IMPAACT P1093

Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

Manual of Procedures

Version 5.1
19 September 2019
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| Section 5                                   | Protocol Implementation – Enrollment Onwards | Version 5.1 19 September 2019 | ● Modified Section 5.3 to incorporate edits and updates on protocol implementation  
|                                              |                  |                                                                            | ● Modified 5.3.1 language and guidance                                   |
|                                              |                  |                                                                            | ● Modified 5.3.2 language and guidance                                   |
|                                              |                  |                                                                            | ● Added 5.3.3 language and guidance on intensive PK sampling in a non-fasted state |
|                                              |                  |                                                                            | ● Added 5.3.4 language for procedures performed on the day of intensive PK sampling in a fasted or non-fasted state |
| Section 6                                   | Adverse Event Reporting | Version 5.1 19 September 2019 | ● No change from Version 5.0                                               |
| Section 7                                   | Laboratory Considerations | Version 5.1 19 September 2019 | ● No change from Version 5.0                                               |
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| Appendix I                                  | Genotyping (Virologic Failure) Specimens BRI PASS THROUGH NOTIFICATION | Version 5.1 19 September 2019 | ● No change from Version 5.0                                               |
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### IMPAACT 1093 Manual of Procedures

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1.0 Study Overview

P1093 is a Phase I/II multi-center, open-label non-comparative study of HIV-infected infants, children and adolescents aged ≥4 weeks to <18 years, and will evaluate the pharmacokinetic (PK) parameters, safety, tolerability and efficacy of dolutegravir (DTG) when administered both prior to starting, and in combination with optimized background therapy (OBT).

Each age cohort consists of two sequential stages: Stage I and II. The objectives of Stage I are to examine PK parameter after intense sampling and evaluate the short-term tolerability and safety of DTG in approximately ten participants allowing the selection of a dose for further study in Stage II. Those enrolled into Stage I will remain in Stage I for the duration of the study. Additional long-term safety and antiviral activity of DTG will be obtained by treating additional participants in Stage II at the accepted dose chosen from Stage I. Longer term safety and antiviral activity of DTG will be assessed from data obtained from those enrolled in Stage II as well as those in Stage I who initiated treatment at the chosen dose for the cohort and remained on this dose. Those enrolled into Stage II will remain in Stage II for the duration of the study. Participants in Stage I or Stage II will progress to the Long-Term Safety Follow-up once the participant has completed 48 weeks of drug and if they are still deriving benefit from the study drug.

Three different formulations of DTG will be evaluated in the following cohorts:

<table>
<thead>
<tr>
<th>COHORT</th>
<th>AGE AND FORMULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort I</td>
<td>Adolescents ≥ 12 to &lt;18 years of age</td>
</tr>
<tr>
<td></td>
<td>(film-coated tablets)</td>
</tr>
<tr>
<td>Cohort IIA</td>
<td>Children ≥ 6 to &lt;12 years of age</td>
</tr>
<tr>
<td></td>
<td>(film-coated tablets)</td>
</tr>
<tr>
<td>Cohort IIB</td>
<td>Children ≥ 6 to &lt;12 years of age</td>
</tr>
<tr>
<td></td>
<td>(granules for suspension or dispersible tablets)</td>
</tr>
<tr>
<td></td>
<td>Note: Dispersible tablets may also be evaluated in this cohort if requested by regulatory authorities.</td>
</tr>
<tr>
<td>Cohorts III</td>
<td>Children ≥ 2 to &lt; 6 years of age</td>
</tr>
<tr>
<td></td>
<td>(granules for suspension) - Closed to Enrollment</td>
</tr>
<tr>
<td>Cohort IV</td>
<td>Children ≥ 6 months to &lt; 2 years of age</td>
</tr>
<tr>
<td></td>
<td>(granules for suspension) - Closed to Enrollment</td>
</tr>
<tr>
<td>Cohort III-DT</td>
<td>Children ≥ 2 to &lt; 6 years of age</td>
</tr>
<tr>
<td></td>
<td>(dispersible tablets)</td>
</tr>
<tr>
<td>Cohort IV-DT</td>
<td>Children ≥ 6 months to &lt; 2 years of age</td>
</tr>
<tr>
<td></td>
<td>(dispersible tablets)</td>
</tr>
<tr>
<td>Cohort V-DT</td>
<td>Infants ≥ 4 weeks to &lt; 6 months</td>
</tr>
<tr>
<td></td>
<td>(dispersible tablets)</td>
</tr>
</tbody>
</table>

In Protocol Version 5.0, Stage I enrollment into Cohorts III-DT, IV-DT, and V-DT continues in Stage I until a minimum of 10 participants in each cohort AND a minimum of 8 participants in each of the weight band groups below, are enrolled:

a) 3 to < 6 kg
b) 6 to < 10 kg
c) 10 to < 14 kg
d) 14 to < 20 kg
2.0 Preparing for the Study

2.1 Investigator Responsibilities

IMPAACT P0193 must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP). Sites must also comply with the Division of AIDS (DAIDS) policies on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials, which are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following web site and must be followed throughout implementation of IMPAACT P1093:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

IMPAACT P1093 also must be conducted in accordance with the IMPAACT Network Manual of Procedures, as well as all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all applicable regulations, policies, and guidelines should be maintained in on-site essential document files. The IMPAACT Network Manual of Procedures is available at:

http://impaactnetwork.org/resources/policies-procedures.htm

The Investigator of Record (IoR), i.e., the Principal Investigator for the study, at each site must sign both a Protocol Signature Page (PSP) and a Form FDA 1572 to formally indicate his or her agreement to conduct the study in accordance with the protocol and all applicable regulations, policies, and guidelines. A copy of the PSP can be found in the IMPAACT P1093 protocol. A PSP must be signed by the IoR and uploaded to the DAIDS Protocol Registration System (DPRS) for all initial Protocol Version s, all full protocol amendments, and all letters of amendment (LOAs). Sites should keep copies of protocol signature page(s) and Form FDA 1572(s) on site with their essential documents.

The obligations and responsibilities assumed by the IoR when signing the Form FDA 1572 and PSP are listed on the respective forms, and for the 1572 available on the DAIDS Regulatory Support Center (RSC) web site:

https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms

Updates to the Form FDA 1572 should be submitted to the DAIDS Protocol Registration Office (PRO). The IoR may delegate his/her obligations and responsibilities for conducting IMPAACT P1093 to other study staff members; however, delegation does not relieve the IoR of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented on the site’s delegation log throughout study implementation. Note that no staff member should fulfill the IoR role in the IoR’s absence; full responsibility and authority over the protocol by anyone other than the IoR may only take place if an additional Form FDA 1572 is completed and submitted to DAIDS.

If there is a change in IoR, a revised Form FDA 1572 and a new PSP should be submitted to the DAIDS PRO. Sites should follow guidance in the current Protocol Registration Manual regarding procedures for a change in IoR with the DAIDS PRO. Outgoing investigators should complete the end of study financial
disclosure form(s) and close-out all delegation log entries. Incoming IoRs must complete required financial disclosure form(s), and complete a new delegation log, including obtaining study staff signatures. Additional details on financial disclosure form requirements for this study are provided in Section 1.1.2 below.

2.2 Financial Disclosure Requirements

In compliance with US Food and Drug Administration (FDA) regulations for studies conducted under an Investigational New Drug (IND) application, a financial disclosure form must be completed by the IMPAACT P1093 Investigator of Record (IoR) at each site as well as by each person listed on the Form FDA 1572 for this study. For IMPAACT P1093, the GSK/ViiV-specific financial disclosure forms must be used to disclose their own financial interests as well as those of their spouses and dependent children:

- Financial Disclosure Form A must be used and completed by each person listed on the Form FDA 1572 prior to the initiation of the study at the site and as a condition of study activation.

- Financial Disclosure Form B must be used in the event any information recorded on Form A changes over time. Likewise, if any new staff are added to the Form FDA 1572 after the study initiation date at the site (i.e., study activation), these staff must complete, sign, and file Form B on site before performing study-related activities. Additionally, Form B will be used at the completion of the clinical trial.

Sample financial disclosure forms may be found on the IMPAACT P1093 website. As specified in the DAIDS Protocol Registration Manual, original completed and signed forms must be filed on-site, along with the Form FDA 1572. Completed Form A do not need to be submitted to DAIDS PRO as part of initial protocol registration but must be filed and retained in the clinical research site’s regulatory binder along with the original and/or updated, signed Forms FDA 1572 for the study, and available for review by site monitors and other sponsor, IMPAACT, and FDA representatives.

Please note that the FDA requirement to maintain financial disclosure documentation for this study is separate and distinct from NIH requirements to identify conflicts of interest, which is done periodically through the Office of HIV/AIDS Network Coordination (HANC). While there may be some overlap in the information collected through these two mechanisms, financial disclosure documentation must be compiled and maintained on-site for each IND study conducted at each site.

2.3 Protocol Registration

The IMPAACT Operations Center will notify the DAIDS Protocol Registration Office (PRO) that sites with SIPs and Site Applications approved by the Protocol Team are permitted to submit for protocol registration for the study. After all required DRA and IRB/EC approvals are obtained, site staff are then responsible for submitting documentation of the approvals and other required documentation to the PRO. Further information can be found in Protocol Section 10.1 and in the DAIDS Protocol Registration Manual, which is available at:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

2.4 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals (as described above) and must complete study activation procedures with the Protocol Team. To help ensure site
readiness for study initiation, the Protocol Team has specified a set of study activation requirements that must be met to obtain approval to begin study implementation. These requirements are provided to sites from the IMPAACT Operations Center Clinical Trial Specialist (CTS) and provided below.

Preparatory Activities
- Protocol registration approval
  - Local regulatory approvals
  - Institutional approvals
  - National regulatory approvals

Laboratory Requirements:
- Laboratory Director CV
- Site SOP for local specimen handling and chain of custody maintenance related to primary study endpoints
- Site SOP for establishing/adopting/maintaining normal ranges
- Age and sex appropriate normal reference ranges
- DCLOT approval (for non-U.S. labs)
- Confirmation of required certifications (CLIA, VQA, IQA as applicable) for protocol-specified tests
- Appropriate validation for protocol-specified tests
- IATA specimen shipping certification (for at least 1 person)
- Obtain MTAs/STAs for specimen shipment to the US, end user/testing laboratory, or repository (if applicable/required)

Pharmacy Requirements
- Drug import permit obtained (if applicable)
- Confirmation of study drug on-site (if applicable)

Other Requirements
- Participation in study-specific start-up training
- GSK specific financial disclosure documents for all staff listed on the FDA 1572 form
- Data Management Requirements—to be specified by IMPAACT Data Management Center
- Delegation of Duties Log (Version 5.0)

3.0 Study Resources

This Section specifies the resources available to IMPAACT P1093 study site staff, including contact information, an overview of study-related informational resources, the Frontier Science Data Management Center (DMC) Portal, and other essential documents.

3.1 Study-Related Information and Communications

All IMPAACT P1093 visits and procedures must be conducted in accordance with the study protocol. The purpose of this manual is to supplement the protocol, not to replace or substitute for it. If this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center CTS of any such inconsistencies.

The Protocol Team has developed study-specific contacts for various types of issues and questions, as summarized below in Figure 3-1.
### Topic

**Clinical user support and adding site staff to protocol email group**

IMPAACT P1093 Protocol Team

**Contact**

User Support
user.support@fstrf.org

(include the protocol number in the subject line of your email message)

### Topic

**Any aspect of protocol interpretation or study implementation not listed below**

IMPAACT P1093 Protocol Team
impaact.teamp1093@fstrf.org

### Topic

**Clinical and toxicity management issues**

IMPAACT P1093 Protocol Team
impaact.teamp1093@fstrf.org

include the protocol number and PID in the subject line of your email message, as applicable)

### Topic

**Participant eligibility**

IMPAACT P1093 Protocol Team
impaact.teamp1093@fstrf.org

### Topic

**Co-enrollment**

IMPAACT P1093 Protocol Team
impaact.teamp1093@fstrf.org

### Topic

**Frontier Science DMC Portal and Medidata Rave study access**

User Support (FSTRF)
user.support@fstrf.org

or by phone: +716-834-0900 x7302

### Topic

**Subject Enrollment System**

DMC Randomization Support Office
rando.support@fstrf.org

or by phone: +716-834-0900 x7301

### Topic

**Study drug (other than study drug orders)**

IMPAACT P1093 Protocol Team
impaact.teamp1093@fstrf.org

### Topic

**Study drug orders**

Clinical Research Products Management Center

BIO.CRPMC.Ph@Thermofisher.com

(or by phone: +301-294-0741)

### Topic

**Expedited Adverse Event (EAE) Reporting**

DAIDS RSC Safety Office
DAIDSRSCSafetyOffice@tech-res.com

or by phone: 800-537-9979 or +301-897-1709

or by fax: 800-275-7619 or +301-8977-1710

### Topic

**DAIDS Adverse Experience Reporting System (DAERS)**

NIAID Clinical Research Management System

CRMSSupport@niaid.nih.gov

or by phone: 1-240-778-2517

(questions also may be submitted from within the DAERS application)

The IMPAACT P1093 protocol also details the circumstances in which Investigators of Record (IoRs) should consult with the Protocol Team. For ease of reference, a summary of issues requiring consultation with the IMPAACT P1093 Protocol Team is provided below in Figure 3-2. IoRs are also encouraged to contact the Protocol Team with any other issues, questions, or concerns related to study drug.
**Figure 3-2**
Requirements for Consultation with the IMPAACT P1093 Protocol Team

<table>
<thead>
<tr>
<th>Issues Requiring Consultation with the Protocol Team</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Implementation</strong></td>
</tr>
<tr>
<td>• A participant requires any of the disallowed medications listed in Protocol Section 4.3.2</td>
</tr>
<tr>
<td>• Adjusting a participant’s dose due to a weight change, per Protocol Section 5.1</td>
</tr>
<tr>
<td>• Selection of initial optimized background therapy (OBT), per Protocol Section 6.3.1</td>
</tr>
<tr>
<td>• Selection of initial empiric background therapy, per Protocol Section 6.3.2</td>
</tr>
<tr>
<td>• Requesting a change in ARV regimens, per Protocol Section 6.3.5 or re-optimization of background therapy after failure, per Protocol Section 6.5</td>
</tr>
<tr>
<td>• If a participant’s HIV-1 RNA PCR test results are not able to be entered into the Laboratory Data Management System (LDMS) within two weeks of sample collection.</td>
</tr>
<tr>
<td>• A participant is confirmed as a virologic failure, per Protocol Section 6.5</td>
</tr>
<tr>
<td>• A female participant with reproductive potential engaging in sexual activity that could lead to pregnancy is unable to utilize two forms of birth control, per Protocol Section 6.7.1</td>
</tr>
<tr>
<td>• A participant is pregnant, per Protocol Section 6.7.2</td>
</tr>
<tr>
<td><strong>Toxicity Management</strong></td>
</tr>
<tr>
<td><strong>General:</strong></td>
</tr>
<tr>
<td>• Grade 3, 4 and 5 clinical adverse events</td>
</tr>
<tr>
<td>• Grade 3 confirmed laboratory AEs within 72 hours of awareness</td>
</tr>
<tr>
<td>• Grade 4 and 5 laboratory AEs initial and confirmatory results within 72 hours of awareness</td>
</tr>
<tr>
<td><strong>Specific:</strong></td>
</tr>
<tr>
<td>• Liver Toxicities per Protocol Section 6.1.3 notify the Protocol Team by email within 24 hours of site awareness</td>
</tr>
<tr>
<td>• Confirmed decline in renal function per Protocol Section 6.1.4</td>
</tr>
<tr>
<td>• Confirmed proteinuria, per Protocol Section 6.1.5</td>
</tr>
<tr>
<td>• Symptoms consistent with peptic ulcer disease persist or worsen on symptomatic therapy</td>
</tr>
<tr>
<td>• Participants requiring anti-TB treatment that includes rifampicin</td>
</tr>
</tbody>
</table>
3.2 Frontier Science Data Management Center (DMC) Portal

The Frontier Science DMC Portal website provides information, documents and tools to assist site staff with the data management aspect of conducting IMPAACT studies, including blank Electronic Case Report Forms (eCRFs), eCRF Completion Guides, Participant Calendar, and the Subject Enrollment System. The DMC Portal can be accessed at https://www.frontierscience.org/portal

3.3 Medidata Rave

Medidata Rave is a clinical trials data management system created and maintained by Medidata Solutions, Inc. Sites will use Medidata Rave to complete all P1093 eCRFs and perform other data management activities for the study. In Rave, sites can enter, view, and modify data, perform quality assurance, respond to data queries, and generate a variety of reports. Medidata Rave can be accessed at https://login.imedidata.com

3.4 Study Web Page

IMPAACT P1093 study-related materials and information can be found on the study webpage of the IMPAACT website: https://impaactnetwork.org/studies/P1093.asp

Resources available on this site include:

- Current version of the protocol
- Current DTG dosing tables
- Current study implementation materials, including the Laboratory Processing Chart

4.0 Participant Accrual and Enrollment

The total sample size is up to 300. The target total number of evaluable participants at the accepted dose across all cohorts is 120.

4.1 Introduction to Informed Consent and Assent

This Section contains reference information and guidance for obtaining informed consent/assent in P1093. For this study, there are three separate consent forms, listed below.

1) Enrollment in Stage I (Protocol Appendix II),
2) Enrollment in Stage II (Protocol Appendix III) and
3) Specimen Storage and Future Use (Appendix IV).

The Specimen Storage and Future Use Consent Form (Appendix IV) was added in Protocol Version 4.0 for all participants. For NIAID sites in Protocol Version 3.0, consent for long term specimen storage was included in the stage-specific forms. For NICHD sites in Protocol Version 3.0 this form replaces the Fact Sheet and Template Consent Form for Specimen Storage at Repositories Funded by the NICHD. Consent for storage and future research use of blood and urine specimens may be declined, with no impact on study participation.

Note: For NIAID sites that participated in Version 3.0, the information in this consent form can be included in the stage-specific consent forms, as long as all of the information for specimen storage and future use contained in this form is included in the stage-specific consent form.
Informed consent/assent is a process by which an individual voluntarily expresses willingness to participate in research, after having been informed of all aspects of the research that are relevant to the decision. Informed consent and assent are rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent/assent process is described in greater detail below. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP) and the informed consent Section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for further information.

US regulations (45 CFR 46) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and by delegation of or to all study staff involved in the informed consent process, to deliver all required information to consenters.

Based on the reviews completed as part of the P1093 protocol development and study activation processes, there is adequate assurance that once a site-specific study activation notice has been issued, a site’s informed consent forms (ICFs) and informed assent forms include all information required by the regulations. However, responsibility for informed consent/assent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consenter/assenter
- Assure that informed consent/assent is obtained in a setting free of coercion and undue influence
- Confirm that the consenter/assenter comprehends the information
- Document the process

Further guidance related to each of these requirements is provided in Sections 3.2 - 3.5 below. Each site must have on file a study-specific SOP for obtaining informed consent/assent that addresses all aspects of the processes consistent with all applicable regulations, DAIDS policies and procedures, and protocol specifications. All sites must follow their SOPs consistently for all P1093 informed consent/assent processes. All site staff involved in obtaining informed consent/assent must be designated on the study-specific delegation of duties log and listed on the FDA Form 1572 for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR’s delegation to these staff.

4.1.1 Deliver all Required Information in a Manner that is Understandable to the Consenter/Assenter

The informed consent/assent process should be conducted in the consenter’s/assenter’s preferred language and should reflect whether the consenter is determined to be literate per site SOPs.

If the consenter/assenter is literate, begin the informed consent/assent process by providing the consenter (and assenter, as appropriate) with a copy of the ICF/assent to read. Also provide any other informational materials developed to complement the ICF/assent form. If the consenter/assenter is not literate, read the materials to him/her. After the consenter/assent has read the materials (or had them read to him or her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, you may note the main points described in each paragraph of the ICF and ask if the consenter/assenter has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the consenter/assent and discuss these thoroughly. Take as much time as needed to address each question or concern.
If the consenter/assenter is not literate, an impartial literate witness must be present during the entire informed consent/assent process. As part of the documentation steps detailed below, the witness will be asked to sign and date the ICF to attest that the information in the ICF was accurately explained to, and apparently understood by, the consenter/assenter, and that informed consent was freely given by the consenter/assenter. ICH-E6 identifies an “impartial” witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The IMPAACT Operations Center has previously received guidance from the US Food and Drug Administration’s GCP office stating that the witness need not be “totally unaffiliated with the study. It may be possible, for example, to designate a "participant advocate" who would be available at each site …” Sites with questions about who may serve as an impartial witness are encouraged to consult with their IRBs/ECs on possible options.

4.1.2 Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence

During informed consent/assent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also describe the alternatives to study participation and emphasize that the availability of medical care and other services routinely obtained from the study site institution will not be affected by the consenter’s/assenter’s decision whether or not to take part in the study. Encourage the consenter/assenter to take as much time needed — and to talk about study participation with others — before making a decision.

When a witness is present during the informed consent/assent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the consenter/assenter, with emphasis on the fact that the witness is there as a protection for the consenter/assenter, not as an agent of the study per se.

4.1.3 Confirm that the Consenter/assenter Comprehends the Information

The consenter/assenter must not be asked to agree to take part in the study, or to sign or make a mark on the ICF, until he/she fully understands the study. Study staff are responsible for ensuring that each consenter/assenter understands all aspects of study participation before signing or marking the ICF.

A variety of approaches can be taken to assess comprehension. One approach uses a semi-structured checklist to guide a discussion in which the consenter/assenter responds to open-ended questions designed to elicit understanding of key concepts. Sample checklists of this type are provided in the Section appendix. Other approaches may include documented discussions with the consenter/assenter as well as structured knowledge quizzes administered to the consenter/assenter.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of aspects of the study, study staff should review those aspects again until the consenter/assenter fully understands them. If after all possible efforts are exhausted, the consenter/assenter is not able to demonstrate adequate understanding, they should not be asked to sign or make a mark on the ICF. Similarly, if the consenter/assenter has concerns about possible adverse impacts if they were to provide consent or indicates that they may have difficulty adhering to the study requirements, they should not be asked to sign or mark the ICF unless or until such issues can be resolved to the satisfaction of the consenter/assenter and the IoR (or designee).
4.1.4 Document the Process

US regulations require that informed consent be documented through the use of a written informed consent/assent form approved by the IRB/EC and signed and dated by the consenter/assenter or the consenter’s/assenter’s legally authorized representative at the time of consent/assent.

To fulfill this requirement, all signature and date blocks on the ICF should be completed in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a consenter’s/assenter’s full surname, and it is strongly recommended that initials not be used in place of a consenter’s/assenter’s full first name. However, if a consenter/assenter commonly signs his/her name using an initial for the first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

If the consenter/assenter is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent/assent form and any other written information was accurately explained to, and apparently understood by, the consenter/assenter, and that informed consent was freely given by the consenter/assenter. The consenter’s/assenter’s printed name, signature, and signature date blocks on the ICF should be completed as described in the Section appendix.

The DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials lists detailed requirements and suggestions for documenting the informed consent process. Study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets similar to the examples provided in the Section appendix. Sites choosing to use coversheets should identify the coversheets as source documents in their study-specific SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consenter/assenter. All informed consent documentation must be maintained on file in participant study records.

In addition to completing the documentation requirements of the ICF itself, each informed consent/assent process should be documented in a signed and dated chart note. The note should document that informed consent/assent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent Section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Informed consent will also be documented on study case report forms (CRFs). Consent decisions for storage and future research use of blood specimens will be recorded on the Specimen Consent/Deconsent Tracking for Non-Protocol Defined Testing CRF (TRK0103).

Regulations require that consenters/assenters be given a signed copy of their ICF. If a consenter/assenter opts not to receive a copy, this should be documented, and the consenter should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF.

4.2 Screening

Refer to Protocol Section 4.4 for an overview of participant recruitment, screening, and enrollment processes for this study. When a potentially eligible participant is identified, the adolescent participant and/or the parent/legal guardian of the infant/child participant will be informed about the study and asked to provide written informed consent/assent per Protocol Section 10.3. Study-specific procedures may not
be performed before written informed consent is obtained. Refer to Section 3.5 of this manual for an overview of general considerations for obtaining informed consent.

Individuals identified as ineligible for the study should be referred for non-study care and treatment as needed. The P1093 Screening Failure and Non-Enrollment Results eCRF (SCR0035) must be completed for each participant who provides informed consent but does not enroll in the study for any reason. Study sites should complete this eCRF as soon as possible after ineligibility is determined so that reasons for non-enrollment can be carefully tracked by the Protocol Team.

Study sites are required to document all screening (including screening failures) and enrollment activity on screening and enrollment logs. Screening and enrollment/randomization logs may be separate or combined. A screened participant is defined as having signed the screening or study consent.

For additional information, refer to the Essential Documents Recordkeeping Requirements appendix available at: https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf

4.3 Screening/Enrolling – Using the Subject Enrollment System (SES)

The Protocol Team will notify the sites in real-time the status of the open cohorts and stages (i.e. open or closed) and the DTG dose. Protocol Version 5.0 Dosing Tables can be found on the P1093 Protocol-Specific Web Page at:

http://impaactnetwork.org/studies/P1093.asp

1. Sites MUST receive a Site Activation E-mail correspondence from the IMPAACT Operations Center (FHI).

2. **BEFORE screening**, after obtaining written informed consent, sites must utilize the PS2001 IMPAACT Screening System to obtain a screening number. This can be found on the DMC Portal:

   - Under ‘Systems’
   - Click ‘Subject Enrollment’

<table>
<thead>
<tr>
<th>Systems (Skip)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Submission System (DSS)</td>
</tr>
<tr>
<td>Order Entry Program</td>
</tr>
<tr>
<td>Resolve</td>
</tr>
<tr>
<td>Subject Enrollment</td>
</tr>
<tr>
<td>eData Distributions</td>
</tr>
</tbody>
</table>

   - The PS2001 IMPAACT Screening Checklist can be found in the study drop down menu (at the end of the list).
3. **BEFORE screening**, sites must email the Protocol Team at impaact.teamp1093@fstrf.org to request a screening slot. In the email message, sites must include the following information:

- Cohort and Stage requested
- Participant age and DOB
- Participant current weight
- Screening number (PID number is optional)
- Planned screening date
- Previous and current ARV regimens with dates (including agents for prophylaxis as PMTCT, where applicable)
- Pre-screening Viral Load result and date available in medical record from the 4 – 12 weeks prior to the planned screening visit date
- Anticipated DTG dosing table (based on current weight)

4. The Protocol Team will review the status of the study and decide whether the individual may be screened or not. **Sites MUST wait to receive permission (GRANTED SLOT) from the Protocol Team in order to proceed with screening evaluations.** An email will be sent by the protocol data manager with the subject “P1093-Request granted to screen PS______”. **IF a screening slot is not currently available for the individual, they will be added onto a waiting list.**

5. **BEFORE enrolling a participant**, sites MUST email the Protocol Team (impaact.teamp1093@fstrf.org) the results of resistance testing and the proposed OBT regimen for
If approved, the Protocol Team will notify the site and if all other eligibility criteria are met, the site can proceed with enrollment.

**NOTE:** Participants < 2 years of age (Cohorts IV-DT, and V-DT) and participants ≥ 2 years of age who are ARV-treatment naive can enroll with genotype results pending, but sites must still email the Protocol Team and indicate that the participant belongs to this group. The site needs to timely communicate the genotype results to the Protocol Team when available.

6. If any individual is consented but DOES NOT enroll for ANY reason, sites MUST notify the Protocol Team of the screening failure and then complete the P1093 Screening Failure eCRF (SCR0035 - P1093 Screening Failure and Non-Enrollment Results) as soon as possible. Note that the SCR0035 eCRF will not be available for keying in Medidata Rave until after the Protocol Data Manager is notified of the screening failure.

### 4.4 Eligibility Determination

The eligibility criteria are specified in Protocol Sections 4.1 and 4.2.

It is the responsibility of the IoR and other designated study staff to ensure that all required assessments are performed and adequately documented, and that only eligible participants who meet eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. In the event that study staff identify that an ineligible participant has been enrolled, the Protocol Team should be consulted immediately.

**Baseline Genotyping**

- At screening, blood should be collected for resistance testing (genotyping).

- This specimen MUST be sent in REAL time to the appropriate location (see the Laboratory Processing Chart for further instructions). Depending on the location of the clinical site, the closest approved laboratory for genotyping may be in-country or out of the country (refer to the Laboratory Processing Chart (LPC)).

- If sending the screening genotype sample to the University of Washington (UW) include the UW requisition form found on the P1093 website:

  http://impaactnetwork.org/studies/P1093.asp

- Turnaround time for the genotyping results will vary for each specialty lab, but is typically approximately 2 weeks from receipt of the sample.

**Baseline Phenotyping**

- At screening, blood should be collected for resistance testing (phenotyping). This test will NOT be run in real time – specimens should be stored at the local site.
5.0 Protocol Implementation – Enrollment Onwards

5.1 Enrollment/Entry

- Please note there will be a waiting list for enrollment into this study if there are not sufficient slots available in a cohort at any particular time.
- The Protocol Team will notify sites in real time regarding the status of the Stage I: mini-cohorts and the full cohorts (i.e., open or closed).
- Once a site has an individual that they want to screen, they must follow the screening procedures as described in Section 3.7 above. If the individual is eligible, based on the screening results, sites may enroll the individual as they would normally through the enrollment system. Sites should note that to be able to complete enrollment, they must have the screening number available.
- Once enrolled into the P1093 study, the following procedures should be completed:
  — Entry visit should be completed within 30 days of the screening visit
  — Refer to the appropriate Schedule of Evaluations (SoEs), Protocol Appendices IA-IG for required clinical and laboratory evaluations for each specific cohort and stage
  — Study drug should also be distributed at this visit
  — Stage I - The participant should be scheduled to come back for the Intensive PK visit between Day 5 and Day 10
  — Refer to Protocol Section 6.3 for instructions on initiation of DTG and Optimized Background Therapy (OBT)

NOTE: Please refer to Section 4.3.2 and Table 11 in the protocol for a list of disallowed ARV Medications prior to intensive PK sampling in Stage I.

Refer to Appendix V Dosing Instructions Dispersible Tablets for instructions for the parent/legal guardian/caregiver on administering the dispersible tablets.

5.2 Microalbumin/Creatinine (M/C) Ratio Laboratory Tests

M/C ratio urine specimens collected at time points indicated in the SoEs must be shipped in REAL TIME, as described in the Lab Processing Chart.

5.3 Stage I: Intensive PK Visit

Intensive PK sampling will generally be done in a fasted state, per Protocol Sections 9.2.1.1 and 9.2.1.2, unless notified by the Protocol Team that PK sampling should be done in a non-fasted state, per protocol Section 9.2.1.3. This section provides additional guidelines regarding intensive PK sampling as well as specific instructions for fasting and non-fasting.

5.3.1 Preparing for the Intensive PK visit

Prior to Scheduled Intensive PK Sampling Visit participants should be reminded of the following:
— The dates and times of the intensive PK sampling.
— The three doses of DTG taken prior to the intensive PK visit should be taken at approximately the same time of the scheduled PK visit.
— The actual dose, in the unit of mg (not the number of tablets or volume of solution), date and time of the three doses of DTG and all background ARVs taken prior to the scheduled PK visit, must be recorded.
— Reasons to reschedule:
  - If any dose is missed within 3 days prior to the scheduled PK visit; the PK visit will need to be rescheduled between 3-7 days later
  - If there is concern that drug exposure/absorption may be comprised due to a recent or current illness (i.e. vomiting or diarrhea), concomitant medications, or any other reason the Protocol Team should be contacted regarding re-scheduling.

5.3.2 Intensive PK Sampling in a Fasted-state

Participants undergoing intensive PK sampling in a fasting state should be reminded of the following:

Cohorts I, II, III, and III-DT:
— ≥6 hours PRIOR to dosing – participants may eat and drink without restriction
— ≥4 to <6 hours PRIOR to dosing – milk, apple/orange juice and water may be consumed; No food
— <4 hours PRIOR to dosing – water ONLY
— From dosing to <2 hours POST dose – apple/orange juice and water may be consumed; no food
— From ≥2 to <4 hours POST dose – participants may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)
— From ≥4 hours POST dose onwards – participants may eat and drink without restriction

Cohorts IV, IV-DT, and V-DT
Participants should not ingest breastmilk, formula, or any other high fat food/liquid for two hours prior to and one hour after dosing on the intensive PK day. Water and other fluids (i.e., apple/orange juice, with the exception of grapefruit juice and oral rehydration solution) can be taken at any time. Participants may consume a light meal of their choice four hours after dosing on the intensive PK day.

Day of intensive PK Sampling Participant Management:
— For participants who vomit within four hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the following 3-7 days
— Document the exact time the DTG dose is taken on the day prior to the PK visit to ensure that the dose taken the following day (PK visit day) is as close as 24 hours from the previous dose (a window of 22-26 hours is allowed)

5.3.3 Intensive PK Sampling in a Non-Fasted State
Participants should abstain from eating or only eat a light snack prior to coming to the clinic. On the day of intensive PK sampling, participants must eat at the clinic, under observation, following the guidelines below.

- Participants must eat at the clinic, under direct observation of site staff, prior to PK sampling.
  - Document the total amount of food consumed and which foods were consumed (solids and liquids, except water) and the date and time the meal was started.
  - The total amount of food consumed must be ≥ 64 g*, 4 oz, or 125 ml. This includes any solid food such as: porridge, rice, egg, fruit, meat as applicable by age.
  - Liquids including milk and juice may accompany the solid food intake, but do not count towards the minimum food requirement for the total amount of food consumed. The volume of milk or similar product should be quantified. This is not required for juice.
  - DTG current dose can be administered from any time after food intake is started and up to 15 minutes after food intake is finished.
  - For participants who vomit within 4 hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the following 3-7 days.
  - Document the exact time the DTG dose is taken the day prior to the PK visit to ensure that the dose taken the following day (PK visit day) is as close as 24 hours from the previous dose (a window of 22-26 hours is allowed).

*64g was chosen as the optimal amount for a child weighing 14-20kg. As an example, 64g is slightly more than one large egg (56g) or 4 ounces of milk (61.2g) Another example for yogurt is half a cup of yogurt is 122.5 grams and 4.3 ounces.

5.3.4 Intensive PK (Day 5-10) – Stage I

General Instructions for Procedures Performed on the Day of Intensive PK Sampling in a fasted or non-fasted state:

- Refer to the SoEs Protocol Appendix I for required clinical and laboratory evaluations for each specific cohort and stage.
- Participants should not miss any of their DTG doses in the 3 days prior to the intensive PK visit.
- Food and liquids may be consumed as detailed above depending on whether the participant is undergoing intensive PK sampling in a fasted or non-fasted state.
- Review any participant documentation of prior dosing and food and/or drink consumption; collect undocumented information by verbal interview. Example templates of PK medication and food history logs are available in Appendix I to assist participants with keeping track of previous dose and meal information. Sites may print copies of these templates should they wish to provide participant with a collection tool.
- Collect the pre-dose PK sample as close as possible to 24 hours after the participants last dose of DTG (within a target window of 22 to 26 hours).
- Administer DTG dose and record actual dose, date and time of the dose administration. The actual dose taken needs to be recorded in the mg unit, not number of tablets or volume of solution.
— Record whether or not the participant vomited within 4 hours after dosing.
— For participants who vomited within 4 hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the following 3-7 days.
— Collect the remaining PK samples at time points specified in the protocol.
— Remind the participant to return to the study site on the following day for collection of the 24-hour PK sample.
— Remember to complete the time unit in the LDMS (see Laboratory Processing Chart for more information).

Record on the eCRF:
— The dates, times, and amounts (in the unit of mg) of the three doses of DTG, as well as all background ARVs, administered prior to the PK visit and the dose administered at the PK visit; the actual dates, times, and doses should be recorded even if they are off-schedule.
— If fasting: whether or not the participant fasted prior to drug administration. Also document any food and liquid that was consumed by the participant during the 0-4 hours post-dose period.
— If non-fasting: whether or not the participant consumed food and liquid as described above; the total amount of food consumed and the actual foods and liquids consumed should be recorded. Also document the start time of the food intake.

When should an intensive PK visit be rescheduled?
— If the site investigator is concerned that drug exposure/absorption may be comprised due to a recent or current illness (i.e. vomiting or diarrhea), concomitant medications, or any other reason. The Protocol Team should be contacted regarding re-scheduling
— If a dose was missed on any one of the 3 previous days
— The participant did not take the DTG dose in the clinic
— The participant vomited within 4 hours after dosing
— If fasting: the participant did not fast as specified above
— If non-fasting: the participant did not consume food as specified above.
— The intensive PK visit MUST be rescheduled AND completed within 3-7 days of the original intensive PK visit. If this timeline cannot be met, sites should contact the Protocol Team for guidance (impaaact.teamp1093@fstrf.org).

5.4 Study Visits – Week 4, 8, 12, 16, 24, 32, 40, 48

• Refer to the appropriate SoEs, Protocol Appendixes IA-IG for required clinical and laboratory evaluations for each specific cohort and stage.
• Please note that weight should be obtained and recorded as part of the physical exam performed at each visit. Remember that an increase in the participant's weight may require a change in the DTG dose. If a dose change is required, weight change is listed as a reason for change on the treatment record eCRFs.

5.5 Population PK Visits – Stage I and Stage II
5.5.1 Objectives of Pharmacokinetic (PK) Evaluation

- Characterize the pharmacokinetics (drug concentration change over time) in participants.
- Evaluate the effect of participant characteristics (i.e., age, gender, race, weight, liver function, concurrent medication, and disease stage) on PK.
- Assess the relationship between PK and drug effect (antiviral activity/response, and experience of AEs).
- Determine appropriate dose(s) in various participant populations or the need of dose adjustment for individual participants.

5.5.2 Before the Population PK Visit

NOTE: Participants DO NOT need to be fasting prior to any of the population PK visits.

- Provide participant or caregiver with a diary card or discuss alternative methods to record DTG dosing history at the visit before the PK sampling visit.
- Instruct the participant or caregiver that he/she must record the time they took their dose of DTG on each of the 3 days prior to the PK sampling visit.
- Please note that participants must take their DTG dose in the 3 days prior to the PK sampling visit at a time in the day that corresponds to the time their next visit is scheduled.
- You must call the participant on the phone 4 days, then 1 day prior to the PK visit with reminders concerning dose times. Remind them to take their dose of DTG on the day of PK sampling visit under observation at the clinic.

5.5.3 Week 4 Population PK

- Review DTG dosing prior to collecting any blood sample.
- Blood draws for Week 4 population PK (see below for additional instructions):

  Pre-dose (0.5mL)

  2-4 hours post-dose (0.5mL)

- The pre-dose population PK sample should be collected as close as possible to 24 hours after the participant's last dose of DTG (i.e., within the target window of 20 to 26 hours). For example, if the dose was taken at 07:00 am the day before the PK visit, the pre-dose blood sample must be taken within the target window between 03:00am-11:00am on the day of the PK visit.
- The pre-dose sample will be collected immediately before the clinic dose (i.e., within 15 minutes), which will be taken under observation at the clinic.
- Administer DTG.
- Record whether or not the participant vomits after dosing.
- Collect the post-dose PK samples at 2 to 4 hours after the participant's witnessed dose.

5.5.4 Week 12 Population PK

- Review DTG dosing with the participant prior to collecting any blood sample.
• Blood draws for Week 12 population PK (see below for additional instructions):

  ONE blood draw: any time point post-dose (0.5mL)

• The population PK sample at Week 12 should be collected anytime within the 24 hours following the previous dose. For example, if a participant normally takes their dose at 8am each day, the participant should come into clinic sometime between 8am (after their dose) but before 8am the following day.

5.5.5 Week 24 Population PK

• Review DTG dosing history prior to collecting any blood sample.
• Blood draws for Week 24 population PK (see below for additional instructions):
  o TWO blood draws: two hours apart any time within 12 to 26 hours post-dose (0.5mL each draw)

5.5.6 Re-Scheduling a Population PK

Population PK sampling should be rescheduled for the next 3-7 days if any of the following situations occur:

• If a dose was missed on any one of the 3 previous days
• The participant did not take the DTG dose in the clinic (if applicable).

5.6 Virologic Failure

If a participant appears to be experiencing virologic failure (as defined in Protocol Section 6.5), the following procedures should be completed:

5.6.1 Consult the Participant

• Inadequate adherence is a common cause for virologic failure and should be explored as a first step in the management of study participants (e.g., at the first indication of inadequate virologic response or rebound).
• Upon notification that a participant’s HIV-1 RNA plasma level qualifies them as a suspected virologic failure, the investigator should query the participant regarding intercurrent illness, recent immunization, or interruption of therapy.

5.6.2 Perform Repeat HIV-1 RNA PCR

A confirmatory HIV-1 RNA sample must be collected ≥ 1 week to ≤ 4 weeks after the date the initial HIV-1 RNA sample suggesting HIV virologic failure or rebound was collected, per Protocol Section 6.5 and the Confirm Suspected Virologic Failure column in the appropriate SoE, Protocol Appendices IA-IG. If a sample cannot be obtained by 4 weeks, samples should be collected as soon as possible beyond 4 weeks from the date of the original sample.
5.6.3 Managing Confirmed Virologic Failure/Endpoint Cases

- If this second viral load test confirms the initial suspected virologic failure (i.e., > 1000 c/ml), the participant should have a “Virologic Failure Visit” which clinical and laboratory evaluations (refer to Virologic Failure column in the appropriate SoEs (protocol Appendices IA-IG) as soon as possible (within 1 to 4 weeks of the confirmatory sample results).

- At the virologic failure visit, blood should be collected for resistance testing (genotyping) and for phenotyping.

- The plasma specimen for genotyping MUST be sent in real time to the Seattle Children’s Research Institute (SCRI) Lab, LDMS lab 238. Please refer to the Laboratory Processing Chart for specific instructions regarding collection, processing and shipping of these specimens. [Please note US sites - Ship Real Time to LDMS LAB 238; Non-US sites ship real-time to BRI as pass through]. The P1093 Specimen Testing Requisition must be included with each shipment. This form and the Laboratory Processing Chart can be found on the Protocol Specific Web Page at the following address: http://impaactnetwork.org/studies/P1093.asp and in Appendix IV of this document.

- If the viral load data is not available on specimen’s ship date, please send the viral load results by email to sheila.styrchak@seattlechildrens.org or ingrid.beck@seattlechildrens.org, as soon as possible. Specimens for resistance testing will not be processed until viral loads are received. Please note the viral load result should correlate with the specimen that is being sent for resistance testing; the viral load result should not be from a specimen collected at an earlier/different time point.

- Upon shipment of a specimen for genotyping testing, please e-mail the Protocol Team at impaact.teamp1093@fstrf.org and include the PID number, CRS number and shipment date so the team can track the specimen and the results.

- Turnaround time for the genotyping results will vary but is typically approximately 2-3 weeks from initial shipment. Results from the genotyping will be made available to the site investigator as soon as they are available.

- The plasma specimen for HIV phenotyping should be stored at the local site until requested for shipment. Please see the Laboratory Processing Chart for instructions.

- Protocol Section 6.5 of the protocol explains the participant’s protocol-based treatment options if they reach virologic failure.

6.0 Adverse Event Reporting

6.1 EAE Reporting

Refer to Section 7 of the protocol and the following resources to guide EAE reporting for this study:

- DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians
- Investigator’s Brochure for DTG
6.2 AE Relationship Assessment

For purposes of *toxicity management* — as specified in Protocol Section 8 — the IoR or designee must assess the relationship of all AEs identified in enrolled infants to study drug according to the categories shown in Figure 6-1. The categories are also used when recording AEs on CRFs.
### Figure 6-1
Relationship Assessment Categories for Toxicity Management

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td>The event and administration of the medication are related in time, and a direct association can be demonstrated.</td>
</tr>
<tr>
<td>Probably related</td>
<td>The event and administration of the medication are reasonably related in time, and the event is more likely explained by the medication than other causes.</td>
</tr>
<tr>
<td>Possibly related</td>
<td>The event and administration of the medication are reasonably related in time, and the event can be explained equally well by causes other than the medication.</td>
</tr>
<tr>
<td>Probably not related</td>
<td>A potential relationship between the event and the medication could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than the medication.</td>
</tr>
<tr>
<td>Not related</td>
<td>The event is clearly explained by another cause not related to the medication.</td>
</tr>
</tbody>
</table>

For purposes of **EAE reporting**, the IoR or designee must report the relationship of EAEs to the investigational dose of DTG to the categories shown in Figure 6-2.

### Figure 6-2
Relationship Assessment Categories for EAE Reporting

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Related               | There is a **reasonable possibility** that the EAE may be related to the investigational dose of maraviroc. Consistent with ICH guidance, the term “reasonable possibility” is intended to convey that there are facts, evidence, or arguments to suggest a causal relationship between the EAE and the investigational dose of maraviroc. Facts, evidence, and arguments that may support a reasonable possibility of a causal relationship include:  
  • A temporal relationship between the EAE and use of the drug  
  • A plausible biologic mechanism for the drug to cause the EAE  
  • Previous reports of similar events associated with the drug (or drugs of the same class)  
  • Resolution of the event after de-challenge (hold/discontinuation of drug)  
  • Recurrence of the event after re-challenge (resumption of drug after a hold)  
  Other potential causes of the EAE (e.g., past medical history, concurrent illness, concomitant medications) should also be considered when assessing whether there is a reasonable possibility that an EAE may be related to the investigational dose of maraviroc. |
| Not related           | There is **not** a reasonable possibility that the EAE may be related to the investigational dose of maraviroc. |
Figure 6-3 presents how the five relationship categories used for toxicity management should be mapped to the two relationship categories used for EAE reporting.

### Figure 6-3
Mapping of Relationship Categories for Toxicity Management to Relationship Categories for EAE Reporting

<table>
<thead>
<tr>
<th>Relationship Category for Toxicity Management</th>
<th>Maps To</th>
<th>Relationship Category for EAE Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Probably related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Possibly related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Probably not related</td>
<td></td>
<td>Not related</td>
</tr>
<tr>
<td>Not related</td>
<td></td>
<td>Not related</td>
</tr>
</tbody>
</table>

### 6.3 Abacavir (ABC) Hypersensitivity Reaction (HSR)

**NOTE:** This Section applies to ALL abacavir containing products. Abacavir or abacavir containing products are also sold under the following brand names:

- **Trizivir - US**
- **Triovir - Brazil**
- **Trizivar – Zimbabwe, South Africa, Namibia**
- **Ziagen – Brazil, South Africa, various African countries**
- **Ziagenavir – Thailand, various African countries**
- **Epzicom**
- **Kivexa**

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR). A detailed clinical description of this reaction (including the type and severity of events that can occur on re-challenge or reintroduction following ABC interruption for non-HSR reasons) and guidance regarding its management are included in the Local Country Prescribing Information for each ABC-containing medication. Investigators must familiarize themselves with this information on ABC HSR in the Local Country Prescribing Information for each of these products prior to initiating participants on ABC therapy. Refer to Protocol Section 6.1.7 for additional information on screening for HLA-B*5701.

In any participant treated with ABC, the clinical diagnosis of suspected HSR (as detailed in the Local Country Prescribing Information) must remain the basis of clinical decision making. Regardless of HLA-B*5701 status, it is important to permanently discontinue ABC and not re-challenge with ABC (e.g., ZIAGEN, EPZICOM, KIVEXA or TRIZIVIR) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

### 6.3.1 Essential ABC use Participant Information

With reference to Local Country Prescribing Information, Investigators must ensure that participants are fully informed regarding the following information on the hypersensitivity reaction prior to commencing ABC therapy:
Participants must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased in individuals who are HLA-B*5701 positive.

Participants must also be informed that HLA-B*5701 negative individuals can also experience abacavir hypersensitivity reaction. Therefore, ANY participant who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT their doctor IMMEDIATELY.

Participants who are hypersensitive to abacavir should be reminded that they must never take any abacavir containing medicinal products (e.g., ZIAGEN, EPZIOCM, KIVEXA or TRIZIVIR) again, regardless of their HLA-B*5701 status.

In order to avoid restarting abacavir, participants who have experienced a hypersensitivity reaction should be asked to return any remaining tablets or oral solution to the Investigator or site staff.

Participants, who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before re-starting abacavir.

Each participant should be reminded to read the Package Leaflet included in the pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

### 6.3.2 How to Handle Abacavir Rash

- Participants should be instructed to contact the investigator as soon as possible if they develop a rash on ABC-containing therapy.
- Participants who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN, and Erythema Multiforme have been reported very rarely in participants taking ABC-containing products. These participants generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.
- If a serious skin reaction develops, ABC (and all other concurrent medication(s) suspected in the investigators causality assessment) should be discontinued, and the participant should not be re-challenged with any ABC-containing medicinal product (i.e., ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).
- As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the participant is receiving should also be reviewed and discontinued as appropriate.

### 6.3.3 Reporting of Hypersensitivity Reactions

All ABC HSR events must be reported as an EAE. In addition to reporting the case as an EAE, In addition, report event on the TRK0097 - IMPAACT P1093 Abacavir Hypersensitivity Reaction Record eCRF.

### 6.4 Liver Toxicity Events

Refer to Protocol Section 6.1.3 for liver toxicity management and guidelines.
If any of the liver toxicity stopping criteria are met, sites are instructed to complete the following procedures:

- **Immediately** hold study drug, unless continuation is approved by the Protocol Team.
- Report the event to the Protocol Team within 24 hours of learning of its occurrence (impaact.teamp1093@fstrf.org).
- Report Hy’s Law liver toxicities (defined under Protocol Section 6.1.3) as an EAE.
- Make every reasonable attempt to have the participant meeting liver stopping criteria return to clinic within 24 hours to perform repeat liver chemistries.
- Make every reasonable effort to schedule a follow-up visit within 72 hours of the last dose to perform the liver event follow up assessments described in Section 6.8.
- Collect a blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours of last dose.
- Complete the BXW0020-Liver Events CRF, and if appropriate, the BXW0021-Liver Imaging and/or BXW0019-Liver Biopsy CRFs (if these tests are performed).
- A specialist or hepatology consultation is recommended.
- Sites should make every attempt to carry out the following clinical and laboratory evaluations:
  - Viral hepatitis serology including:
    - Hepatitis A IgM antibody
    - HBsAg and Hepatitis B Core Antibody (IgM)
    - Hepatitis C RNA; Cytomegalovirus IgM antibody
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
    - Hepatitis E IgM antibody
  - Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
  - Fractionate bilirubin, if total bilirubin is greater than 1.5xULN;
  - Obtain complete blood count with differential to assess eosinophilia;
  - Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
  - Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease;
  - Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
  - Record use of all concomitant medications, acetaminophen, herbal remedies, other over the counter medications, multivitamins (noting especially any that might contain divalent cations like iron, calcium, magnesium) vaccinations or putative hepatotoxins, on the concomitant medications report form.
  - Record any alcohol use on the ‘liver event alcohol intake’ case report form.
6.4.1 PK Sampling if the Liver Toxicity Stopping Criteria are Met

- The site personnel should try their best to schedule the participant to come back into clinic within 72 hours of the participants last dose of DTG, in order to collect a PK sample.

- If possible, sites are requested to collect a 2mL blood specimen for PK analysis within 72 hours of the last dose of study drug taken. This is a requested (not mandated) specimen collection.
  - If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected within 72 hours, do not obtain the PK sample.
  - If the date or time of the last dose is unclear, provide the participant’s best approximation.

- Record the date and actual time of the PK blood sample draw and the date/time of the last dose of DTG prior to blood sample draw on the the PKW0291-IMPAACT P1093 Pharmacokinetics – Population eCRF.

7.0 Laboratory Considerations

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:
https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

The SoEs and Laboratory Processing Chart (LPC) are the primary sources of information on specimen collection, processing, testing, and storage, and shipping for this study; refer to these documents for further operational guidance as needed.

In accordance with US NIH recommendations, pediatric (less than 18 years) blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg over any eight-week period. Adult (18 years and older) blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

In the event blood collection must be limited, available specimens will be prioritized for use in the order specified in the SoEs.

As the transmission of HIV and other blood-borne diseases can occur through contact with contaminated needles, blood and blood products, appropriate precautions should be employed by all personnel when drawing blood and handling clinical specimens for this study in both the clinical and laboratory setting, as recommended by the Centers for Disease Control and Prevention (CDC). Respiratory infections may be transmitted by droplet aerosolization and fomites. All study staff should take appropriate precautions when collecting and handling biological specimens. Guidance on Universal Precautions/ Body Substance Isolation is available from the US Centers for Disease Control and Prevention:

http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html
http://www.cdc.gov/ncidod/dhqp/gl_isolation_standard.html

Additional laboratory reference information can be found in the joint ACTG/IMPAACT Laboratory Manual, which is available at:
Laboratory Data Management System (LDMS):
LDMS must be used at all labs to track the collection, storage, and shipment of the laboratory specimens. Detailed instructions for use of LDMS, including User Manuals, are available at:

http://www.ldms.org

All labs should be utilizing the most up to date version of LDMS. For supported label and printer options, refer to Resources – General Documentation on the LDMS Website. Contact User Support for further information.

Study specific questions about LDMS, shipping and storage for this protocol should be raised with the Laboratory Data Manager at Frontier Science. Questions about LDMS functionality should be directed to User Support.

24-Hour LDMS User Support
Technical support is available 24 hours a day from User Support. Contact information is below:

Email: Ldmshelp@fstrf.org
Phone: (716) 834-0900, extension 7311

Additional Resources:
LDMS website: http://www.ldms.org
Frontier Science DMC portal: http://www.frontierscience.org/portal/

Instructions for Shipments to Quest Diagnostics (Baltimore)

NOTE: The following specimens should be shipped in REAL TIME to Quest Diagnostics (Baltimore):

• Each US clinical site MUST contact the P1093 Quest Diagnostic Lab (BALTIMORE ONLY) at least 2 weeks prior to shipment of their first P1093 Real Time M/C ratio specimen, to arrange for an account to be created to allow for appropriate specimen receipt and result reporting to each clinical site. Contact the Quest Diagnostics’ Special Studies Service Representative (Larry Hirsch) at Larry.A.Hirsch@questdiagnostics.com or 1-410-536-1622.

• A custom P1093 Real Time M/C ratio testing requisition, as appropriate, will be provided to the clinical site/lab to use with specimen submission. The P1093 custom requisition form includes the demographic data entry fields (e.g. PID/SID, Date/Time of Specimen Collection, etc.) that must be completed by site personnel when sending the study participant’s specimen aliquots.

• Ship urine or blood specimens as appropriate, as described by the Lab Processing Chart.

• The site lab will pack and ship the box according to IATA regulations. The shipment must contain an LDSM diskette (or LDMS batch email must be sent to receiving lab), manifest, and box-map. Ship samples via priority overnight courier on a Monday through Thursday schedule. Do not ship on days that occur before a national holiday.

• The site lab must FAX or email a notification to the P1093 Quest Diagnostics Laboratory, Baltimore at 1-410-536-1474 or DGXBaltimoreSpecialStudiesDepartment@questdiagnostics.com PRIOR to shipping using the “IMPAACT Specimen Shipment Notice” from the IMPAACT website. The Quest laboratory can be contacted by telephone at 1-410-247-9100 ext. 2270.
8.0 Data Management

8.1 Responsibilities

Frontier Science is the Data Management Center (DMC) for all IMPAACT studies, including IMPAACT P1093. The DMC Subject Enrollment System (SES) is used to randomize and enroll participants into the study. As members of the IMPAACT P1093 Protocol Team, DMC Protocol and Laboratory Data Managers work closely with the team providing various reports and support to the team, as well as sending and receiving queries to both clinical sites and laboratory personnel.

8.2 Electronic Case Report Forms (eCRFs), Schedules, and Medidata Rave

IMPAACT P1093 data will be collected utilizing Medidata Rave. Each site and associated personnel will receive an email invitation to the study and to required eLearning courses in Medidata. The following P1093 data collection materials will be available on the DMC Portal under Site Support > Medidata Rave Resources > P1093 Resources:

- P1093 Print Matrix: blank PDF copies of all the IMPAACT P1093 eCRFs.
- P1093 eCRF Completion Guide: annotated eCRFs and Data Collection Forms Schedules for IMPAACT P1093.

Additional Medidata Rave resource documents can be found on the DMC Portal under Site Support > Medidata Rave Resources, General Resources and Site Staff Resources Sections. Study site staff will enter required data into the eCRFs, with edit checks applied; data queries will be generated immediately upon saving the entered data. Data are expected to be entered within timeframes specified by the protocol and built into the eCRF screens; queries must also be resolved in a timely manner.

Further information on eCRFs and other IMPAACT data management procedures are provided by the DMC at: https://www.frontierscience.org.

8.3 Data Management Resources

A User Manual for the Subject Enrollment System is available on the DMC portal. Questions about eCRFs and data management procedures for this study should be directed to the Protocol Data Manager(s) at Frontier Science. For further questions or technical support, please contact User Support at 716-834-0900, ext. 7302 or email user.support@fstrf.org.

8.4 Assignment of a Patient Identification Number (PID)

The PID is assigned at the site from a list that is generated by the DMC (Frontier Science) and sent to the sites. If a participant has enrolled on another IMPAACT or ACTG study, the same PID is carried with them for use in the new study; a new PID number would not be assigned.
## APPENDIX I

### P1093 PK Medication & Food History Logs

**Participant PID:** ________________________

<table>
<thead>
<tr>
<th>PK Visit Planned Date</th>
<th>Prior DTG Dosing</th>
<th>Date taken (mmm/dd/yyyy)</th>
<th>Time taken (hh:mm)</th>
<th>Single Dose Amount Taken (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example: APR/11/2011</td>
<td>3 days before the PK visit</td>
<td>APR/08/2011</td>
<td>7:30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>2 days before the PK visit</td>
<td>APR/09/2011</td>
<td>8:25</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
<td>APR/10/2011</td>
<td>8:10</td>
<td>30</td>
</tr>
<tr>
<td>Intensive PK</td>
<td>3 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>3 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>3 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>3 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Time of most recent food intake prior to PK visit (hh:mm) | Type of Meal (full meal, light snack)**

<table>
<thead>
<tr>
<th>Example: 18:45</th>
<th>Full meal (dinner)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX II
Genotyping (Virologic Failure) Specimens
BRI PASS THROUGH NOTIFICATION

P1093 Pass-Through Samples

LDMS Inventory/
BRI Storage Not Required

Genotyping (VIROLOGIC FAILURE) specimens

Ship to **Lab 238 (UW)**:

Attn: Dr. Ingrid Beck
University of Washington Children’s Hospital of Seattle
1900 Ninth Ave
Seattle WA 98101
PHONE: 206–884-3440
FAX NUMBER: 206-884-7311
EMAIL: Frenkellabshipments@seattlechildrens.org
P1093 Pass-Through Samples

LDMS Inventory/
BRI Storage Not Required

Intensive PK Specimens

Ship to **Lab 191 (UAB Pharmacology)**:

Attn: Kedria Walker

University of Alabama at Birmingham
Division of Pharmacology
1670 University Blvd
Volker Hall, Rm 270
Birmingham, AL 35294

PHONE: 205-975-2461
FAX NUMBER: 205-934-6201
EMAIL: kedria@uab.edu
**APPENDIX IV**

**P1093 Specimen Testing Requisition - UW**

**IMPORTANT:** Please use this form when shipping specimens to Seattle Children’s Research Institute (SCRI) Lab, whether it is a direct shipment to SCRI, or if specimens will be sent to BRI first and then on to SCRI in real time. Please contact the team with any questions (impaact.teamp1093@fstrf.org)

Site Name & Number: ______________________________________________________________________

Site Contact Name & Phone Number: ______________________________________________________________________

<table>
<thead>
<tr>
<th>Participant PID</th>
<th>Date of Specimen Collection</th>
<th>Study Visit</th>
<th>Plasma HIV Viral Load* (c/mL)</th>
<th>Laboratory Testing Required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example:</strong> 123456J</td>
<td>March 1, 2011</td>
<td>Screening</td>
<td>45,000</td>
<td><strong>X</strong></td>
</tr>
</tbody>
</table>

*If viral load data is not available on specimen’s ship date, please forward viral load by email to Frenkellabshipments@seattlechildrens.org as soon as possible. Specimens will not be processed until viral loads are received.
Appendix V
Dosing Instructions
Dispensible Tablets
Directions for Parents/Legal Guardian/Caregiver

DTG Dispensible Tablets (Cohorts III-DT, IV-DT, and V-DT):

Confirm the dose to be given and select the appropriate number of dispensible tablets as directed. The following instructions, per Clarification Memorandum #1, should be followed to administer the product.

Option 1: For older children, pour drinking water into the dosing cup.
- For 1-3 tablets use 5 mL of water, for 4-6 tablets use 10 mL of water.
- Add the prescribed number of tablets to the water.
- Swirl the cup gently for 1-2 minutes to fully disperse the tablets.

The medicine will be cloudy. If any lumps of tablet remain, swirl the cup gently until they are gone. Administer the prepared dose to the child. Pour an additional 5 mL of water in the dosing cup, swirl the cup gently for approximately 15 seconds and administer the entire volume to the participant. Wash the dosing cup immediately after administration, allow to dry and store for the next use.

Option 2: For babies and younger children
- Prepare medicine in dosing cup as directed in Option 1.
- Draw up all the medicine into the syringe.
- Place the tip of the syringe against the inside of the infant’s cheek to administer the dose slowly.
- Pour an additional 2 mL of water into the dosing cup, draw it into the syringe, and administer the remaining volume to the infant.
- Wash the dosing cup immediately after administration, allow to dry and store for the next use.

After intensive PK sampling in Stage I and in Stage II each tablet can be dispersed as described above or each tablet can be placed directly on the tongue and directly swallowed. Dispersible tablets may be given as multiples (up to a maximum of 6 tablets), depending on the weight of the child. Once dispersed, the medication should be administered using the supplied dosing cup or syringe, as soon as possible, preferably within 5 minutes but no longer than 30 minutes after preparation.