIX X (Cont.)

the amount of study drugs actually taken within the previous three days, and (2) to determine your/your child's/your baby's special reasons for non-taking each study drug.

International Site (IMPAACT Soweto)

You/your child/your baby will have a study visit every 4 weeks until Week 48 of treatment. After Week 48, the study visits will be every 8 weeks until the study ends in the United States of America. After the study has ended in the United States, you/your child/your baby will continue on study and will have a study visit every 12 weeks until BMS-232632 is approved in South Africa and it is available for distribution to you/your child/your baby off-study, which means that there will be no more clinic visits or laboratory evaluations related to this study, and that clinical care will continue based on your/your child’s/your baby’s doctor decisions. At each one of these study visits, once the United States part of the study has ended, you/your child/your baby will have the same type of evaluations as described above.

Once BMS-232632 is approved in South Africa and it is available for distribution to you/your child/your baby off-study, you/your child/your baby will go off-study, but we (IMPAACT Soweto Site and Bristol Myers Squibb) will continue providing off-study and free of charge to you/your child/your baby, the same anti HIV medicines until they no longer work for you/your child/your baby. Your/your child’s/your baby’s doctor will make this decision and will explain it to you/your child. Your/your child’s/your baby’s doctor and clinical staff will explain which laboratory tests will be needed off-study.

FOR NIAID SITES

Some of your/your child’s blood obtained as part of this study will be stored (with usual protectors of identification) and saved for future IMPAACT-approved HIV-related research.

You will be informed of the results of your/your child's/your baby’s tests done during this study.

If you/your child/your baby permanently stop(s) taking study drugs during the course of this study because of a side effect of a study drug, you/your child/your baby will return for clinic visits every 4 weeks until the side effect stops. During these visits, you/your child/your baby will be checked for any side effects of the study drugs and any new symptoms of HIV disease.

If you/your child/your baby permanently stop(s) taking study medications for any other reason, you/your child/your baby will be asked to return for all regularly scheduled clinic visits. The
APPENDIX X (Cont.)

tests collected at the early discontinuation visit will be the same as those to be administered on the last study visit and previously described in this informed consent form.

NICHD Sites:
Some of your blood specimens collected as part of this study will be stored for testing at a later date as part of this study. There is a separate consent form to explain this and get your/your child’s consent.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 5 children will take part in this version of the study. A total of 183 children are already in this study and are on study drugs.

HOW LONG WILL I BE IN THIS STUDY?

Domestic Sites

You/your child/your baby will be on study until the last subject enrolled into one of the groups receiving BMS-232632 and two anti-HIV drugs, or one of the groups receiving BMS-232632 + ritonavir and two anti-HIV groups, depending of which group you/your child/your baby is enrolled, has reached Week 96 of study treatment.

You/your child/your baby will be in this study for a minimum of 96 weeks and maximum of 384 weeks, depending when you/your child/your baby join(s), although it is not expected to go that far.

International Site (IMPAACT Soweto)

You/your child/your baby will be in this study for a minimum of 96 weeks. You/your child/your baby will remain on study treatment, receiving BMS-232632 or BMS-232632 + ritonavir and the other two drugs to fight HIV, until BMS-232632 is approved in South Africa and it is available for distribution to you/your child/your baby off-study.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you/your child/baby off the study early without your permission if:
APPENDIX X (Cont.)

- the study is cancelled by the U.S.A. Food and Drug Administration (FDA), National Institutes of Health (NIH), the South African Medicines Control Council for South African subjects, the drug company supporting this study (Bristol-Myers Squibb), or the site’s Institutional Review Board (IRB) or Ethics Committee.
- you are/your child/baby is not able to attend the study visits as required by the study

The study doctor may also need to take you/your child/your baby off the study drug(s) without your permission if:

- continuing the study drug(s) may be harmful to you/your child/baby
- you/your child/baby need(s) a treatment that you/your child/baby may not take while on the study
- you are/your child/baby is not able to take the study drug(s) as required by the study

If you/your child/baby must stop taking the study drug(s) before the study is over, the study doctor will ask you/your child/baby to continue to be part of the study and return for some regular study visits and procedures. If you decide to have no further contact, you/your child will be asked to come/bring your baby for a final early discontinuation visit.

WHAT ARE THE RISKS OF THE STUDY?

There is the risk of serious and/or life threatening side effects when non-study medications are taken with study drugs. For your safety, you must tell your/you child's/your baby's clinician and/or the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study. Other side effects besides those listed below and side effects from taking the study drugs together may occur. If any unusual symptoms or changes happen, you should call your/your child's/your baby’s doctor immediately. It is also important that while participating in the study, you/your child do(es) not take any other prescription drugs or over-the-counter medications without first talking to your/your child's doctor or study nurse.

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site.
Specific Protease Inhibitor Risks

The use of potent antiretroviral drug combinations (which commonly include a protease inhibitor) may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

The use of potent antiretroviral drug combinations (which commonly include a protease inhibitor) may also be associated with altered fat metabolism including elevated triglycerides and/or elevated cholesterol.

The use of protease inhibitors may be associated with the development of or the worsening of elevations in blood sugar and diabetes.

There have been reports of increased bleeding in HIV-infected person with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

BMS-232632 (atazanavir, ATV, Reyataz™) Risks

Bristol-Myers Squibb

BMS-232632 is a new protease inhibitor manufactured by Bristol-Myers Squibb (BMS) and is still undergoing early phase I and II studies in HIV-infected adults. For this reason a complete set of risk factors has not been issued by the manufacture. However, the following is a list of the observed side effects in some of the preliminary studies with this drug:

- Vomiting
- Headache
- Nausea
- Diarrhea
- Pain in joints and abdomen
- Lightheadedness
- Palpitations
APPENDIX X (Cont.)

- Abnormal electrocardiograms (very slow electrical conduction in the heart)
- Chest pain, pressure
- Fainting (syncope), blacking-out, passing-out
- Unexpected life threatening changes in the rhythm of the heartbeat (irregular heart beat or heart stoppage that stops blood flow to the body)
- Blood in urine (hematuria)
- Yellow skin (icteric), yellow eye-balls
- Enlarged liver

In these preliminary adult studies the most important side effect observed was hyperbilirubinemia or excessive amounts of bilirubin (a reddish-yellow pigment from the liver) in the bloodstream. This side effect can sometimes be managed by reducing the dose of BMS-232632, while maintaining the good effects of the drug. However, sometimes the drug has to be stopped completely.

Initial results from a study in HIV-negative adults receiving BMS-232632 established that there is a possible risk for this drug to produce abnormalities with the electrical impulses that control the heart beat. However, in the ongoing studies with this drug, there have not been any reported serious adverse events (SAEs) associated with these changes caused by the drug. It is unknown what the effect of BMS-232632 might have on subjects with pre-existing heart problems (cardiac dysfunction); worsening of heart problems (cardiac function and rhythm) may possibly occur.

The ECGs from approximately 48 children enrolled in the study prior to this Version of the protocol, accounting for more than one ECG per subject, found 14 abnormal ECGs, but no one with any symptoms of any heart problem. Abnormal ECGs (very slow electrical conduction in the heart or decreased number of heart beats per minute) may potentially result in abnormal heart rate, decreased heart rate, or missed heart beats. Causing dizziness, fainting, blacking-out, or passing-out.

This drug has been studied in HIV infected adults, but this is the first time this drug is studied in HIV infected children. This drug has been studied in animals. In addition to some of the risks seen above, the following side effects were seen in animals: low energy level, drooping eyelids, fatty liver, loss of balance when changing position, body tremors (shaking), an increase in fat (cholesterol) in the bloodstream, and an increase in chemicals in the bloodstream that may show a problem with the kidneys.

It is not known if humans can get these side effects. But, because this drug is new, it is important for you to be aware of these possible extra side effects and inform your study doctor right away if you get any of these.
Ritonavir (NORVIR®) Risks
Abbott Laboratories

- Stomach and bowel problems including abdominal pain, upset stomach, vomiting, abnormal stools, and loose or watery stools
- An increase in triglycerides
- Numbness and tingling in the arms, legs and around the mouth
- Rash
- Abnormal liver function tests
- Fever
- A change in the sense of taste

Specific Nucleoside Analogue Risks

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Lamivudine, 3TC (EPIVIR ®) Risks
GlaxoSmithKline

The following side effects have also been associated with use of lamivudine:
If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if lamivudine is stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

- Headache
- Feeling tired
- Dizziness
- Numbness, tingling, and pain in the hands or feet
- Depression
- Trouble sleeping
- Rash
APPENDIX X (Cont.)

- Upset stomach, vomiting, nausea, loose or watery stools
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Abnormal pancreatic and liver function blood tests

Zidovudine (RETOVIR®) Risks

GlaxoSmithKline

The following side effects have been associated with use of zidovudine:

- Decrease in the number of white blood cells that help fight infection
- Decrease in the number of red blood cells that may cause weakness, dizziness, and fatigue
- Muscle aches, weakness, and wasting
- Headache
- Upset stomach
- Vomiting
- Decrease in appetite
- Vague overall feeling of discomfort
- Lack of energy
- Feeling tired
- Sleeplessness
- Heartburn

Zalcitabine, ddC (HIVID®) Risks

Hoffman-LaRoche

The following side effects have been associated with the use of zalcitabine:

- Numbness, tingling, and pain in the hands or feet
- Inflammation or swelling of the pancreas with abdominal pain
- Rarely, life-threatening liver failure and death, possibly related to hepatitis B
- Mouth sores and throat sores
- Rash
- Allergic reaction such as an itchy rash
- Decrease in the number of white blood cells that help fight infection
- Changes in heart function that may result in shortness of breath
- Possibly associated with the development of cancer of the lymph nodes

Didanosine (VIDEX) Risks
Bristol-Myers Squibb

APPENDIX X (Cont.)

The following side effects have been associated with the use of didanosine:

- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Deaths from liver failure have been reported in pregnant women receiving the combination of didanosine and stavudine with other anti-HIV drugs.
- Numbness, tingling, and pain in the hands or feet
- Abnormal vision changes
- Upset stomach, vomiting and loose or watery stools
- Headache
- Abnormal pancreatic function blood tests or abnormal liver function blood tests
- Increase in uric acid in the bloodstream

When didanosine is used with other medicines with similar side effects, these side effects may be seen more often and may be more severe than when didanosine is used alone. People who take didanosine together with stavudine, with or without hydroxyurea, may be at greater risk for pancreatitis or liver problems or both. These conditions may result in death.

Stavudine (ZERIT) Risks

Bristol-Myers Squibb

The following side effects have been associated with the use of stavudine:

- Deaths from liver failure have been reported in pregnant women receiving the combination of stavudine and didanosine with other anti-HIV drugs.
- People who take stavudine together with didanosine, with or without hydroxyurea, may be at greater risk for pancreatitis or liver problems or both. These conditions may result in death.
- Numbness, tingling, and pain in your hands or feet
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Rash
- Upset stomach, vomiting and loose or watery stools
- Abdominal pain
APPENDIX X (Cont.)

- Abnormal liver function blood tests or abnormal pancreatic function blood tests
- Rare cases of muscle weakness, which may progress to paralysis and inability to breathe (This may be associated with elevation of lactic acid in the blood).

When stavudine is used with other medicines with similar side effects, these side effects may be seen more often, and may be more severe, than when stavudine is used alone.

**BLOOD DRAWING RISKS AND RISKS OF A HEPARIN LOCK**

Blood drawing may cause some discomfort, fainting, bleeding or bruising where the needle enters the body. A small blood clot may form at the site of venipuncture or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site.

**ELECTROCARDIOGRAM RISKS AND HOLTER MONITORING (24-HOUR ECG) RISKS**

There are no known side effects associated with ECGs. This test is fast, safe and does not require your/your child's/your baby's active participation.

**ARE THERE RISKS RELATED TO PREGNANCY?**

It is not known if the drug or drug combinations in this study harm unborn babies. Tests in pregnant animals do show some risk. The risks to unborn babies for each drug are listed in the section called “What Are The Risks Of The Study?” If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a female pregnant.

Because of the risk involved, you and your partner must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until three months after stopping study drug. You may choose two of the birth control methods listed below:

- Birth control drugs that prevent pregnancy given by pills, shots, placed on the skin (e.g. Patch) or placed under the skin
- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD)

If you are assigned to receive study drugs that do not require the use of two birth control methods, the study staff will discuss your options.
If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices.

**BREAST-FEEDING**

It is unknown whether the study drug or study drug combinations pass through the breast-milk and may cause harm to your infant.

Breastfeeding is not recommended under the U.S.A. guidelines for treatment of HIV-infected women. Additionally, breastfeeding is not allowed while participating in this study.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**

If you/your child/baby take(s) part in this study, there may be a direct benefit to you/your child/baby, but no guarantee can be made. It is also possible that you/your child/baby may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

**WHAT OTHER CHOICES DO I/DOES MY CHILD/BABY HAVE BESIDES THIS STUDY?**

Instead of being in this study you have the choice of:

- treatment with prescription drugs available to you/your child/your baby
- treatment with experimental drugs, if you/your child/your baby qualify(ies)
- no treatment

Please talk to your doctor about these and other choices available to you/your child/baby. Your doctor will explain the risks and benefits of these choices.

**WHAT ABOUT CONFIDENTIALITY?**

**Domestic Sites**

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the
United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).
People who may review your records include: the U.S.A. Food and Drug Administration (FDA), (insert Name of Site) IRB, National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

[The researchers should include language such as the following if they intend to make voluntary disclosure about things such as child abuse]

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. [The researchers should state here the conditions under which voluntary disclosure will be made]

International Site (IMPAACT Soweto)
Efforts will be made to keep your/your child’s/your baby’s personal information confidential. We can not guarantee absolute confidentiality. Your/your child’s/your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your/your child’s/your baby’s name of identify you/your child/your baby personally.

Your/your child’s/your baby’s records may be reviewed by the U.S.A. Food and Drug Administration (FDA), Medicines Control Council of South Africa, the University of the Witwatersrand--Human Research Ethics Committee (HREC), the U.S.A. National Institute of Health (NIH), study staff, study monitors, and Bristol Myers Squibb (pharmaceutical sponsor).

WHAT ARE THE COSTS TO ME?

Domestic Sites
APPENDIX X (Cont.)

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you/your child/baby is/are taking part in a research study.

Only BMS-232632 and BMS-232632 + ritonavir will be provided free of cost by the study, all other anti-HIV drugs that will be used as part of the drug cocktail will be given by prescription and charged to your regular health insurance company.

International Site (IMPAACT Soweto)

There will be no cost to you/your child/your baby for participation in the study. All study costs will be covered by the pharmaceutical sponsor (U.S.A. Bristol Myers Squibb) and the IMPAACT Soweto Site. Taking part in this study will not add costs to you and your/your child’s/your baby’s insurance company if you/your child/your baby have/has one. BMS-232632 and BMS-232632 + ritonavir will be provided free of cost directly through this study as study medications. The other two anti-HIV drugs will be given by prescription and provided free of cost through the IMPAACT Soweto Site Pharmacy.

WILL I RECEIVE ANY PAYMENT?

Domestic Sites

You/your child will not receive any payment for your/your child’s/your baby’s participation in the study.

International Site (IMPAACT Soweto)

You/your child will not be paid to participate in this study, but your/your child’s/your baby’s transport and, when necessary, refreshment costs will be reimbursed adequately.
APPENDIX X (Cont.)

WHAT ABOUT ETHICAL APPROVALS?

International Site (IMPAACT Soweto) (S.A. LEGAL REQUIREMENT)

- This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee.

- The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2000), which deals with the recommendations guiding doctors in biomedical research involving human subjects. A copy may be obtained from me (IMPAACT Soweto Site Principal Investigator) should you wish to review it.

- This study is funded by U.S.A. Bristol Myers Squibb and the IMPAACT.

I (IMPAACT Soweto Site Clinical Principal Investigator) do not have any financial or personal interests with this organization that may bias my actions.

WHAT HAPPENS IF I AM/MY CHILD/BABY IS INJURED?

Domestic Sites

If you/your child/baby are/is injured as a result of being in this study, you/your child/baby will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

International Site (IMPAACT Soweto)

Bristol Myers Squibb (Pharmaceutical Sponsor) has obtained insurance for you and me (Medical Staff) in the event of study related injury or illness. A study-related injury or illness is one that occurs as a direct result of the administration of the study medicine or of study-specific procedures.
Association of the British Pharmaceutical Industry (ABPI) STATEMENT ON COMPENSATION:

Bristol Myers Squibb (Pharmaceutical Sponsor) will provide compensation for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down by the ABPI Guidelines, and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.

- You must notify me immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered.
- If a research related injury occurs, you have not waived any of the legal rights which you otherwise would have as a participant in this study by signing this form.

Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from me (IMPAACT Soweto Site Clinical Staff providing care). I have a copy of the ABPI Guidelines and the Insurance Certificate, should you wish to review them.

The insurance does not cover and Bristol Myers Squibb (Pharmaceutical Sponsor) will not pay for:
- Medical treatment of other injuries or illnesses
- Injury caused by non-observance of the protocol

I (IMPAACT Soweto Site Clinical Staff administering care) am indemnified by Bristol Myers Squibb (Pharmaceutical Sponsor) conditional upon:
- My compliance with the applicable requirements of the study protocol
- My compliance with the regulations of the Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- The handling and administration of the study medication in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents
- The indemnification is not intended to be and is not a substitute for my personal malpractice insurance.

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical
APPENDIX X (Cont.)

study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child/baby to take part in this study or leave this study/take your child/baby out of the study at any time. You/your child/baby will be treated the same no matter what you decide.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

Domestic Sites

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your/your child’s/baby’s rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

International Site (IMPAACT Soweto)

For the duration of the study, you will be under the care of …… (INSERT NAME OF STUDY DOCTOR). If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact me.

Other doctors from this department who are working on this study are:

LIST CONTACT DETAILS AND DESIGNATION (PRINCIPAL INVESTIGATOR/CO- OR SUB-INVESTIGATOR) OF THE STUDY DOCTORS.
The 24-hour telephone number through which you can reach me or another authorized person, is …………………
APPENDIX X (Cont.)

- If want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2229.

- For research information you can contact ……… (NAME AND DESIGNATION OF DEDICATED PERSON – SPONSOR) at………………

- South African Medicines Control Council

  If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

  The Registrar
  SA Medicines Control Council
  Department of Health
  Private Bag X828
  PRETORIA
  0001

  Fax: (012) 323-4474

  e-mail: labusa@health.gov.za
SIGNATURE PAGE

Domestic Sites

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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<tbody>
<tr>
<td>Participant’s Legal Guardian (print)</td>
<td>Legal Guardian’s Signature and Date</td>
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<td>(As appropriate)</td>
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</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print)</td>
<td>Witness’s Signature and Date</td>
</tr>
<tr>
<td>(As appropriate)</td>
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</table>
SIGNATURE PAGE

International Site (IMPAACT Soweto)

I hereby confirm that I have been informed by the study doctor, ....... (INSERT NAME OF STUDY DOCTOR), about the nature, conduct, benefits and risks of clinical study “IMPAACT P1020A, A PK and Safety Study of BMS-232632 in ART-Naïve and ART-Experienced HIV-infected Subjects 91 days to 21 Years of Age.”

- I have also received, read and understood the above written information (Subject Information Leaflet and Informed Consent) regarding the clinical study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerized system by IMPAACT Soweto Site or on his behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

Subject:

<table>
<thead>
<tr>
<th>Printed Name</th>
<th>Signature / Mark or Thumbprint</th>
<th>Date and Time</th>
</tr>
</thead>
</table>

I, ....... (INSERT NAME OF STUDY DOCTOR), herewith confirm that the above subject has been fully informed about the nature, conduct and risks of the above study.

Study Doctor:

<table>
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<tr>
<th>Printed Name</th>
<th>Signature</th>
<th>Date and Time</th>
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</table>

Translator / other person explaining Informed Consent……………………………..(Designation):

<table>
<thead>
<tr>
<th>Printed Name</th>
<th>Signature</th>
<th>Date and Time</th>
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</table>

Witness (If applicable):

<table>
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<tr>
<th>Printed Name</th>
<th>Signature</th>
<th>Date and Time</th>
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</table>
FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at Repositories funded by the National Institute of Child Health and Human Development (NICHD)

PARENT FACT SHEET

When your child joins this NICHD sponsored Study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your child’s body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during a study are kept. Your child’s name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your child’s name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your child’s rights are being protected.

How will my child’s privacy be protected?

The only record that your child participated in this NICHD sponsored study is at the clinic where it is kept separate from your child’s health records and locked away.

Your child’s specimens in the repository will not have your child’s name on them. The specimens will have a special study code. It will be the same code that is on your child’s information in the NICHD sponsored Study from your child’s interviews and examinations. Again, none of this information will have your child’s name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.
Why wouldn’t I find out the results of the research using my child’s specimens?

You will not receive the results of research done with your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child’s specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child’s care right now, but they may be helpful to people like your child in the future. Your child’s specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my child’s specimens?

All of the studies to be done in the future on your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD sponsored Study has to be reviewed by a special committee of people known as an Institutional Review Board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you had agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my child’s specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my child’s specimens?
Appendix XI

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (insert title), your child is being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child’s time in this NICHD sponsored Study.

You do not have to agree to store your child’s specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child’s specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.
Appendix XI

TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child’s DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test.

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ___________________________  __________
    Parent or Legal Guardian Signature   Witness Signature   Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ___________________________
    Participant Signature   Witness Signature   Date

What are the special HIV-related studies that can be done with the repository specimens?
Appendix XI

Researchers in this study would also like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child’s genetic makeup.

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________  ___________________________  
Parent or Legal Guardian Signature  Witness Signature  Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________  ___________________________  
Participant Signature  Witness Signature  Date

What if I have more questions?
Appendix XI
If you have any questions about the repository, about storage, or the use of your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected from my child stored in the repository.

___________________________  ___________________________  
Parent or Legal Guardian Signature  Witness Signature  Date
Appendix XI

FACT SHEET and TEMPLATE CONSENT FORM for
Specimen Storage at the Repository of the National Institute of Child Health and
Human Development (NICHD)

YOUTH FACT SHEET

When you join this NICHD sponsored Study, you will be asked to consent to having some specimens that the doctor or nurse will take from your body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during the study are kept. Your name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your rights are being protected.

How will my privacy be protected?

The only record that you participated in this NICHD sponsored Study is at your clinic where it is kept separate from your health records and locked away.

Your specimens in the repository will not have your name on them, only a special study code. It will be the same code that is on your information in the NICHD sponsored Study from your interviews and examinations. Again, none of this information will have your name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.
Appendix XI

Why wouldn’t I find out the results of the research using my specimens?

You will not receive the results of research done with your specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your care right now, but they may be helpful to people like you in the future. Your specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my specimens?

All of the studies to be done in the future on your specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from you and others from this NICHD sponsored Study has to be reviewed by a special committee of people known as an Institutional Review board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the new study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give consent for the new study.

I gave my consent to testing my specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from you in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests or
Appendix XI

If these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (insert title), you are being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) taken from you. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your time in this NICHD sponsored Study.

You do not have to agree to store your specimens for future tests to take part in this study. You will not lose any benefits to which you are entitled if you decide against storing your specimens.

14.0 TEMPLATE CONSENT/ASSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your DNA).

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test.

I consent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ___________________________  
Participant Signature   Witness Signature   Date
Appendix XI

What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your DNA) either protects them or puts them at greater risk. It may be that researchers use some of your blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your genetic makeup.

I consent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

_________________________________________  ______________________________________
Participant Signature   Witness Signature   Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your samples, contact (Study personnel) at (phone). If you have questions about giving consent or your rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).
Appendix XI

I refuse to have any specimen collected for storage in the repository.

___________________________  ___________________________
Participant Signature   Witness Signature   Date