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

IND#: 110,847
DAIDS ES # 11773

This file contains the current IMPAACT P1093 protocol, which is comprised of the following documents, presented in reverse chronological order:

- IMPAACT P1093 Protocol Signature Page for protocol Version 4.0
- Clarification Memorandum #4, dated 30 January 2018
- Clarification Memorandum #3, dated 11 July 2017
- Clarification Memorandum #2, dated 7 April 2017
- Clarification Memorandum #1, dated 8 December 2016
- Protocol Version 4.0, dated 13 April 2016

Note: Site-Specific Letter of Amendment #1 for protocol V4.0 Chiang Mai University (CRS 31784) and Shandukani Research (CRS 8051), Letter of Amendment Date: 9 December 2016 is not contained in this file.
I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

__________________________________________  
Signature of Investigator of Record                        Date

__________________________________________  
Name of Investigator of Record
(printed)
Clarification Memorandum #4 for:

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
Version 4.0 dated 13 April 2016

DAIDS ES # 11773
IND# 110,847

Clarification Memorandum Date: 30 January 2018

Summary of Clarification and Implementation

This Clarification Memorandum (CM) serves to document the discontinuation of use of the granule for suspension formulation of dolutegravir (DTG) and the transition of participants currently receiving the granule formulation to the dispersible tablet formulation in IMPAACT P1093.

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The clarifications included in this memorandum will be incorporated into the next protocol amendment.

Evaluation of both a granule for suspension formulation and a dispersible tablet formulation was specified in protocol Version 4.0, with instructions provided in protocol Section 3.3 for transition to use of dispersible tablet formulation at each study site. Protocol Section 3.3.1.4 further specifies that children receiving the granule formulation will switch to the dispersible tablet formulation when notified by the Protocol Team that age-specific Stage I data for the dispersible tablet formulation are acceptable. Some study participants in Cohort IIB, Cohort III and Cohort IV are currently receiving the granule formulation.

The Protocol Team now considers age-specific Stage I data for the dispersible tablet formulation to be acceptable to support the switch from the granule formulation to the dispersible tablet formulation for Cohorts IIB, III and IV. There is also adequate information showing pharmacokinetic equivalency between granule and dispersible tablet formulation. Lastly, the pharmaceutical manufacturer has determined that the granule formulation of DTG will not be considered for further development or licensure and there is now limited supply of granules for long term continuation in P1093. Therefore, protocol instructions, as indicated in Section 3.3.1.4 and the Schedules of Evaluations, for switching participants from the granule formulation to the dispersible tablet formulation should now be followed at all sites as soon as the dispersible tablet formulation is available. These instructions are summarized below.

- Each participant currently receiving the granule formulation should be switched to the dispersible tablet formulation at his or her next study visit. The first dispersible tablet dose should be given in the study clinic and observed by study staff.
Participants will receive the equivalent dispersible tablet dose per their current granule dose. Participants receiving the ~0.8 mg/kg granule dose per dosing Table E will switch to the ~0.8 mg/kg dispersible tablet dose per Table L and participants receiving the ~1.25 mg/kg granule dose per Table H will switch to the ~1.25 mg/kg dispersible tablet dose per Table N, as specified in the table below.

<table>
<thead>
<tr>
<th>Current Granule Dose and Dosing Table</th>
<th>New Dispersible Tablet Dose and Dosing Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>~0.8 mg/kg per Table E</td>
<td>~0.8 mg/kg per Table L</td>
</tr>
<tr>
<td>~1.25 mg/kg per Table H</td>
<td>~1.25 mg/kg per Table N</td>
</tr>
</tbody>
</table>

The IMPAACT P1093 protocol version 4.0 Dosing Table Appendix is posted on the study-specific web page: [http://impaactnetwork.org/studies/P1093.asp](http://impaactnetwork.org/studies/P1093.asp)

- Two weeks after switching to the dispersible tablet formulation, an additional ‘Two Weeks Post-Switch Visit’ should be conducted at which palatability and HIV RNA evaluations will be performed; if this visit falls within the window for another scheduled visit, a combined visit can be conducted.

- For participants who have completed 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit,’ in addition to the palatability and HIV RNA evaluations mentioned above, these participants will have population PK specimens collected at this ‘Two Week Post Switch Visit’ and at the next regularly scheduled visit, per the relevant Schedule of Evaluations.

Please contact the Protocol Team with any questions related to this CM or the management of any participants currently receiving the granule formulation of DTG.
Clarification Memorandum #3 for:

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
Version 4.0 dated 13 April 2016

DAIDS ES # 11773
IND# 110,847

Clarification Memorandum Date: 10 July 2017

Summary of Clarifications

This Clarification Memorandum (CM) clarifies the guidelines for general toxicity management.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The clarifications included in this memorandum will be incorporated into the next protocol amendment. Modifications are shown below, using strikethrough for deletions and bold type for additions.

6.1.1 Reporting

AEs will be collected from the start of DTG treatment and until the final follow-up visit after study drug has been stopped.

- Grade 1: All AEs should be recorded on Case Report Forms (CRFs) at each visit.
- Grade 2: All AEs should be recorded on CRFs at each visit.
- Grade 3 or 4:
  - All AEs should be recorded on CRFs at each visit.
  - The Protocol Team must be notified of AEs within 1 business day 72 hours of awareness, by email at impaact.teamp1093@fstrf.org.
  - The investigator should attempt to confirm any unexpected laboratory test results as soon as possible but always within 72 hours. To determine if the result was spurious.
Expedited Adverse Event (EAE) reporting, if appropriate, must be done within 72 hours of the initial result if the value is confirmed or if confirmatory results are not available within 72 hours.

6.1.2 Management

Grade 1 - Continue study drug; routine monitoring.

Grade 2 - Continue study drug; monitor closely with more frequent visits as per site PI, work-up to exclude other causes.

For Grade 3 laboratory AEs, continue study drug while awaiting confirmatory results unless the clinician believes that remaining on study drug would be unsafe and that continuing them would pose little additional risk. Notify the Protocol Team of the confirmatory results at impaact.teamp1093@fstrf.org within 72 hours of awareness.

For Grade 3 clinical AEs and confirmed Grade 3 laboratory AEs abnormalities are confirmed, hold the study drug and concomitant antiretroviral therapy should be withheld until the abnormalities decrease to a Grade 2 or below unless the site clinician, with the approval of the Protocol Team and medical officer, believes that withholding antiretroviral therapy (including study drug) would be harmful to the subject and that continuing them would pose little additional risk.

The protocol team should be informed of all Grade 3 clinical AEs and confirmed Grade 3 laboratory AEs, within 72 hours of awareness, and the site’s plan to hold or continue study drug and concomitant antiretroviral therapy at impaact.teamp1093@fstrf.org.

Grade 4 - Hold study drug and concomitant antiretrovirals immediately unless the site clinician, with the approval of the Protocol Team and medical officer, believes that withholding antiretroviral therapy (including study drug) would be harmful to the subject and that continuing them would pose little additional risk. Attempt to confirm any Grade 4 unexpected laboratory AEs results as soon as possible, but always within 72 hours of awareness of the initial result event, to determine if these results were spurious.

The Protocol Team should be notified of the initial and confirmatory results at impaact.teamp1093@fstrf.org within 72 hours of awareness.

For Grade 4 clinical AEs and confirmed Grade 4 laboratory AEs that are determined to be possibly, probably or definitely related to study drug, study drug medication should be permanently discontinued. For Grade 4 adverse events that are determined to be unrelated or possibly, probably not or not related to study drug, the site investigator should contact the team to determine whether and when study drug may be safely continued (if not previously held) or resumed (if held).

All antiretroviral therapy including study drug should be started or stopped together whenever possible, except when one antiretroviral agent can be substituted for another within class when the etiology of the toxicity can be determined.
Clarification Memorandum #2 for:

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
Version 4.0 dated 13 April 2016

DAIDS ES # 11773
IND# 110,847

Clarification Memorandum Date: 7 April 2017

Summary of Clarifications

This Clarification Memorandum (CM) clarifies the administration of optimized background therapy (OBT) for participants in Stage I receiving a failing ARV regimen that will continue as OBT. In addition, the Schwartz formula for evaluating renal function for 1-year-old participants is corrected.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The clarifications included in this memorandum will be incorporated into the next protocol amendment. Modifications are shown below, using strikethrough for deletions and bold type for additions.

1. Section 3.1, Stage I, 1st paragraph

For those enrolling in Stage I, intensive pharmacokinetics (PK) will be performed over a single day starting with a witnessed dose between days 5-10 after enrollment. Management of the background ARVs prior to the intensive PK varies based on age and ARV status at enrollment summarized below (see Section 6.2.3 for additional details).

- ARV-treatment experienced subjects not currently receiving ARVs will start DTG alone, complete the intensive PK study visit on Day 5-10 and then optimize the ARV regimen immediately after the PK visit.

- ARV-treatment experienced subjects who are currently receiving a failing regimen of ARVs or who recently started an empiric regimen (< 2 years of age) will add DTG to their regimen at study entry, complete the intensive PK study visit on Day 5-10 and then optimize the ARV regimen immediately after the PK visit.
Note: ARV-treatment experienced subjects currently receiving a failing ARV regimen and who will continue this same regimen after entry as OBT, should continue the regimen through entry and the intensive PK visit; there should be no interruption in treatment with the background regimen.

- ART naïve subjects < 2 years of age will start empiric ART plus DTG at study entry and then complete the intensive PK study visit on Day 5-10. For those subjects who started dolutegavir prior to the genotype results being available, the background ARV regimen will be optimized as soon as possible after the intensive PK visit.

2. Section 6.2.3.1 Stage I: Subjects on Stage I will initiate DTG and have their ARV regimen optimized as described below., 1st bullet

- If the subject is on a stable, failing ARV regimen at entry, DTG will be added to the failing regimen at entry and their background ARV regimen will be optimized based on genotype results after intensive PK 24 hour sampling is completed between days 5-10.

Note: Subjects receiving a failing ARV regimen at entry and who will continue this regimen as OBT should continue this regimen during intensive PK sampling; there should be no interruption in treatment with the background regimen.

3. Section 6.1.4 Decline in Renal Function, 3rd paragraph

Schwartz formula: GFR (mL/min/ 1.73 m²) = K x Ht cm/P_{creat}

K=constant Cr mg/mL
Infants < 1 year 0.45
Children 2-12 years 0.55
Female 13-21 years 0.55
Males 13-21 years 0.70
Clarification Memorandum #1 for:

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
Version 4.0 dated 13 April 2016

DAIDS ES # 11773
IND# 110,847

Clarification Memorandum Date: 8 December 2016

Summary of Clarifications

This Clarification Memorandum (CM) addresses inconsistencies in the protocol regarding the study drug regimen in Cohort II; the maximum in-use period of the granule formulation after reconstitution; and selection of the optimized background therapy (OBT) for participants entering Stage II. In addition, clarification regarding the intended interpretation of inclusion criterion 4.1.3.1, and the requirement for collection of samples for genotyping during long-term follow-up are added.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The clarifications included in this memorandum will be incorporated into the next protocol amendment. Modifications are shown below, using strikethrough for deletions and bold type for additions.

1. Section 4.1.3.1, ARV-treatment experienced (not including receipt of ARVs as prophylaxis or PMTCT), the following note is added:

— Currently taking ARVs for treatment but failing:

- Must be on an unchanged, failing therapeutic regimen within the 4 to 12 weeks prior to screening (≤1 log drop in HIV-1 RNA within the 4 to 12 weeks prior to screening).

NOTE: To meet this criterion, two HIV RNA levels are required: one from a date between 4-12 weeks prior to study screening and a second one at study screening. The HIV RNA level at screening must be higher than, equal to or ≤1 log lower than the prior HIV RNA level.

NOTE: Dose adjustments for growth or formula substitutions (i.e. switching from single agent to fixed dose combination) are permitted during this 4 to 12 week period, substitutions of one ARV within the same class for toxicity or tolerability management, or discontinuation
of ARVs are permitted between the HIV RNA measurements and screening or enrollment, also allowed within the 4 to 12 weeks period.

2. Section 5.1 Drug Regimens, Stage II, 1st paragraph

Subjects enrolling in Stage II of each of the following eight cohorts will receive the Stage I approved age and formulation of dolutegravir to be administered orally once daily or, twice daily if on EFV, NVP, FPV/r, or TPV/r as part of OBT, dolutegravir will be dosed twice daily.

3. Section 5.2.2, Dolutegravir Granules for Oral Suspension

1st paragraph
Dolutegravir granules for suspension 1.6 mg/1 mL suspension. When the granules in the bottle are reconstituted with 73 mL of potable (drinkable) water as directed, each container contains 160 mg per 100 mL. Once reconstituted, the suspension is stable for 8-12 weeks in the manufacturer’s container. The reconstituted product should be stored at temperatures up to 30ºC (86ºF). Storage in a refrigerator is fully acceptable and preferred, if available.

3rd paragraph, 6th sentence
The maximum in-use period of the pediatric formulation after it has been reconstituted with water is 8-12 weeks and should may be refrigerated or stored at room temperature up to 30ºC (86ºF). Storage in a refrigerator is fully acceptable and preferred, if available.

3rd paragraph, 12th sentence
The reconstituted suspension should be used within 8-12 weeks of the initial reconstitution, but preferably within a single month.

4. Section 6.2.3.2, Initiation of Dolutegravir and selection of Optimized Background Therapy (OBT), Stage II, 1st sentence

Stage II: Subjects in cohorts I, II, III and III-DT entering Stage II of the trial will have OBT based on screening results, and start that regimen simultaneously with DTG. Subjects in cohorts IV, IV-DT, V, and V-DT will optimize OBT as soon as genotype results are available (See section 6.2.3.3)

5. Appendix IE, Schedule of Evaluations, Long-term Safety Follow-up for Subjects who Continue to Receive Dolutegravir (study-provided or locally), header row, Footnotes 2 and 3

Header Row: Every 12 Weeks [Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, 168,180, and 192 (End of Study Visit)]

2. If determined by the protocol team genotyping may be done at a frequency ≥24 weeks post virologic failure if HIV-1 RNA is >400 c/mL

2. Genotyping to be done for participants post virologic failure, ONLY if requested to do so by the protocol team.
3. Specimens for genotyping and phenotyping should be obtained and stored at this visit, but only sent for processing if the confirmatory HIV RNA test at this visit is > 400 c/ml. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to **protocol Section 6.2.5** and the Laboratory Processing Chart (LPC) for additional details.
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

A Multicenter, Domestic & International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID), The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH)

Pharmaceutical Support Provided by: GlaxoSmithKline

IND#110,847 Held by NIAID
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Final Version 4.0
13 April 2016
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STUDY MANAGEMENT

- For protocol registration questions Email protocol@tech-res.com or call (301) 897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or via fax at 1-800-418-3544 or (301) 897-1701.

- All questions concerning this protocol including questions regarding screening, clinical management of study subjects should be sent via e-mail to impaact.teamp1093@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail. A response should generally be received within 24 hours (Monday - Friday).

- For computer and screen problems email user.support@fstrf.org or call the DMC at (716) 834-0900 x7302.

- For questions or problems regarding study drug supplies, records, and returns, contact the DAIDS Protocol Pharmacist at sisetk@niaid.nih.gov or call (240) 292-4848.

- For Expedited Adverse Event (EAE) questions contact the DAIDS RSC Safety Office via email (RSCSafetyOffice@tech-res.com) or phone (1-800-537-9979 or +1-301-537-1709) or fax (1-800-275-7619 or +1-301-897-1710). For questions about the DAIDS Adverse Experience Reporting System (DAERS), email DAIDS-ESSupport@niaid.nih.gov. Questions may also be sent within the DAERS application.

- Email the Computer Support Group at the Data Management Center (DMC) (user.support@fstrf.org) to have relevant site personnel added to the protocol email group (impaact.protp1093@fstrf.org). Inclusion in the protocol email group will ensure that sites receive important information about the study during its implementation and conduct.
List of Commonly Used Abbreviations and Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>ABC</td>
<td>Abacavir</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATV</td>
<td>Atazanavir</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-24)&lt;/sub&gt;</td>
<td>Area under the drug plasma concentration profile over time of dosing interval</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>C&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Drug plasma concentration immediately prior to dosing</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal observed drug concentration during a dosing interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt;</td>
<td>Minimal observed drug concentration during a dosing interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;24hr&lt;/sub&gt;</td>
<td>Drug plasma concentration at the end of the 24 hour dosing interval</td>
</tr>
<tr>
<td>CAP</td>
<td>College of American Pathologists</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control and Prevention</td>
</tr>
<tr>
<td>cDNA</td>
<td>complementary DNA</td>
</tr>
<tr>
<td>CL/F</td>
<td>Apparent clearance</td>
</tr>
<tr>
<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendments</td>
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<tr>
<td>CRPMC</td>
<td>Clinical Research Products Management Center</td>
</tr>
<tr>
<td>DAERS</td>
<td>DAIDS Adverse Experience Reporting System</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS (United States)</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Management Center</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRV</td>
<td>Darunavir</td>
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<tr>
<td>DSMB</td>
<td>Data Safety and Monitoring Board</td>
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<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
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<td>EC</td>
<td>Ethics Committee</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EFV</td>
<td>Efavirenz</td>
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<td>EIA</td>
<td>Enzyme Immunoassay</td>
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<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ETR</td>
<td>Etravirine</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EVG</td>
<td>Elvitegravir</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FPV</td>
<td>Fosamprenavir</td>
</tr>
<tr>
<td>FTC</td>
<td>Emtricitabine</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GM</td>
<td>Geometric mean</td>
</tr>
<tr>
<td>GMR</td>
<td>Geometric mean ratio</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HHS</td>
<td>Department of Health &amp; Human Services</td>
</tr>
</tbody>
</table>
**IB**  Investigator’s Brochure  
**IC50**  Half Maximal Inhibitory Concentration  
**IMPAACT**  International Maternal Pediatric Adolescent AIDS Clinical Trials Group  
**IgM**  Immunoglobulin M  
**ICF**  Informed Consent Form  
**IQ**  Inhibitory Quotient  
**INR**  International Normalized Ratio  
**IRB**  Institutional Review Board  
**IUD**  Intrauterine device  
**LAR**  Legally Authorized Representative  
**LDH**  Lactate dehydrogenase  
**LMC**  low mineral content  
**LPV**  Lopinavir  
**MSDF**  Missing, Switch or Discontinuation = Failure  
**NIAID**  National Institute of Allergy and Infectious Diseases  
**NICHD**  National Institute of Child Health and Human Development  
**NIH**  National Institutes of Health  
**NRTI**  Nucleoside/Nucleotide Reverse Transcriptase Inhibitors  
**NVP**  Nevirapine  
**OBT**  Optimized Background Therapy  
**OHRP**  Office for Human Research Protections  
**PCR**  Polymerase Chain Reaction  
**PI**  Protease Inhibitor  
**PID**  Patient Identifier  
**PK**  Pharmacokinetic  
**PMTCT**  Prevention of Mother to Child Transmission  
**PRO**  Protocol Registration Office  
**QD**  Once daily  
**RAL**  Raltegravir  
**RE**  Regulatory Entity  
**RNA**  Ribonucleic acid  
**RSC**  Regulatory Support Center  
**RTV**  Ritonavir  
**SAE**  Serious Adverse Event  
**SDMC**  Statistical and Data Management Center  
**SMC**  Study Monitoring Committee  
**SUSAR**  Suspected, Unexpected Serious Adverse Reaction  
\( t_{\text{max}} \)  time \( C_{\text{max}} \) occurs  
\( t_{\text{min}} \)  time \( C_{\text{min}} \) occurs  
\( t_{1/2} \)  half-life  
**TB**  Tuberculosis  
**TDF**  Tenofovir  
**TPV**  Tipranavir  
**UAB**  University of Alabama in Birmingham  
**UGT**  UDP-glucuronosyltransferases  
**ULN**  Upper Limit of Normal  
**US**  United States  
**WB**  Western Blot  
**Vdz**  Apparent volume of distribution  
**ZDV**  Zidovudine
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

DESIGN: Phase I/II, multi-center, open-label, non-comparative intensive PK and safety study

SAMPLE SIZE: Approximately 160 HIV-1 infected infants, children and adolescents to provide a minimum of 120 evaluable* subjects:
- Stage I – a minimum of 10 subjects, per cohort
- Stage II – a minimum of 60 evaluable subjects across all cohorts

*Evaluable is defined as having been treated exclusively on the dose determined to be optimal for a given age cohort and having either completed 24 (or 48) weeks of exposure to the study drug or having been classified as a safety failure, due to a study drug related adverse event occurring during the first 24 (or 48) weeks of treatment.

POPULATION: HIV infected infants, children and adolescents aged ≥ 4 weeks to < 18 years of age.

STRATIFICATION: All subjects enrolled into the study will be stratified at screening into one of nine age specific cohorts as follows:

Cohort I: Adolescents ≥ 12 to <18 years of age
(Film-coated Tablets)

Cohort IIA: Children ≥ 6 to <12 years of age
(Film-coated Tablets)

Cohort IIB: Children ≥ 6 to <12 years of age
(Granules for suspension)
Note: Dispersible tablets may also be evaluated in this cohort if requested by regulatory authorities.

Cohorts III: Children ≥ 2 to < 6 years of age
(Granules for suspension)

Cohort III-DT: Children ≥ 2 to < 6 years of age
(Dispersible Tablets)

Cohort IV: Children ≥ 6 months to < 2 years of age
(Granules for suspension)

Cohort IV-DT: Children ≥ 6 months to < 2 years of age
(Dispersible Tablets)
Cohort V: Infants ≥ 4 weeks to < 6 months of age (Granules for suspension)

Cohort V-DT: Infants ≥ 4 weeks to < 6 months (Dispersible Tablets)

REGIMEN: Three different dolutegravir (DTG) formulations will be evaluated as follows: film-coated tablets; a granule formulation for suspension; and dispersible tablets. The final dose for each formulation and each age cohort will be selected based on real-time PK evaluations and safety to achieve exposure similar to that observed in adults treated with 50 mg QD.

See Sections 5.0-5.4 for details on DTG drug regimens, formulations, drug supply and handling.

TREATMENT DURATION: Stages I and II: 48 Weeks

Long Term Safety Follow-up: All subjects who successfully complete 48 weeks of DTG treatment will continue to receive DTG for a minimum of three years as part of long term safety follow-up. (See Section 6.3 and Appendix IE for details).

HYPOTHESIS: DTG will be generally well tolerated and demonstrate an acceptable safety profile, adequate PK and antiviral activity when used concurrently with an optimized background therapy (OBT) in HIV-1 infected infants, children and adolescents.

OBJECTIVES:

PRIMARY OBJECTIVES

1. To select a dose for each formulation of DTG for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily dose in adults.

2. To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.

3. To evaluate the steady-state pharmacokinetics of DTG in combination with other antiretrovirals (OBT) in treatment-experienced and/or treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves a targeted AUC_{24} (primary PK endpoint) and C_{24h} (secondary PK endpoint) in this population.

SECONDARY OBJECTIVES

1. To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks.

2. To evaluate the effect on immunologic response from baseline to 24 and 48 weeks.
3. To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in subjects experiencing virologic failure.

4. To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population pharmacokinetic analysis.

5. To determine the extended long term (≥48 weeks) safety and tolerability of DTG in HIV-1 infected infants, children and adolescents.

6. To explore the relationship between DTG exposure and the antiviral activity.
1.0 INTRODUCTION

1.1 Background

Triple combination antiretroviral therapy including a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NRTI) has become the standard treatment of HIV infected adults and children. Effective antiretroviral therapy results in a reduction in viral load with a concomitant increase in the CD4 cell count that has been associated with declining morbidity and mortality in HIV-1 infected adults and children (1);(2). However, poor adherence and short and long term toxicities further complicate HIV management and may contribute to the development of drug resistance mutations. Therefore, children and adolescents who have manifested multiple class intolerance and/or harbor drug-resistant virus have an unmet medical need. The development of drugs that block alternative or novel targets in the HIV life cycle are critically important if for children and adolescents who have failed or are unable to tolerate currently available antiretrovirals. In addition, newer agents with novel resistance patterns not overlapping with established classes of therapies are also needed.

Integrase, a viral enzyme essential for HIV-1 replication, mediates the integration of the viral DNA into the host genome. The primary role of the integrase enzyme is to catalyze the insertion of the viral cDNA into the chromosome of infected cells. This process requires two metal dependent consecutive steps in the viral replication cycle, 3’-processing and strand transfer. After the integration of the viral cDNA into the cell’s chromosome, viral genome is transcribed and viral proteins are produced (3). Two metal integrase inhibitors preferentially block the strand transfer step.

Raltegravir (MK-0518, Isentress, Merck) is the first FDA and European Medicines Agency (EMEA) approved HIV integrase strand transfer inhibitor and has demonstrated safety and efficacy in both treatment-naïve and highly antiretroviral (ARV) experienced adult subjects. Based primarily on the 24-week data from two Phase III studies in treatment-experienced subjects, Protocol 018 (BENCHMRK-1) and Protocol 019 (BENCHMRK-2), raltegravir received marketing approval for use in treatment-experienced subjects. Subsequently, 48-week and 96-week data from these Phase III studies, demonstrate the durable antiretroviral effect and favorable long-term safety profile of raltegravir in treatment-experienced subjects (4);(5). More recently, data from a Phase III study in treatment-naïve subjects (STARTMRK) has led to marketing authorization in treatment naïve subjects in the US and EU (6). A second integrase inhibitor, elvitegravir (GS-9137, Gilead) has also shown potent antiviral activity and is now in Phase III clinical trials in adults (7) and phase I/II trials in HIV infected adolescents (8). Raltegravir needs to be administered twice a day, does not need to be boosted with ritonavir but it has wide inter and intra subject pharmacokinetic variability while elvitegravir (EVG) is administered once a day but requires a pharmacokinetic booster.

Clinical resistance to both raltegravir and elvitegravir has been reported in both treatment naïve and treatment experienced subjects. Two mutation pathways emerged among subjects experiencing virologic failure while on raltegravir. One pathway characterized by the N155H mutation lowered the susceptibility to raltegravir by 10-fold. The Q148H/R/K mutation pathway lowered the susceptibility to raltegravir by 25-fold. Additional mutations have decreased raltegravir susceptibility; the most common being the Q148H and G140S conferring >100 fold decrease susceptibility to raltegravir (9). Subjects experiencing virologic failure while on elvitegravir have shown similar mutation pathways as seen with raltegravir (10). As the barrier to the above described resistance is low, there is a need for the development of new integrase inhibitors with different resistance profiles. Preliminary data suggests that elvitegravir exhibits similar resistance characteristics.
Dolutegravir (DTG) is a potent inhibitor of the HIV-1 integrase with a mean IC$_{50}$ between 0.02 and 2.14 nM, when tested against a panel of clinical isolates from group M, clades A, B, C, D, E, F and G, in addition to group O and HIV-2 (11). When tested against a panel of 18 integrase resistant viruses from subjects failing raltegravir or elvitegravir, DTG showed antiviral activity comparable to that seen against wild type viruses in 17 of 18 mutant viruses (8);(12). In addition, DTG showed antiviral activity comparable to that shown against wild type virus when tested against reverse transcriptase inhibitor and protease inhibitor resistant viruses. The antiviral activity of DTG has shown additive or synergistic effects when tested in combination with all anti-HIV therapy classes that have been FDA approved (13).

1.2 Clinical Efficacy

Lalezari et al. (14) conducted a proof of concept Phase IIa, dose-ranging, randomized, placebo-controlled study (ING111521) among 35 HIV infected adults. For ten days, subjects received either DTG monotherapy at the doses of 2 mg, 10 mg, 50 mg or placebo. In the group receiving 50 mg of DTG monotherapy, the mean decline in HIV-1 was 2.5 log$_{10}$ copies/mL and seven out of ten subjects had a VL < 50 copies/mL during the study. DTG was well tolerated with only mild adverse events described including diarrhea, fatigue, and headache. No integrase signature resistance mutations were observed during the 10-day monotherapy study (14).

In the ING111521 Phase IIa study (described above), DTG demonstrated low PK variability and a steady-state half-life ($t_{1/2}$) of 14 hours. At 50 mg once daily, the steady-state PK parameters (%CV) were; AUC$_{24}$ 43.4 (20%) µg h/mL, C$_{max}$ of 3.34 (16%) µg/mL and C$_{24h}$ of 0.83 (26%) µg/mL (Table 1). The ratio of the 10 and 50 mg C$_{24h}$ to the protein binding corrected IC$_{90}$ (0.064 µg/mL), also defined as inhibitory quotient (IQ), were 3 and 13, respectively. Since the doses in this study covered a wide range of 25-fold (2 to 50 mg), a concentration-response relationship was observed between C$_{24h}$ and change in HIV-1 RNA from baseline to day 11 using a maximum effect (E$_{max}$) model. The concentration required to produce 50% of the maximum effect (EC$_{50}$) was estimated to be 0.036 µg/mL (or 36 ng/mL) (15). These data provide a basis for an AUC-and C$_{24h}$-targeted trial in pediatric subjects.
Table 1: Summary of DTG PK Parameters and Mean HIV-1 RNA Reduction from Baseline by Dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>AUC_{24} µg·h/mL</th>
<th>C_{max} µg/mL</th>
<th>C_{24} µg/mL</th>
<th>IQ</th>
<th>Δ Log_{10} HIV-1 RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg QD</td>
<td>2.56 (29%)</td>
<td>0.22 (25%)</td>
<td>0.04 (50%)</td>
<td>0.6</td>
<td>-1.51</td>
</tr>
<tr>
<td>N=9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg QD</td>
<td>10.1 (20%)</td>
<td>0.80 (23%)</td>
<td>0.19 (25%)</td>
<td>3</td>
<td>-2.03</td>
</tr>
<tr>
<td>N=7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg QD</td>
<td>43.4 (20%)</td>
<td>3.34 (16%)</td>
<td>0.83 (26%)</td>
<td>13</td>
<td>-2.46</td>
</tr>
<tr>
<td>N=10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Geometric mean (CV%); IQ=C_{24}/PA-IC_{90} = 0.064 µg/mL

In addition, two ongoing Phase IIb studies in HIV-infected subjects, ING112276 and ING112961, have demonstrated potent antiviral effect in treatment-naive and integrase-inhibitor resistant subjects. In ING112276, a Phase IIb dose-ranging study in treatment-naive, HIV-infected subjects, rapid and sustained antiviral responses across all DTG doses (10 mg, 25 mg, and 50 mg) were observed to Week 24, and antiviral responses were more robust than those seen in the efavirenz (EFV) control arm. Greater than or equal to 90% of subjects receiving DTG achieved the primary endpoint of <50 copies/mL (c/mL) plasma HIV-1 RNA by Week 16 and through Week 24. Neither dose trends nor differences were noted across DTG arms (10 mg, 25 mg, and 50 mg) for efficacy or safety.
All three doses of DTG were generally well tolerated through 48 weeks, and the 50 mg dose was selected for phase III evaluation. At Week 96, the proportion of subjects achieving plasma HIV-1 RNA <50 c/mL was 79%, 78%, and 88% for DTG 10 mg, 25 mg, and 50 mg, respectively, compared with 72% for EFV. The median increase from baseline in CD4+ cells was 338 cells/μL with DTG (all treatment groups combined) compared with 301 cells/μL with EFV (p = 0.155). No clinically significant dose-related trends in AEs were observed, and fewer subjects who received DTG withdrew because of AEs (3%) compared with EFV (10%) (16).

In Study ING112961, a Phase IIb pilot study of HIV-infected subjects with viral resistance to raltegravir (RAL) at Baseline, subjects received DTG 50 mg once daily (Cohort I) or 50 mg BID (Cohort II) while continuing a failing regimen (without RAL) through Day 10, after which the background regimen was optimized, when feasible, for Cohort I, and at least one fully active drug was mandated for Cohort II. Cohort I enrolled 27 subjects and Cohort II enrolled 24 subjects. A rapid antiviral response was observed. More subjects achieved the primary end point in Cohort II (96%), compared with Cohort I (78%) at Day 11. At Week 24, 41% and 75% of subjects had an HIV-1 RNA load of <50 c/mL in Cohorts I and II, respectively (17). At Week 96, 26% of subjects in Cohort I had an HIV-1 RNA load of <50 c/mL. At Week 48, 71% of subjects in Cohort II had an HIV-1 RNA of <50 c/mL. Results from Study ING112961 concluded DTG 50 mg BID with an optimized background provided greater and more durable benefit than the once-daily regimen in patients with prior RAL treatment failure.

1.3 Clinical Pharmacokinetics in Adults

Absorption and Effect of Formulation

Following oral administration, absorption is rapid with average $t_{\text{max}}$ at one to two hours and subsequently the plasma drug concentration declines almost mono-exponentially with average terminal half-life estimated at ~14 hours, supporting once daily dosing.

DTG has been evaluated over the dosage range of 2 to 250 mg (suspension) and 2 to 100 mg (tablet). The rate and extent of absorption of DTG from the tablet formulation were reduced compared to the suspension formulation. At 20 mg dose, plasma AUC (0-∞), $C_{\text{max}}$ and $C_{24}$ were, on average, 30%, 42%, and 26% lower, respectively, for tablet compared to suspension; median $t_{\text{max}}$ was 0.75 hours for suspension and 2.5 hours for tablet. DTG exhibited linear pharmacokinetics with dose proportional increases in plasma exposure at doses from 2 to 100 mg using the suspension formulation, with less than dose proportional PK between 100 mg and 250 mg. For the tablet formulation, PK was close to linear over the dosage range of 2 to 50 mg but less than dose proportional between 50 mg and 100 mg. The PK of two new tablet formulations (AW and AX) were evaluated in protocol ING113674. Preliminary data demonstrate that both new 25 mg tablet formulations demonstrated bioequivalence with the current tablet being used in Phase IIb studies. Therefore, the 25 mg tablet with the 150 mg compression weight (AW) was selected for use in this study and Phase III adult clinical trials since it is a smaller tablet size and has lower PK variability. A 50 mg tablet using this formulation has been manufactured for use in this study and Phase III trials.

PK data (Week 2) are available from the Phase IIb SPRING-1 Study (ING112276) (Table 2). At Week 2, serial samples were obtained in 46 subjects and sparse samples were obtained in 90 subjects for determination of PK parameters. DTG was less than dose-proportional between 10 mg and 25 mg but linear between 25 mg and 50 mg. PK parameters were similar to those reported in ING111521, although higher PK variability was observed around AUC and $C_{\text{max}}$. The increased variability is expected given that these are outpatient HIV-infected subjects and the majority had sparse PK sampling.
Table 2: Summary of Week 2 DTG PK Parameters from ING112276

<table>
<thead>
<tr>
<th>Dose</th>
<th>Tablet</th>
<th>Parameter</th>
<th>Cmax (µg/mL)</th>
<th>AUC (µg.h/mL)</th>
<th>C(\tau) (µg/mL)</th>
<th>Cmin (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>10 mg</td>
<td>N GeoMean</td>
<td>15 1.10</td>
<td>15 16.0</td>
<td>47 0.30</td>
<td>15 0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CV%</td>
<td>37 37</td>
<td>40 40</td>
<td>71 71</td>
<td>64 64</td>
</tr>
<tr>
<td>25 mg</td>
<td>25 mg</td>
<td>N GeoMean</td>
<td>15 1.71</td>
<td>15 23.1</td>
<td>44 0.54</td>
<td>15 0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CV%</td>
<td>43 43</td>
<td>48 48</td>
<td>67 67</td>
<td>68 68</td>
</tr>
<tr>
<td>50 mg</td>
<td>2 x 25 mg</td>
<td>N GeoMean</td>
<td>15 3.40</td>
<td>15 48.1</td>
<td>44 1.20</td>
<td>15 0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CV%</td>
<td>27 43</td>
<td>40 62</td>
<td>62 74</td>
<td>74 74</td>
</tr>
</tbody>
</table>

Pharmacokinetics of DTG granule formulation

A granule formulation of DTG has been developed as an alternative to tablets for use in pediatric populations. In a single-center, randomized, open-label, 5-way crossover study (ING114556) in healthy adults, 20 subjects received a single dose of DTG 50 mg as the Phase III tablet and in 10 grams of granule (0.5% drug load) administered 1) direct to mouth; 2) with purified water; 3) with mineral water containing high cation concentrations; or 4) with a milk-based infant formula. Study treatments were separated by 7 days. Study data demonstrate that the plasma DTG exposures in all granule treatment arms exceeded those of the tablet formulation (Table 3). DTG PK exposure was similar when DTG was mixed with purified or cation-containing mineral water or given direct to mouth. Inter-subject variability was modest with CV% for AUC of 31-43%. DTG was well tolerated with no withdrawals due to AEs. Subjects were asked to assess the taste of the granule with regard to bitterness, color, and effect of sweetener on a scale of 1-5 when taken alone and with the various liquids. The majority of subjects found the taste to be moderately or less bitter. Color preference was mostly acceptable and sweetener had a moderate or strong effect.

The exposure of DTG following administration of the granule formulation alone, with different types of water and with formula exceeded that of the tablet, and DTG exposure from granule formulation was similar when given direct to mouth, or with different types of water, indicating DTG granule can be given without restriction on the type of liquid, or can be administered directly to mouth (e.g., when water that is safe to drink is not available) (Table 3).

Table 3. Treatment Comparison of DTG PK Parameters (Study ING114556)

<table>
<thead>
<tr>
<th>Comparison to tablet</th>
<th>GMR mean ratio (90%CI)</th>
<th>AUC(0-∞)</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granule direct to mouth</td>
<td>1.58 (1.46-1.71)</td>
<td>1.62 (1.49-1.77)</td>
<td></td>
</tr>
<tr>
<td>Granule with purified water</td>
<td>1.57 (1.45-1.70)</td>
<td>1.66 (1.52-1.81)</td>
<td></td>
</tr>
<tr>
<td>Granule with mineral water</td>
<td>1.55 (1.43-1.67)</td>
<td>1.65 (1.51-1.79)</td>
<td></td>
</tr>
<tr>
<td>Granule with formula</td>
<td>1.83 (1.69-1.98)</td>
<td>2.02 (1.86-2.20)</td>
<td></td>
</tr>
</tbody>
</table>

This adult relative bioavailability study utilized an early formulation in which the granules contained 0.5% DTG and were constituted as a suspension containing 2.5 mg/mL. The pediatric granule formulation to be used in the pediatric study has slightly different drug content with 0.4% of drug load (to be dosed as a 1.6 mg/mL suspension). The data from the adult relative bioavailability study showing equivalent exposure through dosing direct to mouth and as a suspension by mixing with water suggest that minor changes to the granule product (0.4% drug load dosed as a 1.6 mg/mL suspension) are unlikely to impact
upon the pharmacokinetics. The design of this pediatric study does allow for dose adjustment if any unforeseen impact on pharmacokinetics is observed.

**Pharmacokinetics of DTG dispersible tablet formulation**

A dispersible tablet formulation has been developed as an alternative to the pediatric granule formulation for administration in younger pediatric populations. In a single center, randomized, open-label, 5-period, single dose, crossover, relative bioavailability study (ING200401) in healthy adults, this study evaluated the PK of DTG given as dispersible tablet formulation compared to a DTG pediatric granule formulation and effect of different types of water on the dispersible tablet in healthy adult subjects. Fifteen healthy subjects were enrolled to provide data from at least 10 evaluable subjects. Subjects had a screening visit within 30 days prior to the first dose of study drug, five treatment periods each with administration of a single dose of study drug followed by 48 hours of serial PK sample collection, and a follow-up visit 7-14 days after the last dose of study drug. Eligible subjects were randomized to one of 5 treatment sequences. Subjects received 1) DTG 20 mg of the pediatric granule formulation reconstituted with purified water (Treatment A); 2) DTG 20 mg of the dispersible tablet formulation dispersed in low mineral content (LMC) water and taken by subject immediately (Treatment B); 3) DTG 20 mg of the dispersible tablet formulation dispersed in Contrex mineral water (5% Contrex / 95% purified water) and taken by subject immediately (Treatment C); 4) DTG 20 mg of the dispersible tablet formulation dispersed in LMC water, held for 30 minutes, re-dispersed, and then taken by subject (Treatment D); 5) DTG 20 mg of the dispersible tablet formulation dispersed in Contrex mineral water, held for 30 minutes, re-dispersed, and then taken by subject (Treatment E). There were washout periods of at least 7 days between treatments. DTG PK parameters were determined from serial PK samples collected over a 48-hour dosing interval and compared between treatments.

Preliminary study results found (Table 4):

- DTG PK exposure following a single dose oral administration of 20 mg dispersible tablets dispersed in low mineral content water is equivalent to that following a single dose oral administration of 20 mg granule formulation reconstituted with purified water.
- DTG PK exposure following a single dose oral administration of 20 mg dispersible tablets dispersed in Contrex mineral water is equivalent to that following a single dose oral administration of 20 mg dispersible tablets dispersed in low mineral content water.
- DTG PK exposure following a single dose oral administration of 20 mg dispersible tablets dispersed in both low and high mineral content water held for 30 minutes before, re-dispersed, and then consumed is equivalent to that following a single dose oral administration of 20 mg dispersible tablets redispersed in both low or high mineral content water and consumed immediately.

**Table 4: Treatment comparison of plasma DTG PK parameters, preliminary data**

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>GMR mean ratio (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC(0-∞)</td>
</tr>
<tr>
<td>Dispersible tablet in LMC&lt;sup&gt;a&lt;/sup&gt; water</td>
<td>1.07 (1.01, 1.13)</td>
</tr>
<tr>
<td>Dispersible tablet in Contrex water</td>
<td>0.944 (0.893, 0.999)</td>
</tr>
<tr>
<td>Dispersible tablet in LMC, held for 30 minutes, then re-dispersed</td>
<td>1.03 (0.971, 1.09)</td>
</tr>
<tr>
<td>Dispersible tablet in Contrex water, held for 30 minutes, then re-dispersed</td>
<td>1.05 (0.988, 1.11)</td>
</tr>
</tbody>
</table>

<sup>a</sup> LMC= low mineral content
Effect of food

The Phase III tablet formulation at a 50 mg dose demonstrated that low, moderate, and high fat meals increased DTG AUC (0-t) by 33%, 41%, and 65%, respectively. Such effect is not considered clinically significant based on accumulated toxicity data and safety and tolerability data in humans receiving DTG to date. DTG can be taken without regard to food.

Accumulation and Time-dependence

Following once daily dose administration, steady state was achieved after approximately 5 days of dosing. DTG (suspension and tablet formulations) showed time-invariant pharmacokinetics. The PK variability of DTG is between low to moderate with between-subject CV% for AUC and C\text{max} of ~20 to 30% and for C\text{τ} of 30 to 50%.

Metabolism and Excretion

DTG is primarily metabolized via UGT1A1 with a minor CYP3A component. DTG is the predominant circulating compound in plasma and renal elimination of unchanged drug is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the feces, but unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate which can be further degraded to form the parent compound. Protein binding in human serum is 99.3%.

Drug Interaction Profile of DTG

The drug interaction profile of DTG has been evaluated in a number of clinical studies in healthy volunteers (Table 5).
DTG has a low propensity to cause drug interactions. In a metabolic probe substudy, DTG did not alter the pharmacokinetics of midazolam, demonstrating that DTG does not induce or inhibit CYP3A4. In vitro studies in liver microsomes against other CYP isozymes demonstrate that DTG would not be expected to affect the exposure of concomitant medications that are metabolized by CYP450 enzymes. In addition, in vitro data demonstrate that DTG did not inhibit UGT2B7 and had only a 20% inhibition of UGT1A1, and this occurred at concentrations (IC50 > 100 μM) that are not clinically relevant. DTG also had no significant effect on tenofovir exposure (Table 6).

### Table 5: Effect of concomitant medications on DTG pharmacokinetics

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>N</th>
<th>DTG Dose</th>
<th>GMR1 (90% CI)</th>
<th>Cτ or C14</th>
<th>AUC</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF 300 mg QD</td>
<td>16</td>
<td>50 mg QD</td>
<td>0.920 (0.816-1.04)</td>
<td>1.01 (0.908-1.11)</td>
<td>0.969 (0.867-1.08)</td>
<td></td>
</tr>
<tr>
<td>DRV/r 600/100 mg BID</td>
<td>15</td>
<td>30 mg QD</td>
<td>0.620 (0.555-0.694)</td>
<td>0.782 (0.722-0.848)</td>
<td>0.892 (0.825-0.965)</td>
<td></td>
</tr>
<tr>
<td>LPV/r 400/100 mg BID</td>
<td>15</td>
<td>30 mg QD</td>
<td>0.944 (0.848-1.05)</td>
<td>0.973 (0.911-1.04)</td>
<td>1.00 (0.937-1.07)</td>
<td></td>
</tr>
<tr>
<td>ETV 200 mg BID</td>
<td>16</td>
<td>50 mg QD</td>
<td>0.121 (0.093-0.157)</td>
<td>0.294 (0.257-0.337)</td>
<td>0.484 (0.433-0.542)</td>
<td></td>
</tr>
<tr>
<td>ETV 200 mg BID + LPV/r 400/100 mg BID</td>
<td>8</td>
<td>50 mg QD</td>
<td>1.28 (1.13-1.45)</td>
<td>1.10 (1.02-1.20)</td>
<td>1.07 (1.02-1.13)</td>
<td></td>
</tr>
<tr>
<td>ETV 200 mg BID + DRV/r 600/100 mg BID</td>
<td>9</td>
<td>50 mg QD</td>
<td>0.63 (0.52-0.76)</td>
<td>0.75 (0.69-0.81)</td>
<td>0.88 (0.78-1.00)</td>
<td></td>
</tr>
<tr>
<td>Multivitamin</td>
<td>16</td>
<td>50 mg single dose</td>
<td>0.679 (0.560-0.824)</td>
<td>0.668 (0.553-0.806)</td>
<td>0.646 (0.540-0.774)</td>
<td></td>
</tr>
<tr>
<td>Maalox</td>
<td>16</td>
<td>50 mg single dose</td>
<td>0.256 (0.211-0.311)</td>
<td>0.264 (0.218-0.318)</td>
<td>0.276 (0.231-0.331)</td>
<td></td>
</tr>
<tr>
<td>Maalox 2 hrs after dolutegravir</td>
<td>16</td>
<td>50 mg single dose</td>
<td>0.703 (0.579-0.853)</td>
<td>0.743 (0.615-0.897)</td>
<td>0.821 (0.686-0.984)</td>
<td></td>
</tr>
<tr>
<td>ATV/r 300/100 mg QD</td>
<td>12</td>
<td>30 mg QD</td>
<td>2.21 (1.97-2.47)</td>
<td>1.62 (1.50-1.74)</td>
<td>1.33 (1.25-1.42)</td>
<td></td>
</tr>
<tr>
<td>ATV 400 mg QD</td>
<td>12</td>
<td>30 mg QD</td>
<td>2.80 (2.52-3.11)</td>
<td>1.91 (1.80-2.02)</td>
<td>1.49 (1.40-1.59)</td>
<td></td>
</tr>
<tr>
<td>Omeprazole 40 mg QD</td>
<td>12</td>
<td>50 mg single dose</td>
<td>0.954 (0.752-1.21)</td>
<td>1.00 (0.808-1.25)</td>
<td>0.915 (0.754-1.11)</td>
<td></td>
</tr>
<tr>
<td>Tipranavir/RTV 500/200 mg BID</td>
<td>13</td>
<td>50 mg QD</td>
<td>0.24 (0.21-0.27)</td>
<td>0.41 (0.38-0.44)</td>
<td>0.53 (0.50-0.57)</td>
<td></td>
</tr>
<tr>
<td>Efavirenz 600 mg QD</td>
<td>12</td>
<td>50 mg QD</td>
<td>0.25 (0.18-0.34)</td>
<td>0.43 (0.35-0.54)</td>
<td>0.61 (0.51-0.73)</td>
<td></td>
</tr>
<tr>
<td>FPV/RTV 700/100 mg BID</td>
<td>12</td>
<td>50 mg QD</td>
<td>0.51 (0.42-0.63)</td>
<td>0.65 (0.54-0.78)</td>
<td>0.76 (0.63-0.92)</td>
<td></td>
</tr>
</tbody>
</table>

1. GMR = geometric mean ratio
Table 6: Effect of DTG on the pharmacokinetics of concomitant medications

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>N</th>
<th>DTG Dose</th>
<th>GMR¹ (90% CI)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cτ</td>
<td>AUC</td>
<td>Cmax</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam 25 mg</td>
<td>10</td>
<td>25 mg once daily</td>
<td>ND</td>
<td>0.953 (0.790-1.15)</td>
<td>ND</td>
</tr>
<tr>
<td>TDF 300 mg QD</td>
<td>16</td>
<td>50 mg once daily</td>
<td>1.19 (1.04-1.35)</td>
<td>1.12 (1.01-1.24)</td>
<td>1.09 (0.974-1.23)</td>
</tr>
</tbody>
</table>

¹GMR = geometric mean ratio

With respect to DTG exposures, no clinically significant drug interactions requiring a dosage change have been observed with lopinavir/ritonavir, darunavir/ritonavir, atazanavir (ATV), atazanavir/ritonavir (ATV/r), fosamprenavir/ritonavir (FPV/RTV), tenofovir, and omeprazole.

ATV increased DTG AUC and Cmax by 91% and 49%; ATV/r increased DTG AUC and Cmax by 62% and 33%. Based on clinical data, the magnitude of the drug interaction is not clinically significant; therefore no dose adjustment is needed. However, such interaction will increase the PK variability. As the key of the PK evaluation in the pediatric study is to evaluate the impact of development (organ maturation, age, or body size) on DTG in order to guide dose selection, it would be optimal to limit other confounding factors that introduce variability as much as possible, especially during the intensive PK evaluation/dose determination in Stage 1. Therefore, use of ATV and ATV/r will be excluded during the intensive PK assessment in Stage 1.

Etravirine (ETR) reduced the steady-state Cτ and AUC of DTG by 88% and 71%, respectively, which could be clinically relevant, particularly in subjects failing RAL therapy. The mechanism for the reduction in DTG exposure is not known, but may be a result of net induction of CYP3A, UGT, and /or P-glycoprotein. The significant decrease in DTG exposure with ETR can be counteracted by adding LPV/r or DRV/r. Other CYP3A and UGT inducers decrease plasma exposures of DTG. Tipranavir (TPV)/RTV and EFV decrease DTG AUC (0-τ) and Cτ by approximately 60% and 75%, respectively.

Predicted AUC and Cτ values in HIV-infected subjects receiving 50 mg of DTG that are achieved in combination with these inducers can be estimated using the geometric mean ratio (GMR) and PK data from the Phase IIb study (Table 2). The resulting PK parameters are similar to those at the 10 mg dose from the SPRING Phase IIb study (ING112276).

At the Week 24 interim analysis for ING111762 (treatment experienced, INI-naïve adults), the observed DTG Cτrough (C0_avg) from DTG 50 mg once daily in combination with OBT was lower with higher variability (geometric mean [CV%] 0.856 μg/mL [140%]) than has been observed in the Phase III treatment-naïve trial ING113086 which demonstrated the geometric mean (CV%) of DTG Cτrough (C0_avg) at 1.18 μg/mL (60%) for DTG 50 mg once daily in combination with dual nucleoside reverse transcriptase inhibitor therapy. The differences in DTG C0_avg observed in the current study are due to the use of metabolic inducers and inhibitors in background therapy (e.g., DRV/r, FPV/r, EFV, TPV/r, ATV/r) in the majority of subjects, as well as less optimal compliance (based on non-detectable DTG concentrations).

The Week 24 data analyses of the Phase III study ING111762 in adults demonstrated that subjects receiving DTG 50 mg once daily in combination with concurrent TPV/r or EFV (n=16) had lower DTG Cτrough (78% lower) and suboptimal virologic responses in comparison with other subjects receiving DTG without TPV/r or EFV, but had comparable virologic responses to those subjects receiving raltegravir (RAL). Although the data were limited, in light of the lower Cτrough observed in the
aforementioned Phase I studies and in ING111762 in subjects receiving these inducers, DTG 50 mg twice daily dosing is recommended in INI-naïve subjects (treatment-naïve or treatment-experienced) requiring TPV/r or EFV in their background therapy. Dolutegravir Ctrough from 50 mg twice daily dosing co-administered with these moderate/strong inducers is estimated at 1.20 μg/mL, which is 40% higher than the geometric mean of Ctrough (C0_avg) observed in ING111762 (0.856 μg/mL). It is expected that DTG 50 mg twice daily with TPV/r, FPV/r, or EFV would demonstrate antiviral response comparable to the response rate observed in subjects receiving DTG 50 mg once daily without TPV/r or EFV.

Therefore, it is recommended that the dose of DTG be increased to twice daily in subjects receiving EFV, FPV/r, or TPV/r concomitantly. The DTG unit dose in mg will still be based on weight banding per the IMPAACT P1093 Dosing Table Appendix which is available at http://impaactnetwork.org/studies/P1093.asp

As the key of the PK evaluation in the pediatric study is to evaluate the impact of development (organ maturation, age, or body size) on DTG in order to guide dose selection, it would be optimal to limit other confounding factors that introduce variability as much as possible, especially during the intensive PK evaluation/dose determination in Stage 1. Therefore, use of ATV, boosted (ritonavir or cobicistat) ATV, FPV, TPV/r, FPV, and EFV will be disallowed during the intensive PK assessment in Stage 1.

DTG is recommended to be taken at least two hours prior or 6 hours after antacids due to reduced absorption resulting from chelation with metal cations in antacids (15). However DTG can be taken with proton pump inhibitors and H2 blockers without restriction. Concomitant administration with a multivitamin containing metal cations modestly decreased DTG AUC (0-τ) by 33% and DTG may be administered concurrently with multivitamins. These dosing recommendations are supported by clinical data (18). Concomitant administration with an antacid, Maalox Maximum Strength, decreased the AUC (0-τ) of DTG by 74%. The reduction in exposure was decreased to 26% when DTG was administered 2 hours before the antacid.

Effect of rifampin on DTG

Rifampin induces UGT1A1 and CYP3A4 which are involved in DTG metabolism. This study (ING113099) evaluated whether increasing the DTG frequency of administration and total daily dose could overcome the anticipated reduction in DTG exposure by rifampin. In an open-label, three-period, fixed-sequence drug interaction study, 11 healthy subjects received DTG 50 mg once daily for seven days (period 1), then DTG 50 mg twice daily for seven days (period 2), then DTG 50 mg twice daily together with rifampin 600 mg once daily (period 3) for 14 days. Twice daily DTG plus rifampin achieved mean PK parameters that were 18-33% higher than once daily dosing alone. Comparing period 3 (DTG twice daily plus rifampin) to period 1 (DTG once daily), the GMR for the 24-hour area under the time-concentration curve (AUC0-24) was 1.33 (90% CI 1.154 to 1.534), and the GMR for the trough at the end of the dosing interval (Cτ) was 1.22 (90% CI 1.01 to 1.48). There were no discontinuations for adverse events (AEs) and no Grade 3 or higher AEs. These data support a strategy of DTG 50 mg twice daily when co-administered with rifampin.

1.4 Clinical Pharmacokinetics in P1093 Cohorts I and IIA

For P1093 Cohort I Adolescents ≥ 12 to < 18 years of age:

During Stage I, nine subjects received DTG film-coated tablets 50 mg and one subject received 35 mg daily. The DTG dosage of approximately 1 mg/kg/day achieved the desired primary endpoint (AUC0-24) and secondary endpoint (C24) with no dose adjustment or modification (Table 7). DTG demonstrated
moderate inter-subject PK variability; geometric mean (CV%) AUC_{0-24} and C_{24} were 46.0 (43%) µg.h/mL and 0.90 (58%) µg/mL, respectively (Table 7) (19).

Table 7: DTG pharmacokinetic parameters in Cohort I, Stage I (N=10)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Median (min, max)</th>
<th>GM</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>14.62 (±2.05)</td>
<td>14.11 (12.23, 17.86)</td>
<td>14.49</td>
<td>14.00</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.16 (±17.93)</td>
<td>50.85 (37.10, 91.40)</td>
<td>55.00</td>
<td>31.38</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>48.50 (±4.74)</td>
<td>50 (35, 50)</td>
<td>48.25</td>
<td>9.78</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>0.90 (±0.19)</td>
<td>0.96 (0.55, 1.09)</td>
<td>0.88</td>
<td>21.50</td>
</tr>
<tr>
<td>T_{1/2} (hr)</td>
<td>12.71 (±5.43)</td>
<td>10.44 (8.24, 24.80)</td>
<td>11.87</td>
<td>42.73</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>3.00 (1.00, 6.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>3.82 (±1.46)</td>
<td>4.01 (1.15, 6.08)</td>
<td>3.48</td>
<td>38.36</td>
</tr>
<tr>
<td>C_{24} (µg/mL)</td>
<td>1.09 (±0.64)</td>
<td>1.14 (0.21, 2.12)</td>
<td>0.90</td>
<td>58.62</td>
</tr>
<tr>
<td>AUC_{0-24} (µg.hr/mL)</td>
<td>51.57 (±22.24)</td>
<td>52.92 (13.05, 84.96)</td>
<td>43.13</td>
<td>45.97</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>1.25 (±0.97)</td>
<td>0.87 (0.59, 3.83)</td>
<td>78.03</td>
<td>1.05</td>
</tr>
</tbody>
</table>

SD; standard deviation, min; minimum value, max; maximum value, GM; geometric mean, CV; coefficient of variation, T1/2; half life, Tmax; time to maximum plasma concentration, Cmax; maximum plasma concentration, C24; concentration 24 hours after dosing, AUC0-24; area under the plasma concentration time curve from time of administration to 24 hours after dosing, CL/F; oral clearance

For P1093 Cohort IIA Children ≥ 6 to < 12 years of age:

In Cohort IIA, eleven children received DTG film-coated tablets. The mean (SD) age was 9.5 yrs (±1.8); weight was 34.9 kg (±11.9). Five subjects (≥ 40 kg of weight) received DTG 50 mg, two subjects (30 < 40 kg ) received DTG 35 mg and four subjects (20 <30 kg) received DTG 25 mg once daily. DTG geometric mean (CV%) AUC_{0-24} and C_{24} were 50.46 (63%) µg.h/mL and 0.92 (89%) µg/mL respectively (20).

1.5 Summary of Safety in Clinical Trials

DTG has been administered to 248 healthy adult subjects and 28 HIV-infected adult subjects in 12 completed and fully analyzed Phase I/Iia clinical studies (i.e., PK and safety dose escalation studies: ING111207, ING111322; drug interaction studies: ING111604, ING111405, ING111603, ING111602, ING112934, ING111854, ING112941; mass balance study: ING111853; thorough QT study [TQTS]: ING111856; and Phase 2a study ING111521). As part of these 12 completed clinical pharmacology studies, 118 healthy subjects have received single doses of DTG up to 250 mg, 130 healthy subjects have received repeat, once-daily doses of DTG at up to 50 mg for up to 19 days, and 28 HIV-infected subjects have received repeat, once-daily doses of DTG at up to 50 mg for up to ten days.

In addition, two Phase I studies are complete with data analysis underway (ING113096 and ING114005) and one Phase I study is ongoing (ING113674) to further characterize the clinical pharmacology of DTG in approximately 54 additional healthy adult subjects (24 healthy adult subjects receiving single 50 mg doses of DTG in ING113674 and 30 healthy adult subjects receiving repeat, once-daily doses of DTG 50 mg to 100 mg for up to 20 days in ING113096 and ING114005).
Finally, 182 HIV-infected adult subjects participating in two ongoing Phase IIb studies ING112276 (SPRING-1) and ING112961 (VIKING) have received repeat, once-daily doses of DTG (10 to 50 mg) for a maximum of 315 days to 30 June 2010.

Thus, to the same date, a total of approximately 512 subjects have been exposed to at least one dose of DTG (ranging from 2 mg to 250 mg).

**Meta Analysis of 12 Completed Phase I/IIa Clinical Pharmacology Studies**

Twelve DTG Phase I/IIa studies have been completed to date (see above) and the safety data from these studies have been pulled together to evaluate the safety profile of DTG.

Table 8: All AE Summary by DTG Dose (reported in ≥7 subjects)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>PBO (n=60)</th>
<th>2 mg (n=17)</th>
<th>5 mg (n=7)</th>
<th>10 mg (n=25)</th>
<th>20 mg (n=19)</th>
<th>25 mg (n=18)</th>
<th>30 mg (n=55)</th>
<th>50 mg (n=104)</th>
<th>100 mg (n=5)</th>
<th>250 mg (n=49)</th>
<th>All Active 572 (n=276)</th>
<th>All (n=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>14 (23%)</td>
<td>6 (35%)</td>
<td>1 (14%)</td>
<td>13 (52%)</td>
<td>10 (53%)</td>
<td>5 (28%)</td>
<td>36 (65%)</td>
<td>44 (42%)</td>
<td>2 (40%)</td>
<td>17 (35%)</td>
<td>131 (47%)</td>
<td>142 (48%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>4 (16%)</td>
<td>4 (21%)</td>
<td>0 (18%)</td>
<td>15 (14%)</td>
<td>0 (6%)</td>
<td>3 (13%)</td>
<td>37 (13%)</td>
<td>39 (13%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3%)</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
<td>0 (9%)</td>
<td>5 (5%)</td>
<td>0</td>
<td>8 (16%)</td>
<td>20 (7%)</td>
<td>21 (7%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (5%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>3 (12%)</td>
<td>2 (11%)</td>
<td>0</td>
<td>7 (13%)</td>
<td>4 (4%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>18 (7%)</td>
<td>21 (7%)</td>
</tr>
<tr>
<td>Ocular Icterus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11 (20%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11 (4%)</td>
<td>11 (4%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (3%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>2 (4%)</td>
<td>7 (3%)</td>
<td>9 (3%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (12%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (5%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>8 (3%)</td>
<td>8 (3%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>7 (3%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (3%)</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>3 (5%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>5 (2%)</td>
<td>7 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

All adverse events are summarized by DTG dose levels and by active vs. placebo and overall (Table 8). The doses include those administered in single and repeated doses. Among the 276 subjects dosed with DTG, AEs observed in at least 3% of subjects are headache (13%), nausea (7%), diarrhea (7%), ocular icterus (4%), abdominal pain (3%), dizziness (3%), and vomiting (3%). No consistent dose-related trends for any individual AE over the DTG dose range of 2~250 mg was observed. All of the ocular icterus events were reported during the co-administration of DTG with ATV or ATV/r. Overall, headache was reported in more subjects receiving DTG (active) than those receiving placebo; however, most of the placebo administration was single dose.

No deaths were reported in these studies nor did any subjects become pregnant. Only one non-fatal SAE was reported for these studies; this was an episode of mania in a healthy subject with an undisclosed relevant medical history of anxiety, bipolar I disorder, post-traumatic stress disorder and cocaine use. This SAE was not considered reasonably attributable to DTG by the investigator.

No healthy subjects experienced a severe or Grade 3 AE with DTG, and only three HIV-infected subjects receiving DTG were reported with severe AEs. Drug-related AEs have been infrequently reported. No
clinically significant trends in treatment emergent clinical chemistries, hematology abnormalities, ECGs or vital signs were noted. Overall, DTG was well tolerated among the 276 subjects dosed with DTG.

**Additional Phase I Clinical Pharmacology Studies (n=3)**

Three additional clinical pharmacology studies were either completed with data analysis underway (n=2) or still ongoing (n=1) by 30 June 2010 with approximately 24 healthy adult subjects receiving single 50 mg doses of DTG (relative bioavailability of DTG tablet formulations ING113674) and 30 healthy adult subjects receiving repeat, once-daily doses of DTG (50 mg) for up to 20 days (drug interactions studies ING113096 [ritonavir boosted tipranavir] and ING114005 [efavirenz (EFV)]).

Only preliminary safety data are available for these studies; there were no deaths, non-fatal SAEs, Grade 3/4 AEs or pregnancies. Four subjects were discontinued from DTG due to treatment emergent events/laboratory toxicities (all four due to ALT elevations observed during co-administration of DTG with ritonavir boosted tipranavir in ING113096). Further details are provided in the DTG IB.

**Ongoing Phase IIb Clinical Trials (n=2)**

ING112276 (SPRING-1) and ING112961 (VIKING) are currently investigating the antiviral activity and tolerability of DTG when used in combination therapy to treat HIV- infection in antiretroviral naïve (n=205) and raltegravir resistant (n=27) adult patient populations, respectively. ING112276 includes a control treatment group involving EFV (n=50) and three treatment groups evaluating different once daily doses of DTG (i.e., 10 mg [n=53], 25 mg [n=51] and 50 mg [n=51]), whereas ING112961 does not have a comparator or control arm and is currently investigating one dose of DTG (cohort I: 50 mg once daily [n=27]; cohort II: 50 mg twice daily, is currently enrolling). Both studies have recently undergone interim analyses on 24 week data.

Eleven subjects exposed to DTG as part of these two studies have developed a SAE up to the cutoff date of 30 Jun 2010 (seven in ING112276 and four in ING112961); two of these subjects subsequently died as result of the reported SAE (febrile bone marrow hyperplasia secondary to B-cell immunoblastic lymphoma and brain mass; both reported from ING112961). None of the SAEs developed by these eleven subjects were considered reasonably attributable to DTG by the reporting investigator. In addition, one female subject receiving DTG in ING112276 became pregnant after the cutoff date for the 24 week interim analysis with the pregnancy still ongoing at 30 June 2010.

A total of four subjects were withdrawn from treatment with DTG due to an adverse event (two in each study), with the event being serious in three out of the four subjects. Both subjects in ING112961 who died were withdrawn due to the SAEs noted above prior to death (~3 months for subject with brain mass and 2 days for the subject with febrile aplasia). Neither event was considered related to DTG. One subject receiving DTG 50 mg in ING112276 had a non-fatal SAE of Burkitt’s lymphoma, which lead to withdrawal for chemotherapy and was not considered related to DTG and another subject receiving DTG 25 mg had dyspepsia, considered reasonably attributable to DTG by the reporting investigator. The single pregnancy in ING112276 also led to withdrawal of DTG as outlined per protocol.

Seventy nine percent of subjects (123/155) in ING112276 and 85% of subjects (23/27) in ING112961 exposed to DTG developed any AE. There were no dose-related trends in either clinical or laboratory adverse events reported among subjects in the DTG treatment groups of ING112276. Headache, upper respiratory tract infection and abdominal pain were more frequently observed in the DTG groups compared to the EFV control group in this study. The most commonly reported AEs in ING112961 were diarrhea and headache (4% of subjects each). The majority of subjects developing an AE in either study
developed AEs with a maximum toxicity of Grade 1/2 (95% [117/123] in ING112276 and 74% [17/23] in ING112961).

No clinically significant trends in treatment emergent hematology abnormalities, vital signs or ECG assessments were noted in either study. In ING112276, no apparent dose-response relationships were observed with specific treatment-emergent, laboratory abnormalities within DTG treatment arms. The only laboratory abnormalities observed on DTG that were not observed in the EFV treatment arm were treatment emergent Grade 1 total bilirubin and Grade 1 creatinine abnormalities and changes in urine protein results. These increases were statistically significantly different than those seen in the EFV control group of the study, but these changes were not progressive in nature and were not associated with clinically significant changes for individual subjects with respect to AEs, graded lab abnormalities or withdrawals. Similar changes in creatinine and urine protein (dip stick results) were observed in ING112961 in an advanced HIV population. Further in vitro and clinical investigations are currently ongoing to better understand the renal and bilirubin changes. Further details are provided in the DTG Investigators Brochure.

**Conclusion**

DTG-based regimens have demonstrated good tolerability, as shown by the last integrated analyses of safety data performed by the Marketing Authorisation Holder (MAH) from the entire DTG clinical program, through to 26 October 2013, as presented in the current Investigator Brochure (IB) for DTG (11). This included Integrated Safety Outputs (ISOs) comprising a total of 1843 subjects who had been exposed to at least one dose of DTG in ViiV-sponsored phase IIb to IIIb clinical trials, with a median duration of exposure of 590 days (range: 1 to 1031 Days) or an equivalent of 2595.2 patient years exposure.

The majority of subjects developed at least one AE (86% [1585/1843]), with diarrhea (18% [335/1843]), headache (13% [242/1843]) and nausea (13% [247/1843]) being most frequently reported.

A small proportion of subjects developed AEs considered of Grade 3 to 4 intensity AE (14% [263/1843]), and in only 2% of subjects (30/1843) were Grade 3 to 4 events considered reasonably attributable to DTG by the reporting Investigators (i.e., ‘drug-related’). A small proportion of subjects developed SAEs and very few developed drug-related SAEs (12% [218/1843]) and <1% [10/1843], respectively), with no trends in the SAEs reported noted across the patient populations. A total of 13 of these SAEs involved a fatal outcome (<1%). None of these deaths were considered drug-related. The majority of the deaths (9/13) involved ART-experienced (INI-resistant) subjects. This observation is not unexpected given the late stage of HIV disease in this patient population.

Few subjects (3% [52/1843]) receiving DTG developed AEs resulting in the permanent discontinuation of IP and withdrawal from the study. There were no discernible trends for AEs leading to withdrawal for the DTG group, as most of these events were isolated cases in individual studies or expected trends for the comparator treatment groups. However, withdrawals due to liver stopping criteria were noted on DTG and comparator groups across the Phase IIb and III studies, and are described in detail in the current IB for DTG (11).

Small increases in serum creatinine have been observed across the DTG dosing arms in ING112276 and ING112961. These changes were not progressive in nature and were not associated with clinically significant changes for individual subjects with respect to AEs, graded lab abnormalities or withdrawals. In addition, changes in urine protein (dip stick) results have been observed in ING112276 and ING112961, with no time- or dose-dependency to these results. Subsequent analyses (as presented in detail in the current IB for DTG (11), have shown that: 1) the small increases in mean serum creatinine
observed in subjects treated with DTG across the entire clinical development program, are related to a likely benign effect on creatinine secretion via blockade of the OCT2 receptor, which is responsible for tubular secretion of creatinine; and 2) dipstick measurements of urinary albumin appeared unreliable, particularly in the EFV controlled studies and the more accurate measurement of albumin/creatinine ratio confirmed there was no difference in the effect of DTG on albumin excretion compared with EFV, RAL or DRV+RTV. Overall, the renal profile of DTG was comparable to RAL, EFV, and DRV+RTV.

Recognized risks for DTG-based therapy include: hypersensitivity reactions (HSRs); hepatitis (most prominent in the setting of hepatitis B virus [HBV]/ hepatitis C virus [HCV] co-infection); depression, suicidal ideation and suicidal behaviors (especially in patients with history of psychiatric illness); and a potentially serious drug interaction with dofetilide. However, as presented in the current IB for DTG (11), relative to other current treatment options, DTG has an acceptable safety profile in patients with HIV who have not been treated before with INIs, and it has the potential to provide significant benefit with optimized background therapy (OBT) in most adults with multi-drug resistance that includes resistance to the currently marketed INIs.

1.6   **Rationale**

There is an unmet medical need for novel and potent antiretroviral therapy for HIV-infected subjects who are experiencing drug resistance or toxicity, or who are failing their current antiretroviral regimen. These subjects are often heavily pre-treated and have very limited therapeutic options. Drugs with new mechanisms of action, such as the HIV integrase inhibitors, demonstrate activity even in subjects with resistance to currently available reverse transcriptase and protease inhibitors.

Younger children, who are infected despite exposure to ARVs in utero and after birth for prevention of mother to child transmission (PMTCT) may have virus that is resistant to currently available medications and also need new options. The purpose of this pediatric study is to determine the appropriate dose for the pediatric DTG formulations and acquire short and long term safety data, intensive and population PK data, and efficacy experience with DTG in HIV-1 infected children with which to guide potential use in children ages 4 weeks through adolescence.

This trial is designed to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of DTG. Results from this trial will be used to support regulatory filing for DTG use in pediatrics. In prior versions of the protocol, only treatment-experienced children were eligible for enrollment. In Version 4.0, enrollment has been expanded to include treatment-naïve infants and children. This expansion is based on information obtained from children and adolescents enrolled into Cohorts I and IIA of the study, establishment of the DTG doses for those age ranges, regulatory approval of DTG for children > 12 years of age, and inclusion of DTG as a recommended first line therapy for adolescents and adults in U.S. Public Health guidelines (21).

The objectives of Stage I are to examine pharmacokinetic parameters after intense sampling and evaluate the short term tolerability and safety of DTG in approximately ten subjects per cohort allowing the selection of a dose for further study in Stage II. Adding DTG to the failing regimen prior to optimizing background therapy will allow more robust analysis of antiviral activity and safety and tolerability of DTG by separating it out from PK effects by simultaneous introduction of an OBT. The intensive PK evaluation is to be performed on Days 5-10 to minimize the risk of sub-optimal doses (as identified by real-time PK evaluation) being used for prolonged periods of time. If the intensive PK were to be performed after the background therapy was optimized (OBT) with an agent affecting DTG exposure, the PK evaluation would need to be delayed for 10-20 days after OBT was started to allow achievement of
steady state for the OBT and DTG. However, concomitant introduction of NRTI agents or lopinavir/r are not expected to alter steady state DTG levels.

The purpose of restricting certain therapy (ritonavir or cobicistat boosted ATV, FPV or TPV, or ATV, EFV and FPV) during the intensive PK evaluation in Stage I is to limit PK variability due to dynamic drug-drug interactions; therefore allowing more consistent PK analysis. As this is the first pediatric trial of DTG to understand how the drug behaves in pediatrics compared to adults; and because data will be used for regulatory approval, the Protocol Team believes that it is important to evaluate and perform intensive PK while limiting the effects of known interactions and thus PK variability. Such design will help to evaluate the true impact of development pharmacology (i.e. age, organ maturation and body size) on the PK of this compound without confounding factors such as drug interactions. GSK believe that no dosage alteration is required for the restricted drugs; however, as children typically have highly variable pharmacokinetics, the team believes it is best to perform dose selection based on data without additional variability from these drug interactions.

1.6.1 Target Pharmacokinetic Exposure for Dose Selection

DTG has demonstrated good short-term safety/tolerability and antiviral activity as monotherapy and combination therapy in Phase IIb and Phase III in adults. Based on Week 24 results from the on-going Phase IIb dose-ranging trial in treatment-naïve subjects, the 50 mg once daily dose was selected for Phase III trials in the INI-naïve patient population. The goal of this study is to determine a pediatric dose that approximates adult exposure (primary parameter is AUC\textsubscript{0-24} and secondary parameter is C\textsubscript{24h}) observed at the 50 mg once daily dose from Phase I and II trials of DTG. Steady state pharmacokinetic data will be collected in real time for dose selection. As it is expected AUC\textsubscript{0-24} should have much lower variability than C\textsubscript{24h} and there has been good correlation between AUC\textsubscript{0-24} and C\textsubscript{24h} after once daily dosing, the primary pharmacokinetic endpoint is the AUC\textsubscript{0-24}, with C\textsubscript{24h} as secondary endpoint. Two sets of PK exposure criteria are developed: the minimal and maximal exposure and the target population exposure. The minimal and maximal exposure is developed for patient management in case of extreme exposure which prevents the subject to be considered as evaluable. The target population exposure (range) is developed for dose selection for the population.

Minimal and Maximal Exposure

Since pediatric pharmacokinetics tend to be more variable than adults, a lower threshold range for both the AUC\textsubscript{0-24} and C\textsubscript{24h} have been identified. Using maximum effect (E\textsubscript{max}) models, the estimated AUC\textsubscript{0-24} required to produce 95% of the maximum virologic response (EC\textsubscript{95}) is 25\mu g.h/mL, and the EC\textsubscript{95} for the C\textsubscript{24h} is 0.5\mu g/mL. Therefore, with the one exception identified below, all subjects must meet these minimum exposure targets. These are to be considered the lowest threshold exposures acceptable in this study. This lower threshold is in place to ensure minimum exposure criteria are met in case, for some reason, the targeted range cannot be met in an individual using the selected dose for the population. Similarly, the maximal exposure (upper threshold) is also defined to ensure subjects are not exposed to extremely high drug concentrations which may cause safety concerns. Based on accumulated data in adults (in Phase I and IIb) to date, DTG is generally well tolerated with no significant safety issues identified. A dose of DTG 50 mg BID was studied in ING112961 (VIKING) and ING112574 (VIKING3) in adult HIV-infected subjects. The exposure (geometric mean, 80%-CI) at steady state following 50 mg BID exposure was 75.1 (50-115) \mu g.h/mL. Therefore, the maximal exposure target is 115\mu g.h/mL for AUC0-24. Which is the upper limits of 80th percentiles around the AUC\textsubscript{24}. Such upper threshold may be adjusted upon availability of further clinical data.
An exception to the minimum exposure target may be allowed. When a subject has a low drug exposure, after consideration of the clinical, pharmacologic, immunologic and virologic data, and upon agreement of the site investigator, study co-chairs, pharmacologist and medical officers, a given subject may be allowed to continue with the study drug at the initial dosing that resulted in the exposures below the minimum target. Individual subjects with extreme PK values (less than the minimal and greater than the maximal exposure as defined above) using the selected dose for the population are eligible for individual dosage adjustment.

**Target Population Exposure**

The proof of concept (POC) study (ING111521) used doses of 2, 10, and 50 mg once daily as monotherapy for 10 days in treatment naïve subjects. Spring-1 (ING112276) is an ongoing Phase IIb trial where treatment naïve subjects are receiving 10, 25, or 50 mg once daily for 96 weeks; preliminary data suggest the regimens are equivalent in antiviral activity and safety for up to 24 weeks. Both studies incorporated intensive pharmacokinetic sampling at steady-state. Table 9 summarizes the pharmacokinetic parameters from 25 subjects at the 50 mg once daily dose (combining these two studies).

### Table 9: Statistic Summary of DTG PK Exposure from Combined Data in ING111521 and ING112276

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Dose (mg)</th>
<th>N Obs</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Median</th>
<th>10th Pctl</th>
<th>25th Pctl</th>
<th>75th Pctl</th>
<th>90th Pctl</th>
<th>Geometric Mean</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCTAU</td>
<td>50</td>
<td>25</td>
<td>48.33</td>
<td>14.63</td>
<td>47.73</td>
<td>30.67</td>
<td>42.32</td>
<td>55.96</td>
<td>67.22</td>
<td>46.14</td>
<td>32.84</td>
</tr>
<tr>
<td>C0</td>
<td>50</td>
<td>24</td>
<td>1.09</td>
<td>0.60</td>
<td>1.02</td>
<td>0.46</td>
<td>0.67</td>
<td>1.32</td>
<td>1.87</td>
<td>0.95</td>
<td>59.69</td>
</tr>
<tr>
<td>CMAX</td>
<td>50</td>
<td>25</td>
<td>3.46</td>
<td>0.84</td>
<td>3.46</td>
<td>2.63</td>
<td>3.04</td>
<td>3.71</td>
<td>4.07</td>
<td>3.38</td>
<td>22.77</td>
</tr>
<tr>
<td>CTAU</td>
<td>50</td>
<td>25</td>
<td>1.08</td>
<td>0.56</td>
<td>0.96</td>
<td>0.60</td>
<td>0.80</td>
<td>1.17</td>
<td>2.26</td>
<td>0.96</td>
<td>56.97</td>
</tr>
</tbody>
</table>

DTG at the 50 mg dose yields a geometric mean (GM) AUC0-24 of 46 µg.h/mL and C24h, 0.96 µg/mL. Based upon these data and the pharmacodynamic (concentration-response) results from the POC trial, it is clear that both the AUC0-24 and C24h are well in excess of the modeled EC90 values for each parameter and it is unlikely that when targeting a 50 mg adult dose exposure in pediatrics the minimal exposure thresholds described above will be breached, assuming similar absorption and disposition characteristics and PK variability in children relative to adults.

The 50 mg adult dose AUC0-24 target value is 46µg.h/mL. However, there will be variability around these targets which are acceptable. Therefore, the target range is defined as follows: the lower limit is selected as 80% of the geometric means (37 µg.h/mL) for AUC0-24. The upper limit for target exposure (AUC24) is selected as the 90th percentiles around the AUC24 (86 µg.h/mL) observed in pediatric subjects in P1093 which is found to be safe. In other words, the goal exposure for AUC0-24 is 46 with an acceptable range of 37 – 86 µg.h/mL. Based on the result from Cohorts I-III from the P1093 study, the target range for C24hr is selected as 0.5 – 2.6 ug/mL. The lower limit is set as the lower 80th percentile of observed data and upper limit is decided as the upper 80th percentile of pediatric observed C24h concentrations. The first 4 subjects (mini cohort) must have a GM AUC0-24 and C24h within this range. Subjects falling below these ranges but above the minimum threshold will be discussed by the team on an individual basis.
1.6.2 Justification of Selection of Initial Dose(s)

The proposed initial starting dose(s) for Cohort I and Cohort IIA using the tablet formulation is presented in Table A in the IMPAACT P1093 Dosing Table Appendix posted on the study-specific web page: http://impaactnetwork.org/studies/P1093.asp

To provide convenience and enhance compliance, DTG is to be dosed at fixed doses by weight band. The proposed initial doses are justified based on review of approved pediatric doses versus adult doses of currently marketed antiretroviral agents as well as predicted exposure in pediatrics through allometric scaling of adult PK parameters. The dosing scheme as proposed in Table A (posted on the study-specific web page referenced above) served as the initial doses for Cohort I. The optimal dose for Cohort I to be selected as well as the initial dose(s) for Cohort IIA will be determined based on observed PK from Stage I in Cohort I by matching the target population exposure as discussed in Section 1.6.1.

As the granule formulation to be used demonstrated higher exposure than the tablet formulation, the proposed initial doses using the granule formulation for Cohort IIB and successive cohorts are calculated by adjusting the tablet dose(s) by a common factor with goal to match target exposure in adults. As DTG exposure from granule formulation given direct to mouth or with different types of water were similar and demonstrated 55-58% higher exposure than the tablet formulation, doses for granule formulation are obtained by dividing the tablet doses by a common factor of 1.55 for each weight band. Under protocol Version 3.0, the pharmacokinetic targets for Cohort IIB Stage I and Cohort III Stage I were met, but required an increased dose of ~0.8 mg/kg (granule formulation); there were no safety concerns in either Cohort. Per protocol, Cohort IV Stage I (≥ 6 months to < 2 years of age) opened for enrollment with an initial dose of ~0.8 mg/kg (granule formulation) and is enrolling.

1.6.3 Justification for the management of HIV-infected children < 2 years of age

There is a particular need for new ARVs like DTG to treat HIV-infected children < 2 years of age. Access to ARVs for pregnant women has increased and rates of vertical transmission have decreased globally (22). However, the expanded use of NNRTIs has also corresponded with rising rates of ARV resistance that limit the utility of NVP for the treatment of infected infants (23, 24). LPV/r is recommended by the World Health Organization as first line for treatment of children < 2 years (25), but there are persistent concerns about the storage requirements and palatability (26).

The clinical management of young HIV-infected children is distinguished by the urgency with treatment must be initiated. HIV-infected children < 2 years of age suffer rapid disease progression and high mortality rates (27). Current guidelines recommended treatment for all HIV-infected children, but initiation is considered “urgent” for children < 2 years of age by the World Health Organization (25) and United States Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (28). Accordingly, national guidelines in limited resource countries often recommend initiation of ART on the basis of a single positive HIV nucleic acid based test, rather than waiting for results from confirmatory testing (29, 30).

P1093 Version 4.0 has expanded eligibility criteria to include children < 2 years who are ART-naive or have recently started ART (< 4 weeks prior). So that treatment initiation remains in accordance with current guidelines and standard of care, children < 2 years of age are allowed to enroll and:
1. Initiate ART with only a single positive nucleic acid test as long as a confirmatory test is pending.
2. Utilize background regimens that are empiric or based on national guidelines while the results of genotype testing drawn at screening are pending. Background therapy will subsequently be optimized based upon the results of the genotype.

1.7 Hypothesis

DTG will be generally well tolerated and demonstrate an acceptable safety profile, adequate PK and antiviral activity when used concurrently with an optimized background therapy (OBT) in HIV-1 infected infants, children and adolescents.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To select a dose for each formulation of DTG for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily adult dose.

2. To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.

3. To evaluate the steady-state pharmacokinetics of DTG in combination with other antiretrovirals (OBT) in treatment-experienced and/or treatment-naive HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves a targeted AUC\textsubscript{24} (primary PK endpoint) and C\textsubscript{24h} (secondary PK endpoint) in this population.

2.2 Secondary Objectives

1. To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks.

2. To evaluate the effect on immunologic response from baseline to 24 and 48 weeks.

3. To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in subjects experiencing virologic failure.

4. To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population pharmacokinetic analysis.

5. To determine the extended long term (≥48 weeks) safety and tolerability of DTG in HIV-1 infected infants, children and adolescents.

6. To explore the relationship between DTG exposure and the antiviral activity.
3.0 STUDY DESIGN

P1093 is a Phase I/II multi-center, open-label, non-comparative study of pharmacokinetic parameters, safety, tolerability, and efficacy of DTG in pediatric populations. The enrollment estimate assumes an approximate 35% dropout rate, and allows for a minimum of 100 evaluable subjects with at least 24 weeks of safety data for those treated exclusively with the selected cohort dose. The study will evaluate three formulations of DTG (film-coated tablets, granules for suspension, and dispersible tablets (DT)), both prior to starting OBT and in combination with OBT, in defined pediatric populations as indicated in the following listing of study cohorts:

There will be nine age specific cohorts of HIV-1 infected children in this study:

**Cohort I:** Adolescents ≥ 12 to <18 years of age (film-coated tablets)

**Cohort IIA:** Children ≥ 6 to <12 years of age (film-coated tablets)

**Cohort IIB:** Children ≥ 6 to <12 years of age (granules for suspension) Note: Dispersible tablets may also be evaluated in this cohort if requested by regulatory authorities.

**Cohorts III:** Children ≥ 2 to < 6 years of age (granules for suspension)

**Cohort III-DT:** Children ≥ 2 to < 6 years of age (dispersible tablets)

**Cohort IV:** Children ≥ 6 months to < 2 years (granules for suspension)

**Cohort IV-DT:** Children ≥ 6 months to < 2 years of age (dispersible tablets)

**Cohort V:** Infants > 4 weeks to < 6 months (granules for suspension)

**Cohort V-DT:** Infants > 4 weeks to < 6 months (dispersible tablets)

This study initially enrolled subjects, receiving the film-coated tablet formulation, sequentially into Cohorts I and IIA. When the pediatric granule formulation became available, evaluation of this formulation was added to protocol Version 3.0 for Cohorts IIB, III, IV and V. Anticipating the availability of the new dispersible tablet formulation, evaluation of this formulation has been added in protocol Version 4.0 (Cohorts III-DT, IV-DT and V-DT). See Section 3.3 below for information on study conduct and the initiation and transition to the dispersible tablets at sites.

Each age cohort, with the exception of Cohort IIB (granules for suspension formulation), will consist of two sequential stages: Stage I and II. Only Stage I will be completed for Cohort IIB. The objectives of Stage I are to examine pharmacokinetic parameters after intensive PK sampling and evaluate the short term tolerability and safety of DTG in approximately ten subjects with the goal of selecting a treatment dose for further study in additional enrollees into Stage II. Those enrolled into Stage I or Stage II will remain in their respective Stage for the duration of the study. Additional long term safety and antiviral activity of DTG will be obtained by treating additional subjects in Stage II. Subjects in Stage I or Stage II will progress to Long Term Safety Follow-up once 48 weeks of drug is completed for that subject and if the site clinician in consultation with Protocol Team determines that they are deriving benefit from the study drug and continued participation is not harmful to the subject.
The Protocol Team will maintain a waiting list for each cohort to ensure facilitated enrollment as well as informing sites and potential subjects as to the status of the various cohorts and stages as the study progresses.

3.1 Stage I

For those enrolling in Stage I, intensive pharmacokinetics (PK) will be performed over a single day starting with a witnessed dose between days 5-10 after enrollment. Management of the background ARVs prior to the intensive PK varies based on age and ARV status at enrollment summarized below (see Section 6.2.3 for additional details).

- ARV-treatment experienced subjects not currently receiving ARVs will start DTG alone, complete the intensive PK study visit on Day 5-10 and then optimize the ARV regimen immediately after the PK visit.

- ARV-treatment experienced subjects who are currently receiving a failing regimen of ARVs or who recently started an empiric regimen (< 2 years of age) will add DTG to their regimen at study entry, complete the intensive PK study visit on Day 5-10 and then optimize the ARV regimen immediately after the PK visit.

- ART naïve subjects < 2 years of age will start empiric ART plus DTG at study entry and then complete the intensive PK study visit on Day 5-10. For those subjects who started dolutegravir prior to the genotype results being available, the background ARV regimen will be optimized as soon as possible after the intensive PK visit.

To minimize the impact of drug-drug interactions on PK variability, use of ATV, FPV, EFV, boosted (ritonavir or cobicistat) ATV, FPV, and TPV will not be allowed PRIOR to the initial PK evaluation in Stage I but may be added as part of OBT after completing the intensive PK or as part of OBT for those in Stage II. Section 4.3.2 and Table 11 describes the medications that are disallowed during Stage I and/or Stage II of each cohort. After obtaining the 24 hour PK sample, the background ARV regimen will be immediately optimized.

The HIV-1 genotype obtained at screening, as well as historical virologic and medication tolerance, will be used to determine an appropriate OBT regimen that must include at least two ARV drugs, of which one must be a fully active drug, in addition to DTG. Sites are asked to send the proposed OBT regimen and resistance profiles by email to the Protocol Team (impaact.teamp1093@fstrf.org) for final approval; the team will respond within two business days. The subject will continue to take the assigned DTG dose with the OBT unless a DTG dose modification is needed, as instructed by the Protocol Team.

If the Protocol Team judges a given subject’s PK data to be non-evaluable (e.g. because of non-adherence), that subject will be replaced for dose finding purposes. Note that a subject could be replaced for evaluating safety, as well as PK, criteria since non-evaluable PK data may create uncertainty about the appropriate exposure to the study medication.

Mini-Cohort

Stage I of each cohort will begin with enrollment of an initial mini-cohort of four subjects. After the fourth subject is enrolled, enrollment into this cohort will temporarily pause to allow for the evaluation of the obtained intensive PK parameters and four week safety reports.
The Protocol Team will review the PK and four week safety data from the mini-cohort and if acceptable, Stage I enrollment will resume, at that dose, to complete enrollment of the full cohort of ten subjects. Simultaneously, enrollment into Stage I of the next sequential age mini-cohort will open, if an acceptable pediatric preparation is available.

If upon review of all PK and safety data from the mini-cohort the dose is not acceptable, the mini-cohort dose will be adjusted. Four new subjects will be enrolled from the waiting list. The new mini cohort, treated at the adjusted dose, will undergo safety and PK evaluations (as previously described). If the PK and safety guidelines are satisfied, full cohort enrollment will resume and Stage I of the next sequential mini-cohort will open. If on review of the mini-cohort data, the dose is still not acceptable, the process will repeat until the PK and safety evaluations result in an acceptable dose for that cohort.

**Full Cohort**

To minimize the impact of drug-drug interactions on PK variability, use of EFV, FPV, ATV, boosted (ritonavir or cobicistat) ATV, FPV, and TPV will not be allowed PRIOR to the initial PK evaluation but may be added as part of OBT. See Section 4.3.2 and Table 11 for a list of additional drugs that may NOT be used at ANY time during Stage I.

If on review of all PK and safety data from the full cohort, the PK and safety criteria have been met, subjects will continue their treatment in the Stage I group. Additionally, Stage II for that cohort will then open for enrollment of additional subjects at the selected dose. Dose selection for each cohort will be approved by the Protocol Team, to include sign off by the DAIDS Medical Officer(s), and GSK representatives.

If on review of all PK and safety data for the full cohort the dose is not acceptable, the cohort dose will be adjusted and a new mini-cohort of four will be enrolled. These four subjects will be enrolled from the waiting list. The mini-cohort process (described previously) will then be repeated.

If on review of the mini-cohort data, the dose is still not acceptable, the dose selection process will repeat until the PK and safety evaluations result in an acceptable dose for that cohort. Subjects in Stage I who are being treated at a dose different from the Stage II selected dose and who have not had their individual dose adjusted (i.e. due to extreme PK values) will have their dose changed to the Stage II selected dose. If individualizing the dose for subjects in this manner results in a dose increase, these subjects will have an additional safety visit four weeks after the dose modification and then will continue their study visits with no further changes in the visit schedule.

**Individual Dose Adjustment**

Subjects undergoing intensive PK assessments who have extremes in PK parameters will be considered for a dose modification if they choose to continue DTG treatment or may need to go off study drug, as these values may represent a safety or efficacy concern. Agreement must be reached between the Protocol Team and site investigator to determine the best course for the subject. For those opting for a dose modification, a repeat intensive PK evaluation, 5-14 days post dose modification, is required. In individual cases, determined by the Protocol Team, repeating the PK evaluation at the original dose may be permitted, to verify the original PK parameters.

See Section 3.3 for enrollment to the mini-cohorts for dispersible tablets.
Figure 1: Algorithm for Cohort Management in STAGE I

General Guidelines:
- Each cohort is evaluated independently
- Younger mini-cohorts will open when the mini-cohort (4 subjects) from the previous older cohort passes the safety (≤4 week data) & PK evaluation, see Section 3.3 for guidelines for enrollment to dispersible tablets (Cohorts III-DT, IV-DT and V-DT).
- A mini-cohort will open when the mini-cohort (4 subjects) from previous cohort passes the safety and PK evaluation, see Section 3.3 for guidelines on enrollment to dispersible tablets (Cohorts III-DT, IV-DT and V-DT).

Cohort: Enroll a mini-cohort (4 subjects) to assess PK and short term safety of DTG.

GUIDELINES to accept DTG dose:
- Safety: Dose is safe and well tolerated (see section 8.5)
- PK Target Population Exposure: Primary Endpoint- Geometric mean (GM) AUC₀–₂₄ target of 37-86µg.h/mL and Secondary Endpoint - C₂₄h of 0.5-2.6µg/mL; minimal exposure: AUC₀–₂₄ of 25µg.h/mL and minimal C₂₄h of 0.4µg/mL; maximum AUC₀–₂₄ of 115µg.h/mL.

Mini-cohort passes safety and PK evaluation

Open mini-cohort for next younger cohort at a dose selected after review of all available data

Accrue additional 6 subjects at this dose; Perform PK and safety evaluation on the full cohort

Protocol team (DAIDS / GSK / IMPAACT) evaluation of full cohort safety and PK data – see guidelines above

Full cohort passes safety/PK guidelines – Dose APPROVED

STAGE II opens to accrual

Mini-cohort does not pass safety and PK evaluation

Adjust dose for a mini-cohort (4 subjects); conduct PK and safety evaluations on the adjusted dose (see above)

Full cohort FAILS safety / PK guidelines – dose NOT APPROVED

Adjust dose for full cohort; conduct PK and safety evaluations

Full cohort safety / PK review INCONCLUSIVE

Send to Study Monitoring Committee (SMC) for review
3.2 Stage II

At the completion of the Stage I full cohort, the recommended dose suggested by the team must be approved by the Protocol Team, which will include sign off by the DAIDS Medical Officer(s) and GSK representatives prior to implementation of Stage II.

Once a dose is approved, Stage II will open for enrollment. Stage II is intended to provide long-term safety, tolerability and efficacy data for dolutegravir given in combination with an optimized background ARV regimen. Local site physicians will determine the OBT for the subject, which must be shared with, and approved by, the Protocol Team. Children and adolescents who have discontinued antiretroviral therapy for at least 4 weeks, or who are on a failing regimen, will have a HIV-genotype performed in real time and will be enrolled provided they have AT LEAST one fully active drug AND one additional drug in their OBT. In Stage II, dolutegravir and the OBT will start simultaneously at study entry. Enrollment into Stage II for each cohort will progress independently.

An approximate total of 60 evaluable subjects will be enrolled in Stage II, as described in Table 10.

### Table 10: Anticipated Accrual in Stages I and II in each Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cohort Description</th>
<th>Minimum Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stage I</td>
</tr>
<tr>
<td>I</td>
<td>Adolescents ≥ 12 to &lt;18 years of age (Film-coated Tablet formulation)</td>
<td>10</td>
</tr>
<tr>
<td>IIA</td>
<td>Children ≥ 6 to &lt;12 years of age (Film-coated Tablet formulation)</td>
<td>10</td>
</tr>
<tr>
<td>IIB</td>
<td>Children ≥ 6 to &lt;12 years of age (Pediatric formulation: Granules for suspension)*</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>Children ≥ 2 to &lt; 6 years of age (Pediatric formulation: Granules for suspension)</td>
<td>10</td>
</tr>
<tr>
<td>III-DT</td>
<td>Children ≥ 2 to &lt; 6 years of age (Pediatric formulation: Dispersible Tablets)</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>Children ≥ 6 months to &lt; 2 years (Pediatric formulation: Granules for suspension)</td>
<td>10</td>
</tr>
<tr>
<td>IV-DT</td>
<td>Children ≥ 6 months to &lt; 2 years (Pediatric formulations: Dispersible Tablets)</td>
<td>10</td>
</tr>
<tr>
<td>V</td>
<td>Infants ≥ 4 weeks to &lt; 6 months (Pediatric formulation: Granules for suspension)</td>
<td>10</td>
</tr>
<tr>
<td>V-DT</td>
<td>Infants ≥ 4 weeks to &lt; 6 months (Pediatric formulation: Dispersible Tablets)</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: Enrollment of children into cohorts using the granules may stop once the dispersible tablet formulation is available (see Section 3.3); therefore the cohorts of subjects receiving granules (III, IV and V) may not reach their full enrollment targets. There will be a minimum of 10 subjects initiating the dispersible tablet formulation for each Cohort (III-DT, IV-DT, and V-DT) in Stage I and there will be a minimum of 6 subjects initiating the dispersible tablet formulation for each Cohort (III-DT, IV-DT, and V-DT) in Stage II.

*Cohort IIB will enroll a minimum of 10 subjects to dispersible tablets if required by the regulatory authorities.

Subjects who successfully complete 48 weeks of DTG treatment will be given the opportunity to continue to receive DTG as part of long term safety follow-up for a minimum of three years. See Section 6.3 and Appendix IE for further information.

The schedule of laboratory and clinical evaluations for this study is outlined in ‘Schedule of Evaluations’ in Appendices IA – IG. In Stage I, real-time intensive PK sampling will be conducted 5-10 days after initiation of DTG, and will be repeated, if requested by the team. In addition, a sparse PK will be
conducted at weeks 4, 12 and 24 weeks for Stage I and Stage II subjects. Additionally, for subjects switching from granules for suspension to dispersible tablet, sparse PK samples will be obtained at the two week post switch visit and the next scheduled visit.

HIV-1 RNA PCR will be performed to assess the effects of study drug on HIV-1 replication. Finally, safety assessments, including hematologic, renal, and liver chemistry tests, will be conducted at these visits.

3.3 Protocol Version 4.0 – Addition of Dispersible Tablets Stages I and II

In addition to the film-coated tablet formulation, there are two pediatric formulations being evaluated in protocol Version 4.0; granules for suspension (Cohorts IIB, III, IV and V) and dispersible tablets (Cohorts III-DT, IV-DT and V-DT). It is anticipated that the dispersible tablet product will become the commercially available pediatric formulation. In a relative bioavailability study in adults, the dispersible tablets resulted in PK exposure that was, on an mg to mg basis, equivalent to granules; there were no identified adverse events. Based on this PK equivalency and safety data, and having passed the PK and safety evaluation for the granules for suspension formulation in the mini-cohort, in Version 4.0, the mini-cohorts treated with the dispersible tablets may enroll simultaneously if the dose from the respective granules for suspension mini-cohort is approved, in contrast to sequential cohort enrollment. This is more fully described below. In the unlikely event that one of these concurrently enrolling Stage I dispersible tablet mini-cohorts does not meet the stated objectives, the Protocol Team will convene to assess all accumulated data and determine whether the failure in one cohort should influence the conduct of the study in another age cohort. Any determination will be shared with participating sites expeditiously.

With varying timelines for IRB approvals and drug importation at U.S. and non-U.S. sites, it is anticipated that DTG dispersible tablets will not be available to all sites simultaneously. Given this reality, enrollment into cohorts with ongoing granules for suspension may continue at each site with approval from the Protocol Team.

3.3.1 Guidelines for Dispersible Tablet Dosing

Once a site has obtained all required approvals of protocol Version 4.0, it should notify the Protocol Team who will notify them of the current dispersible tablet cohorts open and dosing. Sites will be instructed by the Protocol Team according to the following guidelines:

3.3.1.1 At the site level, enrollment into an age-specific dispersible tablet mini-cohort (Stage I) should occur for the next sequential mini cohort and/or for any corresponding age-specific granules for suspension mini-cohort (Stage I) where the pharmacokinetic targets were met and there were no safety concerns. Pharmacokinetic and safety data from the granule in suspension mini-cohorts can be used to inform the selected initial dose for the dispersible tablets. The Protocol Team will inform of sites of this status. For example, when the mini-cohort for III-DT dispersible tablets opens, enrollment into the mini-cohort for IV-DT (dispersible tablets) may also open.

3.3.1.2 At the site level, upon opening of Stage I Cohorts III-DT, IV-DT, or V-DT to enrollment, Cohorts III, IV and V (granules for suspension), respectively will be closed to enrollment.
3.3.1.3 Subjects previously enrolled in Stage I Cohort IIB will switch from granules for suspension to dispersible tablets at the next scheduled visit.

3.3.1.4 Subjects previously enrolled and receiving granules for suspension will continue to receive granules for suspension until notified by the Protocol Team that the PK and safety data from the age-specific dispersible tablet Stage I full-cohort is acceptable and then these subjects will switch to dispersible tablets.

Subjects who switch from granules for suspension to dispersible tablets will have the following additional evaluations as indicated in the Schedules of Evaluations (Appendix I):

- On the day of switch, the initial dose of dispersible tablets should be given in the study clinic and observed by study staff.
- Two weeks after switching to dispersible tablets, the subject should have an additional ‘Switch Visit’ during which a palpability assessment and RNA PCR test will be done; if this visit falls within the window for another scheduled visit, a combined visit can be completed to avoid duplication of procedures.
- For subjects who have completed 24 weeks of follow-up at the time of the ‘Switch Visit’ in addition to the procedures mentioned above, these subjects will have population PK specimens collected at the two week post switch visit and at the next regularly scheduled visit.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

Subjects, who fail the study inclusion / exclusion criteria for viral load or toxicities at screening, may be rescreened after 4 weeks. NOTE: Genotypes do not need to be repeated at screening if they were acceptable at the previous screen.

4.1 Inclusion Criteria

4.1.1 Age: ≥ 4 weeks to <18 years at study entry

4.1.2 Confirmed HIV-1 infection

- Documentation of HIV-1 infection defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. All test methods should be FDA-approved if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT central laboratory.
  - Sample #1 may be tested by non-study public or PEPFAR programs. However, both the result and the assay date must be recorded in the subject’s chart. Source documentation (patient’s medical record/chart, in-country Ministry of Health registers, laboratory results, etc.) must be available if requested.
  - Sample #2 must be performed in a CAP/CLIA-approved laboratory (for US sites) or in a laboratory that operate according to GCLP guidelines and participates’ in appropriate external quality assurance program (for non-US sites).
4.1.2.1 Acceptable tests when subjects are ≤ 18 months of age

Sample #1 and Sample #2 may be tested using any of the following:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid

Note: Subjects ≤ 18 months of age can be enrolled on the basis of one positive test result (from Sample #1) if the results from Sample #2 are pending. The HIV RNA test required at screening per the Schedule of Evaluations may serve as Sample #2 and may be pending at the time of enrollment. However, any subject in whom infection is not confirmed by the results of Sample #2 should discontinue study drug, per Section 6.6 and be followed per Appendix IF.

4.1.2.2 Acceptable tests when subjects are > 18 months of age

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with the two tests for Sample #1, at least one of the three rapid antibody tests for Sample #1 must be FDA approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

4.1.3 Subjects must belong to one of the ARV exposure groups below:

4.1.3.1 ARV-treatment experienced (not including receipt of ARVs as prophylaxis or PMTCT)

Previously took ARVs as treatment, but not currently taking ARVs:
- Must have been off treatment ≥ 4 weeks

OR

- Currently taking ARVs for treatment but failing:
  - Must be on an unchanged, failing therapeutic regimen within the 4 to 12 weeks prior to screening (≤1 log drop in HIV-1 RNA within the 4 to 12 weeks prior to screening).

NOTE: Dose adjustments for growth or formula substitutions (i.e. switching from single agent to fixed dose combination) are permitted during this 4 to 12 week period. Substitutions of one ARV within the same class for toxicity or tolerability management, or discontinuation of ARVs are also allowed within the 4 to 12 weeks period.

OR

- For subjects < 2 years of age, initiated ARVs for treatment < 4 weeks prior to screening.

4.1.3.2 ARV treatment naive (no exposure to ARVs for treatment; could have received ARVs for prophylaxis or PMTCT)
- Age < 2 years

4.1.4 If an infant has received NVP as prophylaxis to prevent mother to child transmission (PMTCT), he or she must have not received NVP for at least 14 days prior to enrollment into Stage I or II.

4.1.5 HIV-1 RNA viral load greater than 1,000 copies/mL of plasma at screening

NOTE: For subjects enrolling into cohorts IV, IV-DT, V, and V-DT, the HIV RNA test performed at screening may be pending at the time of enrollment. If the screening HIV RNA is ≤ 1000 c/mL, the subject should discontinue study drug, per Section 6.6 and be followed per Appendix IF.

4.1.6 Demonstrated ability or willingness to swallow assigned study medications. NOTE: Film coated tablets MAY NOT be crushed or dissolved. Dispersible tablets MAY NOT be cut and must be used in five milligram intervals.

4.1.7 Parent or legal guardian able and willing to provide signed informed consent.

4.1.8 Female subjects who are of child bearing potential and who are engaging in sexual activity that could lead to pregnancy, must use two adequate birth control methods while on study and for two weeks after stopping study drug. Hormonal birth control alone (e.g., pills, shots, or slow release inserts placed under/on 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 (excluding nonoxydyl-9), intrauterine device [IUD], others) also must be used during the
study. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission.

4.1.9 Males engaging in sexual activity that could lead to HIV-1 transmission must use a condom.

4.1.10 Optimized background therapy (OBT):

- Subjects aged ≥2 years of age (Cohorts I, II, III, and III-DT) must have available at least one fully active drug for the OBT to enroll. Historical genotypes obtained within 1 year of screening will be considered by the Protocol Team for determination of fully active drugs if screening genotype testing is inconclusive.
- Subjects < 2 years of age (Cohorts IV, IV-DT, V, and V-DT) can enroll if genotype testing has been obtained with results pending.

Note: Subjects enrolled with genotype results pending but found to have no active drugs per genotype performed at screening should discontinue study drug, per Section 6.6 and be followed per Appendix IF. However, such subjects who have a > 1 log drop in HIV RNA by 4 weeks can continue study drug with approval by the Protocol Team.

4.2 Exclusion Criteria

4.2.1 Presence of any active AIDS defining opportunistic infection

4.2.2 At enrollment, subject < 3.0 kg

4.2.3 Known ≥ Grade 3 of any of the following laboratory toxicities within 30 days prior to study entry: neutrophil count, hemoglobin, platelets, AST, ALT, lipase, serum creatinine and total bilirubin. A single repeat within the 30 days is allowed for eligibility determination. NOTE: ≥ Grade 3 total bilirubin is allowable, if the subject is on ATV.

4.2.4 ANY known Grade 4 laboratory toxicities within 30 days prior to study entry. NOTE: Grade 4 total bilirubin is allowable, if the subject is on ATV.

4.2.5 The following liver toxicities within 30 days prior to study entry: ALT > 3x ULN AND direct bilirubin is > 2x ULN

4.2.6 Any prior history of malignancy, with the exception of localized malignancies such as squamous cell or basal cell carcinoma of the skin

4.2.7 Clinical or symptomatic evidence of pancreatitis, as determined by the clinician

4.2.8 Use of any disallowed medications at time of screening (see Section 4.3.2 for a complete list of disallowed medications)

4.2.9 Known history of exposure to integrase inhibitor treatment by the subject or subject’s mother prior to delivery/cessation of breast feeding

4.2.10 Known resistance to an integrase inhibitor
4.2.11 Women who are pregnant or breastfeeding.

4.2.12 Subject is currently participating in or has participated in a study with a compound or device that is not commercially available within 30 days of signing informed consent, unless permission from both Protocol Teams is granted

4.2.13 Subject is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study to a non-IMPAACT study site

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

4.2.15 Subject has used, or anticipates using, chronic systemic immunosuppressive agents or systemic interferon (e.g. for treatment of HCV infection) within 30 days prior to beginning DTG study treatment. Systemic corticosteroids (e.g. prednisone or equivalent up to 2 mg/kg/day) for replacement therapy or short courses (≤30 days) are permitted. (See disallowed medications Section 4.3.2)

4.2.16 Any condition that would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.

4.2.17 Active TB disease and/or requirement for treatment that includes rifampin at the time of the screening visit. However, subjects who need rifampin treatment while on DTG will be allowed to continue in P1093 provided the DTG dose is adjusted according to Section 6.1.8.

4.3 Concomitant Medication Guidelines

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Disallowed Medications section below.

4.3.1 Precautionary Medications

DTG should be administered two hours before or six hours after taking antacid products containing divalent cations (e.g. aluminum and magnesium) or iron supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable.

It is the responsibility of the investigator to check on potential drug-drug interactions between background antiretroviral therapy and other concomitant therapies, before placing a subject on a specific medication.

4.3.2 Disallowed Medications

For clarity, the following information on disallowed ARV medications is summarized in Table 11.

**Disallowed ARV Medications for Stage I Subjects BEFORE the Intensive PK Only**

The following medications are disallowed prior to the initial intensive PK evaluation for Stage I subjects only, since they could significantly increase or decrease the levels of dolutegravir due to
enzyme induction or inhibition and result in increased PK variability. However, these medications 
ARE allowed in Stage I subjects as part of OBT after the intensive PK evaluation has been 
completed:

- Atazanavir (ATV) 
  - Boosted (ritonavir or cobicistat) Atazanavir 
- Efavirenz (EFV) 
  - Boosted (ritonavir or cobicistat) Fosamprenavir 
- Fosamprenavir (FPV) 
  - Boosted (ritonavir or cobicistat Tipranavir

**Disallowed ARV Medications for Subjects on Stage I (BEFORE and AFTER the Intensive PK) 
and Stage II subjects**

When constructing a subject’s background ART regimen, the following medications are 
progressed for Stage I and Stage II subjects because no PK data about co-administration are 
available and/or they could significantly decrease the levels of dolutegravir due to enzyme 
induction:

- Nevirapine (NVP): Nevirapine has significant drug-drug interactions with dolutegravir 
  resulting in lowered dolutegravir exposure. The expectation that PK interaction data would 
  become available, led protocol Version 3.0 to allow concurrent therapy with increased (BID) 
  dolutegravir dosing. Data has not been become available and concomitant dolutegravir and 
  nevirapine use is not permitted in protocol Version 4.0. Prior historical NVP treatment is 
  permitted but NVP treatment has to be discontinued 14 days prior to initiation of 
  dolutegravir.
- Etravirine (ETR): Etravirine UNLESS it is co-administered with lopinavir/ritonavir or 
  darunavir/ritonavir; these boosted protease inhibitors have been shown to counteract 
  etravirine enzyme induction. Thus, dolutegravir may be co-administered with etravirine if the 
  subject is receiving concomitant lopinavir/ritonavir or darunavir/ritonavir.
- Raltegravir (RAL) 
- Elvitegravir (EVG)

Additionally, due to their enzyme induction potential, the following medications, or their 
equivalents, must NOT be administered concurrently with DTG:

- Barbiturates 
- Oxcarbamazepine 
- Pioglitazone 
- Troglitazone 
- Rifampin (NOTE: see Section 6.1.8 regarding TB exclusion) 
- Rifabutin 
- Phenytoin 
- Phenobarbital 
- Carbamazepine 
- St. John’s wort

Dolutegravir may inhibit the renal tubular secretion of dofetilide resulting in increased dofetilide 
concentrations and potential for toxicity.

- Dofetilide
The following medications are also prohibited:
- Medications for HCV therapy

Table 11. Summary of Disallowed ARV Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>STAGE I</th>
<th>STAGE II</th>
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<tbody>
<tr>
<td></td>
<td>Allowed Prior to Intensive PK</td>
<td>Allowed After Intensive PK (OBT)</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>Atazanavir (ATV)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Atazanavir / Ritonavir (ATV/r)</td>
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<td>Yes</td>
</tr>
<tr>
<td>Tipranavir / Ritonavir (TPV/r)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nevirapine (NVP)**</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fosamprenavir / Ritonavir (FPV/r)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fosamprenavir (FPV)</td>
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<td>Yes</td>
</tr>
<tr>
<td>Etravirine (ETR)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Etravirine with Lopinavir / Ritonavir (ETR/ LPV/r)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Etravirine with Darunavir / Ritonavir (ETR/ DRV/r)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Elvitegravir (EVG)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*May NOT be given as part of OBT if it is in combination with TPV/r
**Due to insufficient drug interaction data with concomitant nevirapine and dolutegravir use and concern that dolutegravir exposure will be significantly lower concomitant NVP use will no longer be permissible in protocol Version 4.0. Prior historical NVP treatment is permitted but NVP treatment has to be discontinued 14 days prior to initiation of dolutegravir.

4.4 Protocol Registration and Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE).

Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to
ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Subjects meeting the study eligibility criteria will be enrolled through the Data Management Center (DMC) registration screens. Written informed consent for study participation must be obtained before any study related procedures are performed.

Sites interested in screening potential subjects into MUST request and receive permission from the Protocol Team in order to proceed with screening visits. Prior to emailing the team to get permission to screen a patient the sites must complete the PS2001 IMPAACT Screening Checklist within the Subject Enrollment System to obtain a screening number, which should be included in the screening request. Sites should contact the Protocol Team at impaact.teamp1093@fstrf.org with any screening timeline deviations. A slot may be recalled if deviations from the timeline are not approved by the Protocol Team. For all subjects from whom informed consent is obtained, but who are deemed ineligible or who do not enroll into the protocol for any reason, a Screening Failure Results form must be completed and keyed into the database.

NOTE: If the subject has a milestone birthday that will change cohort assignment, it is the site's responsibility to notify the DMC data manager to request a cohort assignment change.

4.5 Co-enrollment Procedures

Co-enrollment is permitted except for protocols that would violate the exclusion criteria and where permitted by local/country regulations. All co-enrollments in protocols require the assent of the protocol chairs of the main protocol and the co-enrollment protocols.

5.0 STUDY TREATMENT

Study treatment is defined as dolutegravir film-coated tablets, dolutegravir granules for suspension (granules mixed with liquid) for oral administration or dolutegravir dispersible tablets. Refer to Section 6.2.3 for further instructions regarding the timing of initiation of dolutegravir and OBT. Once protocol Version 4.0 is approved and the dispersible tablets are available on site, see Section 3.3.1 for guidelines for initiating dispersible tablets cohorts and switching subjects receiving granules in follow-up to dispersible tablets.

5.1 Drug Regimens

All dosing tables referenced below are available in the IMPAACT P1093 Dosing Table Appendix posted on the study-specific web page: http://impaactnetwork.org/studies/P1093.asp.

Weight will be measured and recorded at each visit to verify the subject is receiving the appropriate dose based on the current dosing table. If a subject’s weight change requires a dose adjustment, the dose adjustment should be made, the Protocol Team must be notified, although Protocol Team approval for a weight-based dose adjustment is not required. Dose adjustments for
weight decreases will only be made if the weight decrease persists for two consecutive study visits.

Subjects enrolled into a given age cohort will remain in that cohort throughout their participation in the study. It is possible that the dose chosen for one age cohort (based upon a “mg/kg” target) may differ from the approved target dose for the next older age cohort. In this case, the subject will stay on their current dose and will “grow” into any subsequent increase in dosing, as per the original dosing table; their dose should not be automatically decreased as they age. This approach is supported by acceptable safety and tolerance observed in adults treated with dolutegravir 50 mg PO BID. The study team will continue to monitor protocol safety and, if any signals are noticed that require a modification to this approach; the sites will be contacted as to any necessary changes for individual subjects or cohorts.

Stage 1
Subjects enrolled to Stage I of the study will be stratified at screening into one of the following nine age specific cohorts. Subjects who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of dolutegravir changed to twice daily.

Cohort I: Adolescents ≥ 12 to <18 years of age
- Dolutegravir film-coated tablets
- Subjects will take an initial starting dose orally of dolutegravir tablet(s) at approximately 1 mg/kg once daily per Table A.
- Dolutegravir tablets must be swallowed whole and may not be crushed or dissolved before administration.

Cohort IIA: Children ≥ 6 to <12 years of age
- Dolutegravir film-coated tablets
- Subjects will take an initial starting dose orally of dolutegravir tablet(s) at approximately 1 mg/kg once daily per Table A.
- Dolutegravir tablets must be swallowed whole and may not be crushed or dissolved before administration.

Cohort IIB: Children ≥ 6 to <12 years of age
- Dolutegravir granules for suspension (1.6 mg/mL). Note: Dispersible tablets may also be evaluated in this cohort if requested by regulatory authorities.
- Subjects will take an oral starting dose of dolutegravir granules for suspension or dispersible tablets at approximately 0.8 mg/kg once daily per Table E for granule in suspension and Table I for dispersible tablets.
- The initial dose of dispersible tablets will be administered in the clinic and observed by study staff.

Cohort III: Children ≥ 2 to < 6 years of age
- Dolutegravir granules for suspension (1.6 mg/mL)
- Subjects will take an oral starting dose of dolutegravir granules for suspension at approximately 0.8 mg/kg once daily per Table E for granule in suspension.

Cohort III-DT: Children ≥ 2 to < 6 years of age
- Dolutegravir dispersible tablet
• Subjects will take an oral starting dose of dolutegravir dispersible tablets at approximately 0.8 mg/kg once daily per Table L for dispersible tablets.
• The initial dose of dispersible tablets will be administered in the clinic and observed by study staff.

Cohort IV: Children ≥ 6 months to < 2 years
• Dolutegravir granules for suspension (1.6 mg/mL)
• Subjects will take an oral starting dose* of dolutegravir granules for suspension once daily per the dose determined by review of all available data, including Cohort III, as well as any relevant bioavailability studies. Refer to the selected Dosing Table.

Cohort IV-DT: Children ≥ 6 months to < 2 years
• Dolutegravir dispersible tablets.
• Subjects will take an oral starting dose* of dolutegravir dispersible tablets once daily per the dose determined by review of all available data, as well as any relevant bioavailability studies. Refer to the selected Dosing Table.
• The initial dose of dispersible tablets will be administered in the clinic and observed by study staff.

Cohort V: Infants ≥ 4 weeks to < 6 months
• Dolutegravir granules for suspension (1.6 mg/mL)
• Subjects will take an oral starting dose* of dolutegravir granules for suspension once daily per the dose determined by review of all available data, including Cohort IV as well as any relevant bioavailability studies. Refer to the selected Dosing Table.

Cohort V-DT: Infants ≥ 4 weeks to < 6 months
• Dolutegravir dispersible tablets.
• Subjects will take an oral starting dose* of dolutegravir dispersible tablets once daily per the dose determined by review of all available data as well as any relevant bioavailability studies. Refer to the selected Dosing Table.
• The initial dose of dispersible tablets will be administered in the clinic and observed by study staff for tolerability.

*Note: The initial starting Cohort dose selected and any Cohort dose adjustments will be communicated to study sites by the Protocol Team. For individual subject dose adjustments, sites will be notified by a PID specific e-mail from the Protocol Team, see Section 6.2.4

Stage II

Subjects enrolling Stage II of each of the following eight cohorts will receive the Stage I approved age and formulation of dolutegravir to be taken orally once daily or twice daily if on EFV, NVP, FPV/r, or TPV/r as part of OBT.

Cohort I: Adolescents ≥ 12 to <18 years of age – dolutegravir film-coated tablets.
Cohort IIA: Children ≥ 6 to <12 years of age – dolutegravir film-coated tablets
Cohort III: Children ≥ 2 to < 6 years of age – dolutegravir granules for suspension
Cohort III-DT: Children ≥ 2 to < 6 years of age – dolutegravir dispersible tablets
Cohort IV: Children ≥ 6 months to < 2 years – dolutegravir granules for suspension
Cohort IV-DT: Children ≥ 6 months to < 2 years – dolutegravir dispersible tablets
Cohort V: Infants ≥ 4 weeks to < 6 months – dolutegravir granules for suspension
Cohort V-DT: Infants ≥ 4 weeks to < 6 months – dolutegravir dispersible tablets

5.1.3 Changing Dolutegravir Study Product Formulation

Provisions for changing study product formulations is outlined below.

- Aging subjects who are taking the granule formulation will be allowed to switch to the film-coated tablet formulation after the Week 4 study visit, if they request to do so, upon approval of the Protocol Team.
- Subjects entering Cohorts III-DT, IV-DT and V-DT and receiving dispersible tablets must continue to receive the dispersible tablets through Week 48. After Week 48, those subjects who reach the appropriate age and weight may elect to change to film-coated tablets upon approval of the Protocol Team.
- See Section 3.3 for guidelines for switching subjects receiving granules to dispersible tablets in follow-up.
- The Protocol Team will retain the ability to modify subjects’ dose and formulation as per the protocol, based on PK data, age, weight, and/or other variables.

5.1.4 Duration of Study Drug Regimen

Stage I: Minimum of 48 weeks

Long term follow-up: Subjects who successfully complete 48 weeks of dolutegravir treatment will continue to receive dolutegravir as part of long term safety follow-up. For additional information please refer to Section 6.3.

Stage II: 48 weeks

Long term follow-up: Subjects who successfully complete 48 weeks of dolutegravir treatment will continue to receive dolutegravir as part of long term safety follow-up. For additional information please refer to Section 6.3.

5.2 Study Product Formulation

5.2.1 Dolutegravir film-coated Tablets

Dolutegravir film-coated tablets in 10 mg, 25 mg, and 50 mg per tablet. Store at 15°C to 30°C (59°F to 86°F). Dispense and store only in the original manufacturer’s container with the desiccant. The desiccant should remain in the bottle.

5.2.2 Dolutegravir Granules for Oral Suspension

Dolutegravir granules for suspension 1.6 mg/1 mL suspension. When the granules in the bottle are reconstituted with 73 mL of potable (drinkable) water as directed, each container contains 160 mg per 100 mL. Once reconstituted, the suspension is stable for 8 weeks in the manufacturer’s container. The reconstituted product should be stored at temperatures up to 30°C (86°F). Storage in a refrigerator is fully acceptable and preferred, if available.
Preparation of oral suspension by the site pharmacist

In order for the product to be dosed as 1.6 mg/mL suspension in glass bottles: The dolutegravir pediatric granules 0.4% w/w are to be reconstituted into a suspension containing 1.6 mg/mL through the addition of water by the site pharmacist as follows:

Using a graduated syringe, the dispensing pharmacist, will measure 73 mL of potable (drinkable) water (in two portions) to mix with the dolutegravir granules; the resulting concentration of the suspension after it is mixed is 1.6 mg/mL of dolutegravir if reconstituted as directed. Insert a bottle adapter into the neck of the bottle and replace the child resistant cap. The bottle must be shaken for about one minute to ensure homogeneity. After shaking, visually check to ensure that there is no non-dispersed material adhering to the bottom or sides of the bottle. If non-dispersed material is observed, additional shaking is required as above. The maximum in use period of the pediatric formulation after it has been reconstituted with water is 8 weeks and should be stored up to 30°C (86°F). Storage in a refrigerator is fully acceptable and preferred, if available. The suspension should not be frozen. The dolutegravir pediatric suspension reconstituted from granules should be dispensed in the same amber glass bottle in which the granules were mixed with water. An oral dispenser will also be provided with each bottle. The suspension must be retained within the bottle in which it is dispensed and not transferred to any other container except the dosing syringe used for administration. The reconstituted suspension should be used within 8 weeks of the initial reconstitution, but preferably within a single month. Following reconstitution, the suspension in EVERY glass bottle should be shaken EVERY day, irrespective of whether doses are being taken from that particular bottle. Failure to follow this instruction may lead to variability in dosing.

5.2.3 Dolutegravir Dispersible Tablets

Dolutegravir dispersible tablet, 5 mg per tablet. Product may be stored at temperatures up to 30°C (86°F). Storage in a refrigerator is fully acceptable, if available. Once a bottle is opened the product has an in-use shelf life of 60 days providing the product is stored in the original package to protect from moisture, with the bottle tightly closed. Do not remove the desiccant.

Each tablet is to be dispersed using 2 to 5 mL of water and consumed, as soon as possible, but not longer than 5 minutes after reconstitution. Dispersible tablets may be given as multiples (up to a maximum of 4 tablets), depending on the weight of the child. Once dispersed, the medication should be consumed from the supplied dosing cup or syringe within five minutes.

5.3 Study Drug Supply, Acquisition and Accountability

5.3.1 Study Drug Supply and Acquisition

Dolutegravir study products will be supplied by GSK. All dolutegravir study products are available through the NIAID Clinical Research Products Management Center (CRPMC).

Other components of the ARV regimen will not be supplied by the protocol.

The IMPAACT pharmacist can obtain dolutegravir by following the instructions in the manual "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks" in the section Study Product Management.
Oral syringes and dosing cups in which to measure water for dispersion and to administer the dispersed product will be packaged with the dispersible tablets and will be provided to the parent/caregiver. Additional instructions for administration of dolutegravir for the parent/caregiver can be found in the Manual of Procedures.

5.3.2 Study Drug Accountability

The IMPAACT pharmacist is required to maintain complete records of all study products received from CRPMC. All unused dolutegravir must be returned to the CRPMC after the study is completed or terminated at domestic sites. The procedures to be followed are given in the manual, "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks" in the section Study Product Control.

Non-US IMPAACT pharmacists should follow the instructions on the Study Product Destruction Form. The only study products for this protocol to be included on the Study Product Destruction Form are the dolutegravir study products.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, must be used and is available on the RSC website at (http://rsc.tech-res.com/safetyandpharmacovigilance).

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normal ranges will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular lab, the site should use the latest edition of the Harriet Lane Handbook for normal ranges/values and document this for monitoring purposes. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2.

General guidelines for AEs are provided below:

6.1.1 Reporting

AEs will be collected from the start of DTG treatment and until the final follow-up visit after study drug has been stopped.

- Grade 1: All AEs should be recorded on Case Report Forms (CRFs) at each visit.

- Grade 2: All AEs should be recorded on CRFs at each visit.

- Grade 3 or 4:
  - The Protocol Team must be notified of AEs within 1 business day, by email at impaact.teamp1093@fstrf.org.
  - The investigator should attempt to confirm any unexpected laboratory test results as soon as possible but always within 72 hours to determine if the result was spurious.
Expedited Adverse Event (EAE) reporting, if appropriate, must be done within 72 hours of the initial result if the value is confirmed or if confirmatory results are not available within 72 hours.

6.1.2 Management

**Grade 1** - Continue study drug; routine monitoring.

**Grade 2** - Continue study drug; monitor closely with more frequent visits as per site PI, work-up to exclude other causes.

**Grade 3** – Continue study drug while awaiting confirmatory results unless the clinician believes that remaining on study drug would be unsafe.

If Grade 3 abnormalities are confirmed, the study drug and concomitant antiretroviral therapy should be withheld until the abnormalities decrease to a Grade 2 or below unless the clinician, with the approval of the Protocol Team and medical officer, believes that withholding antiretroviral therapy (including study drug) would be harmful to the subject.

**Grade 4** - Hold study drug and concomitant antiretrovirals immediately unless the clinician, with the approval of the Protocol Team and medical officer, believes that withholding antiretroviral therapy (including study drug) would be harmful to the subject and that continuing them would pose little additional risk. Attempt to confirm any unexpected laboratory results as soon as possible, but always within 72 hours of the event to determine if these results were spurious. The Protocol Team should be notified of the results at impaact.teamp1093@fstrf.org.

For confirmed Grade 4 AEs that are possibly, probably or definitely related to study drug, study medication should be permanently discontinued. For Grade 4 adverse events that are determined to be unrelated or probably not related to study drug, the investigator should contact the team to determine when study drug may be safely resumed.

All antiretroviral therapy including study drug should be started or stopped together whenever possible, except when one antiretroviral agent can be substituted for another within class when the etiology of the toxicity can be determined.

6.1.3 Liver Toxicities

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of DTG and the follow-up period. Study drug (dolutegravir) will be stopped if any of the following liver chemistry stopping criteria is met:

- **Hy’s Law**: ALT > 3xULN and bilirubin > 2xULN; Direct Bilirubin > 35% of Total Bilirubin.
  NOTE: Hy’s Law is a prognostic indicator that a pure drug-induced liver injury (DILI) leading to jaundice, without a hepatic transplant, has a case fatality rate of 10-50%. Increased ALT or total bilirubin are relatively common (particularly in HIV/AIDS) but the combination of ALT > 3xULN and total bilirubin > 2xULN is rare in drug development and of clinical concern.

- ALT ≥ 10xULN; In this case, if another cause of ALT elevation is identified, the subject may be re-challenged after receiving the approval of GSK, IMPAACT and DAIDS.
• ALT > 3xULN with symptoms of hepatitis or hypersensitivity (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia). In this case, if another cause of ALT elevation is identified, the subject may be re-challenged after receiving the approval of GSK, IMPAACT and DAIDS.

• ALT > 5xULN for more than 2 weeks. In this case, if another cause of ALT elevation is identified, the subject may be re-challenged after receiving the approval of GSK, IMPAACT and DAIDS. Subjects who develop ALT ≥ 5xULN should be followed weekly until resolution or stabilization (ALT < 5xULN on 2 consecutive evaluations).

If any of the above liver chemistry stopping criteria are met, sites are instructed to do the following:

• Immediately withhold study drug
• Report the event to the Protocol Team by email within 24 hours of learning of its occurrence (impaaact.teamp1093@fstrf.org)
• Report Hy’s Law liver toxicities (see above) to the RSC as an EAE
• If possible, collect a 2mL blood draw for pharmacokinetic analysis from the subject within 72 hours of the last dose taken, and record the date and time of the last dose taken as well as the date and time of the pharmacokinetic sample collected. NOTE: If the timeframe is greater than 72 hours since the last dose, the specimen should not be collected.
• Complete and submit the liver toxicity CRFs within 1 week to the DMC

6.1.4 Decline in Renal Function

Subjects who experience an increase in serum creatinine to a Grade 2 or above or from Grade 2 (baseline) to Grade 3 or above, must return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine microalbumin/creatinine ratio, as well as serum creatinine should be done at this confirmatory visit. If the creatinine elevation is confirmed (with or without proteinuria), the investigator should contact the Protocol Team to discuss additional follow-up and medical management.

Subjects who experience progression to an estimated GFR (calculated by the Schwartz formula) of <50 mL/min (1.73m²) must return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine microalbumin/creatinine ratio should be done at this confirmatory visit (in addition to the serum creatinine). If an estimated GFR of <50 mL/min (1.73m²) is confirmed, then DTG should be withheld and the investigator should contact the Protocol Team to discuss the rationale for restarting study drugs (if appropriate).

Schwartz formula: GFR (mL/min/ 1.73 m²) = K x Ht cm/Pcreat

\[ K = \text{constant} \quad \text{Cr mg/mL} \]

- Infants < 1 year: 0.45
- Children 2-12 years: 0.55
- Female 13-21 years: 0.55
- Males 13-21 years: 0.70

Consideration for confounding factors (e.g. background ART therapy; other medications; dehydration and concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If subjects are also receiving TDF, then a switch to an alternative nucleoside
should be considered if restarting DTG. Current local prescribing information should be consulted for additional details on dosing background ART therapy in renal-impaired subjects. If DTG is re-initiated, it should have been withheld for no more than 4 weeks.

6.1.5 Proteinuria

Subjects with an abnormal urine microalbumin/creatinine ratio (>300 mcg/mg) that represents a change from a normal baseline and no associated increase in creatinine should have a repeat spot urine microalbumin/creatinine ratio and serum creatinine assay performed within 2 to 4 weeks. If confirmed, then consideration should be made for additional evaluation after consultation with the Protocol Team (impaaact.teamp1093@fstrf.org). Additional evaluation may include nephrology referral.

Subjects with an abnormal urine microalbumin/creatinine ratio (>300 mcg/mg representing a change from baseline) and a serum creatinine increase to grade 2 toxicity or above, should have confirmation of both results within 2 to 4 weeks. If confirmed, DTG should be withheld, and the Protocol Team should be immediately contacted. Agreement on further management and restarting DTG should be agreed between the investigator and Protocol Team.

6.1.6 Peptic Ulcer Disease

Symptoms suggestive of peptic ulcer disease (e.g., epigastric pain, nausea, vomiting, bloating, etc.) are relatively common but are also non-specific.

Subjects with such symptoms should be treated symptomatically as appropriate (e.g., H₂ blockers or proton pump inhibitors) and be evaluated and treated as appropriate for H. pylori. However, patients with these symptoms should not be prescribed cation-containing antacids for concomitant use, because significant reduction in DTG exposure has been observed when these drugs were co-administered. If deemed necessary, DTG should be administered 2 hours before or 6 hours after taking antacid products.

If symptoms consistent with peptic ulcer disease persist or worsen on symptomatic therapy, then the Protocol Team should be consulted regarding further management, which may include but is not limited to discontinuation of DTG.

6.1.7 Abacavir (ABC) Hypersensitivity (HSR)

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR).

Where HLA-B*5701 screening is considered standard of care, it is recommended that investigators screen for the presence of the HLA-B*5701 allele in any subject for whom an Abacavir (ABC)-containing product (e.g., ZIAGEN™, TRIZIVIR™, EPZICOM™, KIVEXA™) may be considered as part of the optimized background regimen and HLA-B*5701 status is unknown (even if the subject has previously tolerated ABC). Use of ABC in subjects known to carry HLA-B*5701 is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and only under close medical supervision.

Reporting of Abacavir Hypersensitivity Reactions
All cases of potential abacavir hypersensitivity MUST be reported as an EAE (see Section 7.2). In addition, the ABC HSR CRF must be completed and submitted to the DMC within one week of the onset of the hypersensitivity reaction.

6.1.8 Management of Subjects Co-infected with TB

Subjects presenting at the Screening visit with active Tuberculosis (TB) co-infection are not eligible to participate in the study due to multiple drug interactions, overlapping toxicities, and other complications affecting treatment outcomes. Subjects who are already enrolled and are on therapy who become exposed to TB, and subsequently require an anti-TB treatment that includes the use of rifampin, may be allowed to continue in the study if their ART options are compatible with co-administration of rifampin. Continuation requires the approval of the Protocol Team. Management of these subjects is as follows:

- When administration of the rifampin-containing anti-TB treatment begins, subjects will switch to the Schedule of Evaluations in Appendix IG, and will increase their DTG dose from once daily to twice daily (dose is based on weight). DTG study treatment duration continues to be administered twice daily while subject is on the rifampin containing anti-TB therapy.

- While on the rifampin-containing anti-TB therapy, to ensure the DTG dose is appropriate, intensive pharmacokinetic sampling will occur two weeks after the start of anti-TB treatment at the following times, per Appendix IG:
  - Pre-dose, and at 1, 2, 3, 4, 6, 8, and 12 hours post-dose will be performed.

- Individual dose adjustments may be made to the initial DTG dose following the Week 2 intensive pharmacokinetic study and is subject to approval of the Protocol Team. If the subject assessed is adherent to therapy but does not achieve the minimum AUC$_{0-24}$ of 25 µg.h/mL after dose adjustment they may continue on study treatment after consideration of the clinical, pharmacologic, immunologic and virologic data, and upon agreement of the site investigator, study co-chairs, pharmacologist and medical officers, a given subject may be allowed to continue with the study drug at the dosing that resulted in the exposures below the minimum target.

- Population PK time points at weeks 4 and 12 should remain the same as the Schedule of Evaluations (Appendix IG).

- It is estimated the subject will be on anti-TB treatment for approximately 24 weeks. Upon discontinuation of the rifampin containing anti-TB therapy, the subject’s DTG dose will revert back to once daily administration unless on EFV, FPV/r, or TPV/r. The subject should complete the remainder of the first 48 weeks of DTG therapy on their original schedule of evaluations, or if they have completed 48 weeks of DTG therapy, they should move to long term follow-up (Appendix IE). For example, if the subject was at week 16 when they were started on rifampin, and they complete 24 weeks of rifampin therapy, they would then go back to week 40 of their original SOE.

6.1.9 Antiretroviral Drug-Related Toxicity

Unanticipated and anticipated toxicities from the HAART regimen will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE
Grading Table), Version 1.0, December 2004, Clarification August 2009, which is available on the RSC website at (http://rsc.tech-res.com/safetyandpharmacovigilance/).

The Protocol Team should be contacted via email within 1 business day for any ≥ Grade 3 toxicities. Anticipated toxicities resulting from components of the HAART regimen will be managed by the subject’s clinician, in discussion with the Protocol Team, according to best clinical practice. Within class changes and in rare cases across class changes, will be allowed for toxicity after consultation with the Protocol Team. Hypersensitivity reactions to Abacavir (ABC) should be noted as such and should be managed by the subject’s clinician according to standard clinical practice.

6.1.10  Follow-up of Abnormal Events and Laboratory Values

All abnormal clinical events and laboratory values occurring in enrolled subjects will be followed closely until they return to baseline. The urgency and frequency of repeat evaluations will depend on the clinical significance of the specific abnormality. Study clinicians will provide appropriate clinical management of adverse events according to their best medical judgment and local practice. Alternate explanations will be sought for all clinical and laboratory abnormalities.

6.2  Study Management Plan

The DMC will maintain a web page informing sites as to the availability of enrollment slots per cohort. The Protocol Team, including the co-chairs, medical officers, pharmacist, and pharmacologist, will respond to sites who contact the team with questions regarding toxicity management, dose modifications, or other issues within one business day. Team responses will include the entire team.

Sites will be given seven days to respond to queries to allow the team to meet GSK data delivery requirements. Sites will be contacted by the protocol data manager or co-chairs regarding any query responses or data issues that are outstanding after seven days.

All DTG dose modifications will be recommended by the Protocol Team. See Section 6.24 for information on dose modifications for a mini-cohort or full cohort. The Protocol Team will review the Stage I mini-cohort data for each cohort to determine whether a dose adjustment is required, before opening enrollment to a full cohort. The Protocol Team will review the complete set of Stage I dose finding data for each full cohort and make a dose recommendation which must be approved by the DAIDS Medical Officer, IMPAACT representatives and GSK representatives. If all agree, Stage II opens to enrollment. If the dose fails, the dose is adjusted at the discretion of IMPAACT, the DAIDS Medical Officer, and GSK and without delay in the study.

If there is disagreement among IMPAACT, GSK and/or the Protocol Team, the study monitoring committee (SMC) will be asked to review the data, with the understanding that no dose will proceed to Stage II without GSK approval. Further information on the SMC can be found in Section 8.1.

The Protocol Team will notify sites of the change in dose and request that the site clinician and pharmacist provide acknowledgement of receipt and action taken (changed dose or did not change dose). This management does not apply to dose changes due to weight gain.

Subjects who screen to enter the mini-cohort of Stage I of their age cohort but cannot enroll because the mini-cohort is filled will be given first priority to enroll when the remaining six slots are opened for that
cohort. If Stage I enrollment is completed before a screened subject can enroll, that subject will be given first priority for enrollment on Stage II.

6.2.1 Screening

Subjects will be asked to undergo the following evaluations at screening to be eligible for enrollment:

- Medical history and physical exam
- Pregnancy test (for females of child bearing age)
- Hematology, chemistries, lymphocyte subsets and lipid profiles
- Urinalysis
- Confirmation of HIV-infection
  NOTE: for subjects ≤ 18 months of age results may be pending at the time of enrolment: see Section 4.1.2
- HIV-1 RNA PCR
  NOTE: for subjects ≤ 18 months of age results may be pending at the time of enrolment: see Section 4.1.5.
- Real time genotyping for resistance testing
  NOTE: for subjects in Cohorts IV, IV-DT, V and V-DT results may be pending at the time of enrolment; see Section 4.1.10.
- Phenotyping where possible

Further details can be found in the Schedule of Evaluations (Appendix I).

6.2.2 Study Visits

DTG will be initiated at enrollment. Refer to Section 5.0 for details on formulation or administration of the drug. Steady state DTG levels will be achieved within 5 days of drug initiation.

For subjects in Stage I of each cohort of the trial, an intensive pharmacokinetics (PK) evaluation will be performed between days 5 and 10, as well as population PK’s at weeks 4, 12 and 24. DTG levels will be assayed in real time (ideally within two weeks) and the Protocol Team will evaluate the results of each mini-cohort and full cohort. Subjects in Stage II will not have an intensive PK evaluation, but will undergo population PK’s at Weeks 4, 12 and 24.

6.2.3 Initiation of Dolutegravir and selection of Optimized of Background Therapy (OBT)

6.2.3.1 Stage I: Subjects on Stage I will initiate DTG and have their ARV regimen optimized as described below.

- If the subject is on a stable, failing ARV regimen at entry, DTG will be added to the failing regimen at entry and their background ARV regimen will be optimized based on genotype results after intensive PK 24 hour sampling is completed between days 5-10.
- If the subject is NOT currently taking ARVs at entry, but is ARV treatment experienced, DTG will be started as monotherapy and the
background ARV regimen optimized based on genotype results after intensive PK 24 hour sampling is completed between days 5-10.

- For Cohorts IV, IV-DT, V, and V-DT:
  - If the subject recently initiated ARV treatment (< 4 weeks prior to screening), DTG will be added to the existing regimen and intensive PK 24 hour sampling will be completed between days 5-10. Promptly after the intensive PK sampling, the ARV regimen will be optimized based on the genotype results from screening.
  - If the subject is ARV naïve, a preliminary background therapy regimen (see 6.2.3.3) will be initiated after screening labs have been obtained. PK 24 hour sampling will be completed between days 5-10. Promptly after the intensive PK sampling, the ARV regimen will be optimized based on the genotype results from screening.

6.2.3.2 Stage II: Subjects in cohorts I, II, III and III-DT entering Stage II of the trial will have OBT based on screening results, and start that regimen simultaneously with DTG. Subjects in cohorts IV and V will optimize OBT as soon as genotype results are available (See section 6.2.3.3)

6.2.3.3 Optimized background therapy (OBT) selection and initiation.

- The subject’s physician will be responsible for determining the best OBT, guided by the clinical setting, resistance data, the subject’s ARV history and adherence considerations. Regimens should be shared with, and approved by, the Protocol Team prior to the intensive PK visit.

- For Cohorts I, II, III, III-DT OBT must contain AT LEAST one fully active drug AND one additional drug. For cohorts IV, IV-DT, V and V-DT, OBT will ideally contain AT LEAST one fully active drug AND one additional drug, pending the results of the genotype (if not available in real time). However, after enrollment, if the genotype result does not allow for OBT that includes one active drug, a subject can either withdraw from the study or continue on that OBT regimen until the 4 week HIV RNA testing result are available; if they have a > 1 log drop in HIV RNA by 4 weeks then the subject can continue in the study. In these cases consult the Protocol Team and if appropriate, an exception may be granted.

- For subjects in cohorts I, II and III, the prescriptions should have already been obtained from a pharmacy and the pills must be available during the PK visit to have the first dose observed immediately upon completion of the PK evaluations. For subjects in cohorts IV and V, the PK should be completed on day 5-10, and OBT initiated as soon as possible thereafter when results are back from screening genotype and when agents are available.

- Preliminary background therapy (applicable to ART naïve subjects in cohorts IV, IV-DT, V, and V-DT) are chosen per country guidelines or otherwise designed by the local provider, but it must not include
disallowed medications (4.3.2) and must be approved by the Protocol Team.

**Permitted Changes to ARV Regimens during the Study (Stages I and II)**

No changes, re-optimization or intensification in background ARV therapy after initial optimization will be permitted prior to protocol-defined virologic failure, with the exception of a single substitution of a component of OBT with another approved compound for the management of drug toxicity. Formula substitutions (substituting single agents for fixed dose combinations and vice versa of the same ARV) are not classified as a change and are permitted during the study. Any changes must be discussed with the Protocol Team (impaact.teamp1093@fstrf.org). Unless the change is specifically permitted, subjects who have one or more new agents added to the optimized background HAART regimen will be considered virologic failures.

6.2.4 Cohort Dosing Management (See dosing tables posted on the study-specific web page http://impaactnetwork.org/studies/P1093.asp)

**Stage I**

Stage I will begin with enrollment of a mini-cohort of 4 subjects. Enrollment to the cohort will pause upon entry of the fourth subject to allow for evaluation of PK and safety results.

If the mini-cohort PK data are acceptable and 4 week safety data are acceptable (see Section 8.5.1), enrollment in Stage I will open to complete the full cohort and Stage I of the next sequential age cohort will open.

If on review of all PK and safety data the dose is not acceptable, the mini-cohort dose may be, assuming dose-proportionality, adjusted using the formula below:

\[
\frac{\text{Current Drug Dose}}{\text{Geometric Mean Drug AUC}_{(0-24)}} = \frac{\text{New Drug Dose}}{46 \mu g.h/mL}
\]

If the dose needs to be modified, and there are sufficient subjects available on the waiting list, a new mini-cohort will be accrued. If a subject’s dose is reduced, an additional 4 weeks of safety data is not required. Those undergoing dose modification do not need subsequent modifications of their background regimen. Subjects enrolled in the mini-cohort who did not meet PK targets may be switched to the new dose with approval from the Protocol Team, as applicable.

Once the PK guidelines are satisfied and safety data are acceptable for a mini-cohort, enrollment in Stage I will open to complete the full cohort. These subjects will receive the dose determined acceptable by the Protocol Team after review of all PK and safety data. Simultaneously, Stage I of the next sequential mini-cohort will open. If on review of the mini-cohort data, the dose is still not acceptable, the process will repeat until the PK and safety evaluations result in an acceptable dose for that cohort.

Approximately 10 subjects per cohort are needed in Stage I to provide data for the Stage II dose selection. If a different number of subjects are needed for any cohort for Stage I, this will be communicated to the sites by a protocol amendment. Subjects opting to discontinue in Stage I prior to completion of the intensive PK will be replaced for PK purposes only. Such subjects should be replaced for safety evaluation if they have not discontinued treatment due to an adverse
Subjects who are replaced for PK purposes because they have discontinued due to toxicity will NOT be replaced with respect to applying the safety guidelines to their cohorts; rather, they will continue to be counted as failures. However, subjects who do not discontinue the study due to toxicity, but who are replaced for the PK analysis due to unevaluable data (e.g. they have extremely low levels indicative of non-adherence) will only be replaced for the safety analysis, if their safety data are also deemed unevaluable.

Once PK and safety data are available for the full cohort, the Protocol Team will recommend a Stage II dose for that cohort. The recommended dose must be approved by the Protocol Team, to include DAIDS Medical Officer(s) and GSK representatives, prior to use in Stage II.

Note: Individualized dose adjustments may be made on a case-by-case basis by the recommendation of the team. Dose adjustments will not be permitted for subjects who are unwilling to repeat the intensive PK. The Protocol Team may request that a subject undergo repeat intensive PK sampling at the same dose if a subject’s results appear to be of questionable validity. The Protocol Team may request PK sampling OR modified PK sampling at its discretion. If a subject has experienced a ≥ Grade 2 toxicity that began after initiation of study drug, that subject will be reviewed by the Protocol Team before any dose change and will be considered for individualized dosing if there is a cohort dose change. If individualizing the dose for subjects in this manner results in a dose increase, these subjects will have an additional safety visit 4 weeks after the dose modification, and then continue on study visits with no further changes in the visit schedule.

If Stage I subjects’ DTG dose is equivalent to the Stage II selected dose, the Stage I exposure at the final dose will be considered in the Week 24 and Week 48 primary data analyses. Subjects whose Stage I dose is different from the Stage II selected dose and who have not had individual dose adjustments (i.e. due to extreme PK values) will have their dose changed to the Stage II dose upon selection of the dose by the team and approval by the IMPAACT, the DAIDS Medical Officer, and GSK; a repeat of PK may be required as determined by the IMPAACT, the DAIDS Medical Officer, and GSK representatives.

Stage II

Stage II is intended to provide long-term safety, tolerability and efficacy data for DTG given in combination with an optimized background ARV regimen. Enrollment into each cohort of Stage II will progress independently. At least 12 slots in Stage II will be reserved for each cohort. And the remaining Stage II slots (approximately 60) will likely be assigned without restriction to age or formulation, however the team may choose to give preference to subjects in particular age groups or formulations. Treatment duration of Stage II is 48 weeks, per subject, on the selected dose.

6.2.5 Virologic Failure for Subject Management

Virologic FAILURE in this study is defined as:

- A confirmed decrease in HIV RNA of < 1.0 log_{10} at or after week 12 unless the HIV RNA is < 400 copies/mL.

OR
A confirmed HIV RNA > 400 copies/mL starting at Week 24 or beyond on 2 consecutive measurements at least 1 week and within 4 weeks apart;

Virologic REBOUND in this study is defined as:

- Confirmed HIV-1 RNA > 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after an initial confirmed response (on 2 consecutive measurements at least 1 week apart) of HIV-1 RNA < 400 copies/mL;

OR

- Confirmed > 1.0 log10 increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart). For the purposes of this study, nadir is defined as the lowest HIV-1 RNA while on study drug that is > 400 copies/mL.

NOTE: A confirmatory (repeat) HIV-1 RNA measurement should be performed ≥ 1 week to ≤ 4 weeks of the initial suspected failure or rebound.

NOTE: Subjects should continue to be evaluated for virologic failure beyond Week 48. Either for the first time or in subjects who experience virologic failure on multiple occasions, provided that at least 24 weeks have lapsed from the prior virologic failure drug resistance samples.

Subjects, who are confirmed as virologic failures as defined above, should follow the schedule of evaluations for Virologic Failure as described in Appendix IA – IE. At the confirmed virologic failure visit, a specimen should be drawn that should be sent for resistance testing (genotyping and phenotyping), as described in Appendix IA - IE. Subjects may then, at the discretion of the subject’s clinician and with the approval of the Protocol Team:

- Be taken off study drug and followed as per Appendix IF, ‘Subjects who Discontinue Study Provided Dolutegravir’.

OR

- Have background therapy re-optimized, with the subject remaining on study drug;

OR

- Continue with no changes made to the current regimen.

Any re-optimization of background therapy that includes experimental drugs must first be approved by the Protocol Team, DAIDS Medical Officer and GSK representatives, emailing the team at impaact.teamp1093@fstrf.org.

6.2.6 Viral Resistance Samples/Testing

For all subjects, blood samples for viral resistance assays and integrase resistance will be collected and stored at entry. In addition, to evaluate development of resistance to DTG and to other antiretroviral therapies, used in the treatment regimen, blood samples will be collected at confirmed virologic failure (as defined above) and at Premature Discontinuation of Study Drug (if not already obtained at virologic failure) to assess development of genotypic or phenotypic resistance to DTG and/or OBT.
6.2.7 Algorithm for Resistance Testing

- If a subject reaches virologic failure at 24 weeks and discontinues because of viral failure, the earliest sample with a corresponding HIV-1 RNA result above 400 copies/mL should be sent for all resistance testing, as outlined in the Laboratory Processing Chart which can be found on the P1093 protocol specific webpage: [http://impaactnetwork.org/studies/P1093.asp](http://impaactnetwork.org/studies/P1093.asp)

- If a subject is a viral failure but continues in the study (on study drug), the second consecutive sample with a corresponding HIV RNA result above 400 copies/mL will be sent for all testing. In addition, resistance testing will be done for subjects who continue on study after confirmation of virologic failure if HIV RNA is >400 copies/mL.

- If a subject discontinues from the study early, a sample will be sent for resistance testing if the subject's HIV RNA level is above 400 copies/mL at the time of discontinuation.

Sites should notify the Protocol Team of all confirmed virologic failures. A request for genotyping and phenotyping should also be sent to the team upon confirmation of the virologic failure.

6.3 Long Term Safety Follow-up

Subjects who successfully complete 48 weeks of DTG treatment will continue to receive DTG as part of long term safety follow-up and will be seen in clinic every 12 weeks for safety visits, see Appendix IE for details. Study drug will be provided for the duration of the study, including the three year safety follow-up period defined in the protocol. Thereafter, subjects will be transitioned into care and treatment outside of the study, see Section 10.6.

6.4 Pregnancy

6.4.1 Pregnancy Testing

Female study subjects of reproductive potential are defined as girls who have reached menarche for at least 24 consecutive months i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure (hysterectomy or bilateral oophorectomy). All study subjects must agree to NOT participate in a conception process (e.g. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization).

If participating in sexual activity that could lead to pregnancy, female subjects of childbearing potential must agree that two reliable methods of contraception will be used simultaneously while receiving the study drug and for two weeks after stopping the study drug. Hormonal birth control alone (e.g., pills, shots, or slow release inserts placed under/on the skin) would not be considered adequate. An effective, medically accepted barrier method of contraception (i.e., female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm (excluding nonoxydyl-9), intrauterine device [IUD], others) also must be used during the study. Condoms are recommended because their appropriate use is the only contraception method effective for
preventing HIV-1 transmission. Use of an IUD may increase the risk of pelvic inflammatory disease.

All female subjects of child bearing potential must have a negative pregnancy test at Screening and at Day 0 to be eligible for enrollment, randomization and administration of DTG. Pregnancy testing will be conducted at ALL visits and at any time during the trial when pregnancy is suspected. Additionally, a pregnancy test should also be performed prior to DTG re-administration, when dosing is disrupted for more than 7 days. Pregnancy tests may be performed on either blood or urine.

At every visit (or some other more frequent interval), pregnancy prevention will be discussed with the subjects, including specific counseling, provision of information and advice as needed. Verbal confirmation of the use of 2 methods of contraception should be obtained. This discussion should be documented in the subject’s study record.

6.4.2 Pregnancy

Any subject who becomes pregnant (intrauterine) while participating in this study, will be discontinued from study drug immediately. However, these subjects should remain on study but off study drug and followed per Appendix IF, in case of any safety issues until the birth of the baby. Any pregnancy that occurs during study participation must be reported to the team immediately, as well as to the RSC as an EAE.

The pregnancy must also be followed to determine outcome (including premature termination) and status of mother and child(ren), which will be recorded and submitted to SDMC using the Pregnancy Outcome form within one week of the site becoming aware of the outcome. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

HIV-1 infected women who are pregnant should be treated according to the Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Peri-natal HIV Transmission in the United States: Tables - April 29, 2009 (http://www.aidsinfo.nih.gov/Guidelines/). HIV-1 infected women in other countries who are pregnant should be treated according to the local standard of care recommendations.


6.5 Criteria for Study Discontinuation

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

6.5.2 The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.

6.5.3 The subject requires treatment with medications that are disallowed while on this study.
6.5.4 Virologic failure and subject does not meet the criteria for continuation of study treatment.

6.5.5 Non-adherence of study medications.

6.5.6 The Protocol Team has determined that there would be no benefit to continue on study and receive DTG.

6.6 Criteria for Treatment Discontinuation

6.6.1 Pregnancy (see Section 6.4). In the event that a subject becomes pregnant, sites are encouraged to register the subject’s pregnancy in the Antiretroviral Pregnancy Registry (http://www.apregistry.com/reg.htm)

In US, Canada: 1-800-258-4263, or International: 1-910-679-1598

6.6.2 New data become available that indicate treatment should be discontinued.

6.6.3 Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.1

6.6.4 Liver toxicities (see Section 6.1.3)

6.6.5 The investigator determines that further participation would be detrimental to the subject's health or well-being.

6.6.6 HIV infection not confirmed per Section 4.1.2

6.6.7 Subject was enrolled but found to have HIV RNA \( \leq 1000 \) copies / mL at screening (applies only to Cohorts IV, IV-DT, V and V-DT).

6.6.8 Subject was enrolled but found to have no active drugs per genotype performed at screening (applies only to Cohorts IV, IV-DT, V and V-DT who enrolled with genotype results pending); however, such subjects who have a > 1 log drop in HIV RNA by 4 weeks can continue study drug per consultation with the Protocol Team.

NOTE: In the event of treatment discontinuation, subjects will be asked to continue on study for 4 weeks after they discontinue study drugs or until the adverse event resolves.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact NIAID Clinical Research Management System at CRMSsupport@niaid.nih.gov. Questions may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com)

7.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study for the period defined in Section 7.4.

The study agents for which expedited reporting are required are DTG tablets, DTG granules for suspension (granules mixed with liquid) and DTG dispersible tablets for oral administration.

- In addition to the EAE Reporting Category identified above, other adverse events that must be reported in an expedited manner are:
- All grade 4 toxicities,
- All pregnancies,
- Hy’s law liver toxicities (see Section 6.1.3)
- Abacavir (ABC) hypersensitivity (HSR) (see Section 6.1.7)
- All pregnancy complications, elective terminations and spontaneous abortions

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, must be used and is available on the DAIDS RSC Web site: http://rsc.tech-res.com/safetyandpharmacovigilance/

7.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is the duration of the study.
- After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

NOTE: For reporting of all adverse experiences the Investigator will determine the causality and relationship to study drug. However, in regards to subject safety and PK evaluations which will support the selection of a dose for a given cohort, the Protocol Team will also have input as to the causality and drug relation of specific adverse experiences.
8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase I/II study whose primary objectives are to assess the safety and pharmacokinetics of DTG administered to HIV-1-infected infants, children and adolescents with ages ranging from 4 weeks to < 18 years. The sample will be stratified into the following groups:

- **Cohort I:** Adolescents ≥ 12 to <18 years of age (tablets)
- **Cohort IIA:** Children ≥ 6 to <12 years of age (tablets)
- **Cohort IIB:** Children ≥ 6 to <12 years of age (granules for suspension)
- **Cohorts III:** Children ≥ 2 to < 6 years of age (granules for suspension)
- **Cohort III-DT:** Children ≥ 2 to < 6 years of age (dispersible tablets)
- **Cohort IV:** Children ≥ 6 months to < 2 years (granules for suspension)
- **Cohort IV-DT:** Children ≥ 6 months to < 2 years of age (dispersible tablets)
- **Cohort V:** Infants ≥ 4 weeks to < 6 months (granules for suspension)
- **Cohort V-DT:** Infants ≥ 4 weeks to < 6 months (dispersible tablets)

A minimum of ten subjects will be enrolled into each cohort in Stage I of the study for purposes of dose finding. Additional subjects will be enrolled into Stage II of the study and treated at the doses determined optimal for their cohorts on the basis of Stage I results. The total sample will provide a minimum of 120 evaluable subjects who have been treated exclusively at the doses judged to be optimal for their age cohorts (see Schema for breakdown by cohort).

Accrual to Stage I for Cohorts I, IIA, IIB, III, IV and V of the study will follow an algorithm in which younger children’s exposure to the study medication is contingent upon success in meeting safety and pharmacokinetic guidelines in the older strata. Thus Cohort I will be the first to open, with enrollment in Cohort IIA contingent upon whether the members of Cohort I meet the guidelines for safety and PK parameters. Cohort IIB will then open once members of Cohort IIA pass safety and PK criteria and a pediatric formulation is available. A similar approach will be used for the rest of the younger cohorts, each of whose opening will be contingent upon successful results from the next older age cohort. Accrual to Stage I for Cohorts III-DT, IV-DT and V-DT may be simultaneous, rather than sequential, using the current dose from the respective granules for suspension cohort (see Section 3.3 for more details).

Switching of formulation for subjects previously enrolled in Cohorts III, IV, and V (Stages I and II) from granules for suspension to dispersible tablets is allowed, contingent upon the respective full cohort’s having passed safety and PK criteria (see Section 3.3.1).

The study will be monitored intensely by the Protocol Team, which includes DAIDS representatives and senior scientific management at GlaxoSmithKline, the pharmaceutical partner. The team will review
safety and pharmacokinetic data at least twice a month during the dose finding stage (Stage I) with the aim of determining the optimal dose for each cohort, while protecting subject safety.

In addition the IMPAACT Network will appoint a P1093 Study Monitoring Committee (SMC) to provide impartial review in situations where subject safety is in question. In accordance with IMPAACT and DAIDS procedures, this committee will be composed of one clinician from the IMPAACT Protocol Development and Monitoring Committee; two clinicians appointed by the IMPAACT Treatment Scientific Committee associated with the network but not directly involved in the conduct of study; and an independent statistician appointed by the IMPAACT Statistical and Data Management Center (SDAC). The SMC will all be independent of the Protocol Team and its pharmaceutical partner, GlaxoSmithKline.

Per IMPAACT/DAIDS procedures, members of the P1093 SMC will have:

1) No financial interest in the study;
2) No planned authorship in publication of study results; and
3) No involvement in the conduct of the study.

Initial tests of safety and PK will examine data from the first 4 subjects (mini-cohort) of Cohort I to determine whether further accrual to that cohort may proceed without dose adjustment and whether the next youngest cohort will be allowed to open. These tests will proceed as follows: The starting dose administered to the first four subjects of this cohort will be evaluated on the basis of PK data, based on a blood sample taken 5-10 days after the start of therapy on that dose. For subjects who meet PK targets, safety will be evaluated on the basis of all available data collected through the fourth week on that dose. For subjects who fail to meet PK targets and are required to have a dose adjustment, safety will be evaluated on the basis of data gathered until the time of the visit at which the dose is adjusted. This will ensure that, for any subject needing PK determined dose adjustment, adverse events attributed to the starting dose must have occurred while the subject was still on that dose. However, this also means that for such subjects, the safety of the starting dose may be assessed on the basis of less than 4 weeks of study drug exposure.

The overall safety and PK data of the first 4 subjects on a given cohort will be evaluated with respect to the safety guidelines specified in Section 8.5 and the PK guidelines specified in Section 1.5.1. If the first 4 subjects of this cohort meet both sets of guidelines, then 6 additional subjects will be accrued to this cohort, and the next younger cohort will begin to accrue its first 4 subjects. If the first 4 subjects of the older cohort fail either the safety or the PK guidelines in this initial test, then the starting dose will be adjusted in the appropriate direction, (upwards for inadequate PK values; downwards for safety failure), if this is feasible. Four new subjects will be treated at the new dose, and an initial evaluation of safety and PK will be made on the basis of data from these subjects. The evaluation will proceed as described above. In the final assessment of Stage I results, the starting dose of a fully accrued cohort (N = 10) will be evaluated on the basis of safety and PK guidelines. Failure with respect to the safety and/or PK guidelines will result in a dose adjustment within this cohort, with the starting dose adjusted in the appropriate direction, if this is feasible. New subjects will be started on the new dose and evaluations will proceed as described above.

If the Protocol Team judges a given subject’s PK data to be unevaluable (e.g. because of non-adherence), that subject will be replaced for dose finding purposes. Note that the subject would be replaced for evaluating safety, as well as PK, criteria, if unevaluable PK data reflect uncertainty about appropriate exposure to the study medication.

Once the dose finding procedures have been completed for each cohort, the Protocol Team will review all safety and PK data and will make final recommendations concerning the doses to be administered during
Stage II of the study. These recommendations will be reviewed by the Protocol Team. The purpose of this review process will be to take account of all available information in determining whether the dose finding algorithm has converged on the best dose for further study in Stage II or whether adjustments are needed. As part of this review process, safety and PK data will be broken down on the basis of the dosing adjustments that have been made because of the inducing or inhibiting effects of the background regimens. If there is evidence that some adjustments may have been associated with undesirable PK levels or with safety concerns, these adjustments may be modified for Stage II or further data may be gathered prior to opening Stage II.

Subjects accrued to Stage II of the study will be administered the doses determined for their age cohorts, with no individual dose adjustments on the basis of PK allowed. For purposes of analysis, data from these subjects will be combined with the data from the Stage I subjects who have been treated at the optimal doses determined for their cohorts and who have not required individual PK determined dose adjustments, such that their total exposure to the study drug has been at the optimal dose. Sensitivity analyses will be performed to determine whether the exclusion of subjects whose doses have been adjusted creates a selection bias which impacts upon any results.

Subjects from Cohorts III, IV and V (Stages I and II) who switched from granules for suspension to the dispersible tablets will be included in secondary analyses whose purpose would be to (1) identify safety issues for all children exposed to the study drug, and (2) determine whether the results of those starting treatment on granules differed descriptively from those of the primary analysis.

Study accrual is designed to yield at least 120 evaluable subjects for the weeks 24 and 48 safety analyses; some coming from Stage I and some from Stage II. For these safety analyses “evaluable” will be defined as “having been treated exclusively on the dose determined to be optimal for a given age cohort and having either completed 24 (or 48) weeks of exposure to the study drug or having been classified as a safety failure, due to a study drug related adverse event occurring during the first 24 (or 48) weeks of treatment”. Although the primary safety analyses will focus on the effects of exposure to the optimal dose level for 24 weeks, secondary analyses will include all safety data collected from first subject exposure to 48 weeks and until the end of the study. This will include data representing the final dose for each cohort, as well as data gathered during the dose finding stage which may represent exposure to doses which have failed. This will also include data from subjects whose individual doses have been adjusted, with results broken down by the times at which different dose levels were taken.

### 8.2 Endpoints and Outcome Measures

For safety reporting and monitoring purposes, a drug related adverse event is defined as an adverse event that is judged to be definitely, probably or possibly related to the study drug.

8.2.1 Primary Endpoints:

8.2.1.1 Toxicity through Week 24

- All adverse events or lab toxicities of Grade 3 or higher severity
- Adverse events or lab toxicities of Grade 3 or higher severity judged to be at least possibly attributable to the study medication
- Termination from treatment due to a drug-related adverse event
- Death

8.2.2 Primary Response Variables
8.2.2.1 Pharmacokinetics
- AUC0-24

8.2.3 Secondary Endpoints:

8.2.3.1 Toxicity through week 48 and beyond
- All adverse events or lab toxicities of grade 3 or higher severity.
- Adverse events or lab toxicities of grade 3 or higher severity judged to be at least possibly attributable to the study medication.
- Termination from treatment due to a drug-related adverse event.
- Death

8.2.3.2 Plasma HIV-1 RNA (copies/mL) <400 copies/mL and <50 copies/mL.

8.2.3.3 Pharmacokinetics
- C24h, C0, Cmin, Cmax, CL/F, Vz/F and t1/2

8.2.4 Secondary response variables
- CD4/8 counts and percent
- Genotypic and phenotypic measures of resistance at baseline and at virologic failure
- Disease progression as measured by change in CDC category

8.3 Randomization and Stratification

There will be no randomization. In each stage, subjects will be stratified into cohorts defined by age and formulation, as described in Section 8.1.

8.4 Sample Size and Accrual

Total accrual will depend upon the number of subjects who must be accrued to yield at least 120 evaluable subjects for purposes of the primary safety analyses. There is some uncertainty concerning the number needed to complete the dose finding procedures in Stage I and the number who may be lost to follow-up for reasons other than treatment failure. Each successful cohort on Stage I will include 10 subjects; the majority of whom will have been treated continuously on the dose that has been chosen for Stage II. This will likely yield additional subjects from Stage I who will contribute to the evaluation of the optimal dose. Thus, we anticipate accruing approximately 160 subjects to ensure that the total sample includes at least 120 evaluable subjects who have been treated only on the optimal dose and that the quotas for each cohort, specified in the Schema, have been filled.

The selection of a sample size of ten subjects in Stage I for each age cohort is based on feasibility and historical pediatric recruitment experience of GSK and IMPAACT, as well as justification to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance (CL/F) and volume of distribution (Vd) for DTG with an at least 78% power.

Variability (CV%) in CL/F and Vd for each age cohort are predicted based on the population PK model developed using adult data from ING111521 and ING112276. In the adult population PK model, CL/F and Vd are modeled as the following:

\[
\text{CL/F (L/hr)} = 0.873 \times (\text{WT/70})^{0.713} \times \text{EXP}(\text{eta1}), \text{eta1} \sim N(0, 0.0857)
\]

\[
\text{Vd (L)} = 17.5 \times (\text{WT/70})^{1.02} \times \text{EXP}(\text{eta2}) + 1.6, \text{eta2} \sim N(0, 0.0365)
\]

where WT is body weight in kg.
Using predicted variability in CL/F and Vd, simulations (10,000 simulations with a sample size of 10 for each simulation) were performed to estimate % chance for 95% CI of geometric mean estimates of simulated CL/F and Vd to fall within 60% to 140% of the point estimates (equivalent to power).

Table 12 presents the projected weight range, predicted mean and variability (coefficient of variability, CV) in CL/F and Vd, and estimated power for a sample size of 10 in each age cohort.

<table>
<thead>
<tr>
<th>Age Cohort</th>
<th>Projected Weight Range (kg)</th>
<th>PK Parameter</th>
<th>Predicted Mean</th>
<th>Predicted CV</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-18yr</td>
<td>30-100</td>
<td>CL/F</td>
<td>0.85</td>
<td>0.38</td>
<td>94.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vd</td>
<td>18.1</td>
<td>0.34</td>
<td>98.5</td>
</tr>
<tr>
<td>6-&lt;12yr</td>
<td>17-52</td>
<td>CL/F</td>
<td>0.54</td>
<td>0.38</td>
<td>95.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vd</td>
<td>10.3</td>
<td>0.30</td>
<td>99.7</td>
</tr>
<tr>
<td>2-&lt;6yr</td>
<td>10.7-23</td>
<td>CL/F</td>
<td>0.21</td>
<td>0.34</td>
<td>98.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vd</td>
<td>5.77</td>
<td>0.21</td>
<td>100</td>
</tr>
<tr>
<td>6mo-&lt;2yr</td>
<td>6.75-15.1</td>
<td>CL/F</td>
<td>0.13</td>
<td>0.34</td>
<td>98.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vd</td>
<td>4.28</td>
<td>0.19</td>
<td>100</td>
</tr>
<tr>
<td>4wk-&lt;6mo</td>
<td>3.77-9.26</td>
<td>CL/F</td>
<td>0.084</td>
<td>0.35</td>
<td>97.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vd</td>
<td>3.18</td>
<td>0.16</td>
<td>100</td>
</tr>
</tbody>
</table>

Power for a sample size of 10 and CV of 0.45, which is 20% higher than the highest predicted CV, was estimated to be >78%. Power for a sample size of 9 and CV of 0.45, was estimated to be >68%.

8.5 Safety Guidelines for the Evaluation of Stage I Starting Doses

The attribution of relationship of serious adverse events to study drug for the purposes of employing the start, stop and pause rules will be by consensus among the site investigator and the Protocol Team. If unanimous agreement between them cannot be established, the relevant data will be reviewed by the P1093 Study Monitoring Committee, which will make the final judgment concerning the relationship between study drug and the adverse event. Within this committee the decision will be determined by the majority opinion of the P1093 Study Monitoring Committee clinicians. Gradation of relationship will use the following terminology: ‘Not related’, ‘Probably not related’, ‘Possibly related’, ‘Probably related’ or ‘Definitely related’.

Tables 13 and 14 below use a multinomial response model to assess the probability of failing the safety criteria under each of the hypothetical situations in those tables. The calculations are performed as follows: Each of the total number of subjects represents a trial, which may have 1 of 3 mutually exclusive outcomes: (1) a life threatening drug-related adverse event or a grade 4 event judged to be at least probably related to treatment; (2) a Grade 3+ event, not satisfying the criteria set forth in #1, immediately above, but judged to be at least possibly related to study treatment and resulting in termination of study treatment; and (3) a relatively benign outcome, satisfying neither the criteria in #1 nor #2, immediately above.

Each table has its sets of results under which the set of trials would pass the safety criteria. The probability of passing the safety criteria represents the sum of the probabilities of these sets of results, and “1 minus the probability of passing the safety criteria” represents the probability of failing them. The “True Toxicity Rates” presented in the tables, along with the true rate of having neither of the types of
toxicity represented by the true toxicity rates (which is 1 - the sum of the true toxicity rates), provide the probabilities for the outcomes which are used in the multinomial calculations for each of the hypothetical situations.

8.5.1 Safety Guidelines for the First Four Subjects Started at a Given Dose Level in Each Stage I Cohort

For each Cohort, the frequency of adverse reactions to the starting dose of the study medication will be evaluated on the first 4 subjects. The data will extend to the week 4 visit for subjects not requiring PK determined dose adjustment or until the visit on which the dose is adjusted, as described above. Further accrual into this cohort will be contingent upon meeting the following safety guidelines.

If any of the first 4 subjects has a life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication, or 2 or more subjects have terminated study drug due to a grade 3+ drug-related adverse event stop accrual into this dose group, until a safety review by the Protocol Team has been conducted. All of the relevant safety and pharmacokinetic data will be reviewed to determine whether it is safe to continue the attempt to find an optimal dose for this cohort. If the team determines that it is safe to proceed, it will make any changes in the dosing and monitoring procedures which have been judged to be necessary. If there are any concerns regarding safety, the P1093 Study Monitoring Committee will then review all of the relevant safety and pharmacokinetic data, along with the recommendations of the Protocol Team, and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

The protocol will only proceed if this review has led to a recommendation that it is safe to do so and the team, including the study chair, medical officer and GlaxoSmithKline representatives, agree. The safety review may lead to a recommendation that the dose be de-escalated. Before implementing such a recommendation, the Protocol Team will review the PK data to determine whether a lower dose is likely to achieve adequate drug exposure.

If none of the first 4 subjects has experienced a life-threatening drug-related adverse event or a Grade 4 event that is probably or definitely attributable to the study medication and fewer than 2 of these 4 subjects have terminated study drug due to a grade 3+ drug-related adverse event, then this group has passed the initial safety guidelines. If these 4 subjects also meet the PK guidelines, accrue 6 more subjects to this group and evaluate the safety and PK results of the overall cohort of 10 subjects.

Given the small sample sizes within each cohort, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible:

1) In a group where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines;

2) In a group where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study medication were used extensively among the subject population at the dose level under question. The hypothetical situations presented in Table 13 range from conditions under which a given dose level would cause a high incidence of severe and life threatening drug-related adverse
events to conditions under which severe drug-related adverse events would be relatively rare and would not be life threatening. For each of these hypothetical situations, we assume that a sample of four subjects is drawn from the subject population and that the safety guidelines, summarized above, are followed.

For example, Table 13 shows that there is a 78% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening drug-related adverse event is 50%.

**Table 13: Probability of Failing Dose Escalation Guidelines under Potential Rates of True Toxicity**

<table>
<thead>
<tr>
<th>True Toxicity Rates</th>
<th>Probability of Failing Safety Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Life Threatening drug-related adverse events that would result in Tx discontinuation, excluding Grade 4 events probably or definitely attributable to study medication</td>
<td>Probability of Failing Safety Guidelines</td>
</tr>
<tr>
<td>Life Threatening drug-related adverse events (including death) or Grade 4 events probably or definitely attributable to study medication</td>
<td>Probability of Failing Safety Guidelines</td>
</tr>
<tr>
<td>.50</td>
<td>.00</td>
</tr>
<tr>
<td>.50</td>
<td>.05</td>
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<tr>
<td>.50</td>
<td>.25</td>
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<tr>
<td>.25</td>
<td>.00</td>
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<tr>
<td>.25</td>
<td>.05</td>
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<td>.05</td>
<td>.25</td>
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<tr>
<td>.00</td>
<td>.05</td>
</tr>
<tr>
<td>.00</td>
<td>.25</td>
</tr>
</tbody>
</table>

Assuming that it would be undesirable to accrue additional subjects at a dose that had these true rates of adverse events, the 22% chance of NOT failing the safety guidelines would represent the probability of error. The table also shows that there is a 1% chance of failing, when the true rate of non-life threatening drug-related adverse events is only 5% and the true rate of life threatening drug-related adverse events is zero. Assuming that the potential benefits associated with exposing additional subjects to this dose of the drug would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

8.5.2 Safety Guidelines for the Total Group of Ten Subjects Started at a Given Dose Level in Each Stage I Group

The final safety guidelines applied to a given starting dose of the study medication within a group will make use of data from all subjects started at that dose. The data will extend to the week 4 visit for subjects not requiring PK determined dose adjustment or until the visit on which the dose is adjusted, as described above. If any of these subjects has a life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication, or more than 25% terminated study treatment due to grade 3+ drug-related adverse event, this starting dose will fail the safety guidelines for the cohort under investigation. If none of these subjects has experienced a life-threatening drug-related adverse event or a Grade 4 event that is probably or definitely attributable to the study medication and no more than 25% terminated study treatment due
to Grade 3+ drug-related adverse events, then this starting dose will pass the safety guidelines for the group under investigation.

If any of these subjects has a life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication or more than 25% terminated study treatment due to Grade 3+ drug-related adverse event, this starting dose will fail the safety guidelines for the cohort under investigation. Should this occur, the Protocol Team will review all of the relevant safety and pharmacokinetic data in an attempt to determine whether it is safe to continue the attempt to find an optimal dose for this cohort. If the team determines that it is safe to proceed, it will make any changes in dosing and monitoring procedures which are judged to be necessary. If there are any concerns regarding safety, the P1093 SMC will then review all of the relevant safety and pharmacokinetic data, along with the recommendations of the Protocol Team, and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

Following Table 13, the hypothetical rates of "true toxicity" which could occur if the study medication were used extensively among the subject population at the dose level are again presented in Table 14, this time assuming that a sample of ten subjects is drawn from the subject population and the safety guidelines allows no subject with life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to study medication or no more than 2 subjects who terminated study treatment due to Grade 3+ drug-related adverse event.

### Table 14: Probability of Failing Dose Escalation Guidelines Under Potential Rates of True Toxicity

<table>
<thead>
<tr>
<th>True Toxicity Rates</th>
<th>Probability of Failing Safety Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-life threatening drug-related adverse event that would result in treatment discontinuation, excluding Grade 4 events probably or definitely attributable to study medication</td>
</tr>
<tr>
<td>.50</td>
<td>.00</td>
</tr>
<tr>
<td>.50</td>
<td>.05</td>
</tr>
<tr>
<td>.50</td>
<td>.25</td>
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<td>.25</td>
<td>.00</td>
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<td>.25</td>
<td>.05</td>
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<td>.05</td>
<td>.25</td>
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<tr>
<td>.00</td>
<td>.05</td>
</tr>
<tr>
<td>.00</td>
<td>.25</td>
</tr>
</tbody>
</table>

For Example, Table 14 shows that there is a 98% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening drug-related adverse event is 50%.

### 8.6 Analyses

#### 8.6.1 Summary of Dose Finding Data
The analysis of dose finding data will consist of descriptive statistics summarizing the safety and PK data from the dose finding phase of the study. (See Section 9.0 for PK analysis). The safety data will be broken down by cohort and will present the results of the safety evaluations applied to each starting dose tested within each cohort, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each cohort, every adverse event of Grade 3 or higher will be listed, along with subject demographics, the dose prescribed to the subject at the time of the event and the Protocol Team’s assessment of the probability that this event was due to the study treatment (not related, possibly related, probably related or definitely related).

8.6.2 Analysis of Data Representing Exposure to the Doses Judged to be Optimal for Each Cohort

These analyses will be stratified by Age Cohort. The findings will be presented both in aggregate and broken down by this stratification factor, with estimates bounded by 95% confidence limits. Given that the small sample sizes within strata will provide limited power for statistical tests of differences across age groups, interpretation of the results will depend upon whether differences across strata are great enough to be considered to be clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have the greatest statistical precision. However, if results vary across strata to a clinically important extent, interpretation of results should take account of the issues represented by the stratification factor.

8.6.2.1 Primary Analyses (performed on data through the Week 24 visit)

Safety

The primary safety analysis will include only subjects whose starting doses have been those judged to be optimal for their groups. Stage I subjects whose doses have been adjusted for inadequate PK will be excluded. Stage I subjects who have been removed from treatment due to toxicities while on the optimal dose will be included and treated as safety failures in the primary safety analysis. Sensitivity analyses will be performed to determine whether the exclusion of subjects whose doses have been adjusted creates a selection bias which impacts upon any results.

Each subject’s safety data will be summarized as: the worst grade of adverse event experienced during the first 24 weeks (and 48 weeks) of exposure to the optimal dose of the study treatment and the worst grade of adverse event judged to be at least possibly due to study treatment during this time period. Frequency distributions of these safety outcomes will be presented in the aggregate and broken down by age cohort. Listings of all Grade 3+ events will be provided, broken down by type of toxicity (hepatic, hematologic, etc.).

The proportions of subjects experiencing Grade 3+ adverse events will be presented in aggregate and broken down by age, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of subjects exhibiting Grade 3+ events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.
Table 15: Percent of Subjects Experiencing Grade 3+ Adverse Events (or Grade 3+ Adverse Events Attributed to the Study Medication) With Exact 95% Confidence Intervals

<table>
<thead>
<tr>
<th>N</th>
<th>% With Grade 3+ Adverse Events</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0%</td>
<td>0% -- 31%</td>
</tr>
<tr>
<td>20</td>
<td>0%</td>
<td>0% -- 17%</td>
</tr>
<tr>
<td>40</td>
<td>0%</td>
<td>0% -- 9%</td>
</tr>
<tr>
<td>60</td>
<td>0%</td>
<td>0% -- 6%</td>
</tr>
<tr>
<td>90</td>
<td>0%</td>
<td>0% -- 4%</td>
</tr>
<tr>
<td>150</td>
<td>0%</td>
<td>0% -- 2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>% With Grade 3+ Adverse Events</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10%</td>
<td>0.3% -- 45%</td>
</tr>
<tr>
<td>20</td>
<td>10%</td>
<td>1% -- 32%</td>
</tr>
<tr>
<td>40</td>
<td>10%</td>
<td>3% -- 24%</td>
</tr>
<tr>
<td>60</td>
<td>10%</td>
<td>4% -- 21%</td>
</tr>
<tr>
<td>90</td>
<td>10%</td>
<td>5% -- 18%</td>
</tr>
<tr>
<td>150</td>
<td>10%</td>
<td>6% -- 16%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>% With Grade 3+ Adverse Events</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20%</td>
<td>3% -- 56%</td>
</tr>
<tr>
<td>20</td>
<td>20%</td>
<td>6% -- 44%</td>
</tr>
<tr>
<td>40</td>
<td>20%</td>
<td>9% -- 36%</td>
</tr>
<tr>
<td>60</td>
<td>20%</td>
<td>11% -- 32%</td>
</tr>
<tr>
<td>90</td>
<td>20%</td>
<td>12% -- 30%</td>
</tr>
<tr>
<td>150</td>
<td>20%</td>
<td>14% -- 27%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>% With Grade 3+ Adverse Events</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>30%</td>
<td>7% -- 65%</td>
</tr>
<tr>
<td>20</td>
<td>30%</td>
<td>12% -- 54%</td>
</tr>
<tr>
<td>40</td>
<td>30%</td>
<td>17% -- 47%</td>
</tr>
<tr>
<td>60</td>
<td>30%</td>
<td>19% -- 43%</td>
</tr>
<tr>
<td>90</td>
<td>30%</td>
<td>21% -- 41%</td>
</tr>
<tr>
<td>150</td>
<td>30%</td>
<td>23% -- 38%</td>
</tr>
</tbody>
</table>

Table 15 presents exact 95% confidence intervals around various potential rates of grade 3+ adverse events which might be observed in a total sample of 100 evaluable subjects, a sample of 10 subjects representing the minimal sample that could be accrued within any of the Stage I stratification factors and potential sample sizes that might occur if subgroups are analyzed (N = 20, 40, 60, 90) This table indicates that confidence intervals will be quite wide around the minimal sample size of 10 subjects within a given stratum, but would be reasonably precise around samples of 90-150 subjects.

8.6.2.2 Key Secondary Analyses

Safety
Safety assessments will be performed on long term data collected through Week 48. These analyses will be similar to the Week 24 analyses described in Primary Analysis above.

**Viral Load**

Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed at weeks 24 and 48. For regulatory submission purposes, at both of these time points the primary definition of virologic outcome will be calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA’s snapshot algorithm. Subjects will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest. (This window will be defined in the analysis plan.) In addition subjects will be classified as virologic failures at either of these time points if they meet any of the following conditions prior to that time point:

a) Discontinuation of study treatment;  
b) Change in background therapy not allowed in the protocol;  
c) Change in background ART substitutions permitted per protocol, unless the decision to switch is documented as being before or at the first on-treatment visit after switching to OBT where HIV-1 RNA is assessed (Week 4) or subject’s HIV-RNA is <400/<50 copies/mL before the switch.

Subjects who only discontinued a background ARV or who had formula substitutions (substituting single agents for fixed dose combinations and vice versa of the same ARV) in their OBT are not considered as having OBT changes and will not be analyzed as virologic failures. Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is on-treatment within the visit of interest window. The proportions of subjects meeting the criteria for virologic success at each of these time points will be bounded by exact 95% confidence intervals, and will be presented both in the aggregate and broken down by age cohort.

**Table 16: Percent of Subjects Meeting Criterion for Virologic Success with Exact 95% Confidence Intervals**

<table>
<thead>
<tr>
<th>N</th>
<th>% Undetectable RNA</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10%</td>
<td>0.3% -- 45%</td>
</tr>
<tr>
<td>20</td>
<td>10%</td>
<td>1% -- 32%</td>
</tr>
<tr>
<td>40</td>
<td>10%</td>
<td>3% -- 24%</td>
</tr>
<tr>
<td>60</td>
<td>10%</td>
<td>4% -- 21%</td>
</tr>
<tr>
<td>80</td>
<td>10%</td>
<td>4% -- 19%</td>
</tr>
<tr>
<td>100</td>
<td>10%</td>
<td>5% -- 18%</td>
</tr>
<tr>
<td>10</td>
<td>30%</td>
<td>7% -- 65%</td>
</tr>
<tr>
<td>20</td>
<td>30%</td>
<td>12% -- 54%</td>
</tr>
<tr>
<td>40</td>
<td>30%</td>
<td>17% -- 47%</td>
</tr>
<tr>
<td>60</td>
<td>30%</td>
<td>19% -- 43%</td>
</tr>
<tr>
<td>80</td>
<td>30%</td>
<td>20% -- 41%</td>
</tr>
<tr>
<td>100</td>
<td>30%</td>
<td>21% -- 40%</td>
</tr>
<tr>
<td>10</td>
<td>50%</td>
<td>19% -- 81%</td>
</tr>
</tbody>
</table>
Table 16 presents exact 95% confidence intervals around various potential rates of virologic success which might be observed in a total sample of 100 subjects or in subsamples of various sizes (N=10, 20, 40, 60, 80). Subjects whose OBT is changed after initial optimization will be considered treatment failures in these analyses, unless the change is one specifically allowed by the protocol.

**CD4/8**

Change in CD4/8 count and percent from baseline to weeks 24 and 48 will be bounded by 95% confidence intervals and presented both in the aggregate and broken down by age cohort and by accrual to Stage I vs. Stage II.

**HIV Drug Resistance**

The incidence of HIV drug resistance will be presented descriptively at baseline and at the point of failure for subjects who meet the criteria for virologic failure. Subjects will be evaluated for HIV genotypic and phenotypic drug resistance to the OBT and to DTG.

**Interim Analysis of Data from Cohort I**

An interim analysis presented results based upon the 24 week data from Cohort I. This focus was primarily on safety data, presented as described in Section 8.6.2.1 and pharmacokinetic data, presented as described in Section 9.0. A secondary analysis of virologic success, as described in Section 8.6.2.2 was also presented. The results of these analyses were used as part of a pediatric regulatory submission for DTG.
8.7 Monitoring

Since Phase I studies are not routinely reviewed by a Data and Safety Monitoring Board (DSMB), it is the responsibility of the Protocol Team to interpret safety data, and make decisions regarding drug-related adverse events that are needed to protect subjects from undue risk. In addition the IMPAACT Network will appoint a P1093 Study Monitoring Committee (SMC) to provide impartial independent reviews in situations where subject safety is in question, as previously described.

The safety and tolerability of the study agent will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is required that the data required for the toxicity reports be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available.

Reports compiled by the Data Management Center (DMC) will be reviewed and discussed by the Protocol Team on conference calls held at least every 4 weeks (or less frequently once Stage I is complete), and by the P1093 Study Monitoring Committee under conditions previously specified. Data on accrual, pharmacokinetics and toxicity will be reviewed. Adverse events will be monitored not only in the dose finding stage of the study, but throughout the follow-up period. If the Protocol Team identifies any potentially treatment-related toxicities, which may compromise subject safety, it will determine whether the study needs to be suspended or modified. If this occurs, the P1093 Study Monitoring Committee will review all relevant data and will determine whether, and under what conditions, the study will be allowed to proceed.

8.7.1 Rules for Suspending Accrual to Assess Safety Following an Adverse Event

Accrual will be temporarily suspended if any subject has a life threatening drug-related adverse event or any Grade 4 event that may not be judged to be life-threatening but is judged to be probably or definitely attributable to the study medication. Following temporary suspension of accrual, the team will further review the safety data within 48 hours of notification of the event to determine if continuation of accrual is appropriate. If the team agrees that the study drug is likely to be safe for additional subjects, they may allow accrual to resume. The P1093 SMC will be informed of this decision, and the study will not reopen without the approval of this committee. Regulatory agencies will be notified of the event and the team’s decision after this review of the safety data has taken place.

8.7.2 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility quarterly, first based on site registration and then on accrual. Initially, the team will monitor site registration quarterly to ensure that an adequate number of sites have registered to complete the protocol. If less than one-third of eligible sites have registered after the protocol has been approved for six months, the team will re-assess the feasibility of the protocol and the reasons why sites have not registered, and will amend the protocol accordingly. Once one-third of eligible sites have registered, the team will assess accrual on a quarterly basis. If any open group has not accrued half its subjects within 6 months of opening, the team will identify the reasons for lack of accrual and possibly amend the protocol accordingly.
9.0 CLINICAL PHARMACOLOGY PLAN

Since pediatric pharmacokinetics tend to be more variable than adults, a lower threshold range for both the AUC\textsubscript{0-24} and C\textsubscript{24h} have been identified. Using a maximum effect (E\textsubscript{max}) model, the modeled AUC\textsubscript{0-24} required to produce 90% of the maximum virologic response (EC\textsubscript{90}) is approximately 18 µg.h/mL, and the EC\textsubscript{90} for the C\textsubscript{24h} is approximately 0.3 µg/mL. Therefore, all subjects must meet these minimum exposure targets.

The AUC\textsubscript{24} is the primary target to be attained and the C\textsubscript{24h} is secondary. The AUC\textsubscript{0-24} target value is 46 µg.h/mL and the C\textsubscript{24h} is 0.75 µg/mL. However, there will be variability around these targets which are acceptable. The range for AUC\textsubscript{24} is 37 to 86 µg.h/mL. The lower range is 80% of the geometric mean in adults receiving 50 mg once daily in SPRING-1. The upper range is based on further data collected from Viiv studies. A DTG dose of 50 mg BID was studied in ING112961 (VIKING) and ING112574 (VIKING3) in adult HIV-infected subjects. In Viking study (ING112961), 50 mg BID dose was as well tolerated as the 50 mg QD dose with the 50 mg BID dose observed AUC\textsubscript{24} (min, max) in the range of 37.86 – 199.74 ug.h/mL.

The AUC\textsubscript{24} (geometric mean, 80%CI) at steady state following 50 mg BID exposure (from VIKING and VIKING 3) was 75.1 (50-115) µg.h/mL. Therefore, the maximal exposure target is now set at 115 µg.h/mL based on these new data. The target C\textsubscript{24h} is 0.75 µg/mL with a range of 0.5 to 2.6 µg/mL. This target and range are based on E\textsubscript{max} modeled data as well as current data collected in P1093. Of all PK data collected to date (n=39), the geometric mean C\textsubscript{24h} is 0.77 µg/mL which was rounded to 0.75 µg/mL. The coefficient of variation (CV) around C\textsubscript{24h} in adults was approximately 20-30%. In this population, the CV is currently 78%. Due to the inherent increase in variability in P1093 subjects, the range around the C\textsubscript{24h} has been widened to accommodate this variability while still providing a C\textsubscript{24h} range well in excess of the DTG EC\textsubscript{90}. Our lower range is 0.5 µg/mL and the upper range is 2.6 µg/mL. The lower value is approximately the 35\textsuperscript{th} percentile of the current population values and the upper value is the 95\textsuperscript{th} percentile. There have been no toxicities observed at the upper range and the lower range is still significantly above the EC\textsubscript{90} (0.3 µg/mL). The maximum lower limit acceptable for C\textsubscript{24h} is 0.4 µg/mL and the maximum upper limit is undefined as no toxicities have been observed at these exposures. If the C\textsubscript{24h} goal is not met, the team will review the PK, virologic, and clinical data, and make a determination as to whether the dose is deemed acceptable. Subjects falling below the minimum threshold (AUC\textsubscript{0-24} 25 µg.h/mL, and C\textsubscript{24h} 0.4 µg/mL) will be discussed by the team on an individual basis (Section 1.6.1).

9.1 Pharmacology Objectives

The clinical pharmacology objectives are:

1. To evaluate the steady-state pharmacokinetics of DTG and its various formulations in combination with other antiretrovirals in treatment-experienced and HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves a targeted AUC\textsubscript{0-24} (primary PK endpoint) and C\textsubscript{24h} (secondary PK endpoint) in this population.

2. To evaluate the steady state plasma concentration profiles and pharmacokinetic parameters of dolutegravir administered as the film-coated tablet, the oral-granules for suspension and the dispersible tablet - pediatric formulations.

3. To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population pharmacokinetic analysis.
9.2 Primary and Secondary Data

All concentration-time samples will be registered in the Lab Data Management System (LDMS) database. All PK samples (including intensive and population PK) will be sent to the University of Alabama (UAB) Laboratory (see the Laboratory Processing Chart). The study database will be kept up to date by close tracking of samples. As part of Stage I, the intensive PK sample assays and pharmacokinetic calculations will be performed in real-time and the results will be reported and discussed with the Protocol Team.

9.2.1 Intensive PKs (Stage I only)

Steady-state pharmacokinetic parameters will be determined from plasma concentration-time profiles using non-compartmental methods (WinNonlin version 5.2.1, Pharsight Corp., Mountain View, CA). Calculated pharmacokinetic parameters will be: area-under-the-curve (AUC$_{0-24}$), maximum plasma concentration ($C_{\text{max}}$), time to $C_{\text{max}}$ ($t_{\text{max}}$), plasma concentration observed at end of 24 hour dosing interval ($C_{24\text{h}}$), plasma concentration observed immediately to dosing of 24 hour dosing interval ($C_0$), minimum plasma concentration ($C_{\text{min}}$), apparent clearance ($CL/F$), apparent volume of distribution ($V_z/F$), and terminal half-life ($t_{1/2}$). AUC$_{0-24}$ will be determined using the linear-log trapezoidal rule. $C_{\text{max}}$, $T_{\text{max}}$, $C_0$, $C_{24\text{h}}$, and $C_{\text{min}}$ will be taken directly from the observed concentration-time data.

9.2.1.1 Cohorts I, II III, and III-DT

Regimen, dosage, dosing intervals, and timing relative to meals will be reviewed at the screening/entry visit to ensure that entry criteria are met. The importance of adherence and of reporting deviations in adherence will be emphasized. The pharmacokinetic evaluation will be performed between days 5 and 10 after treatment initiation. Date and time of doses taken 3 days prior to the PK visit should be recorded. Subjects should have no missed doses 3 days prior to the scheduled PK visit. The pharmacokinetic evaluation should be scheduled so that the pre-dose PK samples and the witnessed dosing of DTG are as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Subjects must be fasted for 6 hours prior to dosing. Liquids including milk and juice may be consumed up to 4 hours prior to dosing. Water may be consumed as desired. Subjects may consume a light meal of their choice four hours after dosing on the intensive PK day. High fat foods should be avoided. For subjects 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 7 days. Additionally, any subject who cannot have PK studies completed when initially scheduled must have them rescheduled and have background therapy optimized within seven days of the originally scheduled PK tests. If for some reason they cannot be completed at this time, background therapy should be optimized once this is known. The subject will remain on study and will be included for safety analyses but will be replaced for PK analyses.

Blood samples will be drawn at time points specified in the footnotes in Appendix IA. Actual sampling time will be recorded and used in the PK analysis.

9.2.1.2 Cohorts IV, IV-DT, V, and V-DT (Stage I)
The pharmacokinetic evaluation will be performed between Days 5 and 10 after treatment initiation. Date and time of doses taken 3 days prior to the PK visit should be recorded. Subjects should have no missed doses three days prior to the scheduled PK visit. The pharmacokinetic evaluation should be scheduled so that the pre-dose PK samples and the witnessed dosing of DTG are as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Subjects should not ingest breastmilk, formula or any other high fat food/liquid) for 2 hours prior to and 1 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. Subjects may consume a light meal of their choice four hours after dosing on the intensive PK day. For subjects who vomited 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 seven days.

Additionally, any subject who cannot have PK studies completed when initially scheduled must have them rescheduled and have background therapy optimized within seven days of the originally scheduled PK tests. If for some reason they cannot be completed at this time, background therapy should be optimized once this is known. The subject will remain on study and will be included for safety analyses but will be replaced for PK analyses. Subjects must be withdrawn from the study if parent/caregiver refuses intensive PK.

Blood samples will be drawn at time points specified in the footnotes in Appendix IC. Actual sampling time will be recorded and used in the PK analysis.

9.2.2 Population PK (Stage I & II)

Population pharmacokinetic evaluations will be scheduled at Weeks 4, 12 and 24. In addition population PK sampling will be scheduled for subjects who have completed 24 weeks of follow-up and who have switched from granules for suspension to dispersible tablets. Population PK will be collected at the 2 week post-switch visit and at the next scheduled visit per footnotes in Appendix IA, IB, IC, ID and IE. These evaluations should be scheduled so that the pre-dose PK sample and the witnessed dosing of DTG are as close to possible to 24 hours (generally 22-26 hours) after the previous dose.

9.2.2.1 Cohorts I, II, and III

In all cases, the subject will need to provide a self-reported time and date of their last dose. Appendix IA and IB footnotes describe the sampling time points for Stage I and II respectively.

9.2.2.2 Cohorts IV and V

In all cases, the subject will need to provide a self-reported time and date of their last dose. Appendix IC and ID footnotes describe the sampling time points for Stage I and II respectively.

These data will be pooled to build a population pharmacokinetic model to assess pediatric DTG exposure and possible changes in exposure during the course of the study. This population pharmacokinetic model will be created using NONMEM version VII or higher software program. The model may also be used to determine if covariates, such as
age, weight, sex, BSA, and concomitant medications alter DTG pharmacokinetic parameters in pediatric subjects. Alternatively, the ADAPT 5.0 software for individual and population pharmacokinetic modeling may be used.

10.0 HUMAN SUBJECTS

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs / ECs for the recruitment of prisoners.

10.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs in accordance with 45 CRF 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to subjects or others.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 4.4).

10.2 Vulnerable Subjects

The NIH is mandated by law to ensure that children be included in clinical research when appropriate. This study responds to that mandate and will provide clinical research data to inform ARV treatment guidelines for pediatric populations. Nonetheless, the children who take part in this study are considered vulnerable subjects per the U.S. Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to infant and child subjects as described in 45 CFR 46 Subpart D (for children).

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 4.4, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination. However, it is generally expected that the consent of one parent is sufficient for this study.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx
10.3 Informed Consent

Written informed consent for study participation will be obtained before any study-specific procedures are performed. The informed consent process will be conducted prior to screening.

The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. 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 subject (or parent or legal guardian).

Subjects providing assent or parents or legal guardians will also be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been completed. Future research testing of residual specimens may be declined with no impact on other aspects of study participation.

It is generally expected that only one parent or legal guardian will provide informed consent for the child’s participation in this study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 10.2; all IRB/EC requirements will be followed.

Should the parent or legal guardian of an enrolled child die or no longer be available for any reason, no further study-specific visits or procedures may be performed until informed consent for continued study participation is obtained from a locally authorized guardian. Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx and all study sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

10.4 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 or the subject’s parent or legal guardian, except as necessary for monitoring by IMPAACT, the FDA, the Office for Human Research Protections (OHRP) or other country-specific regulatory authorities, the NIAID, the local Institutional Review Board (IRB) or Ethics Committee (EC), or GlaxoSmithKline (GSK).

10.5 Study Discontinuation

The study may be discontinued at any time by the NIAID, the IRB or EC, GSK, the FDA, OHRP, IMPAACT or other country-specific governmental agencies as part of their duties to ensure that research subjects are protected.
10.6 Access to Dolutegravir at the Close of the Study

Subjects will be transitioned into care and treatment outside of the study at the end of the study as per local standards. If the DTG formulations are not locally available for a subject completing study then DTG will be provided by the pharmaceutical partners following the subject’s completion of the study through a mechanism outside of the protocol, or until one or more of the following events occur:

- Until the age-appropriate formulations provided by the study are available from another source (e.g. government programs, aid programs, assistance programs etc.) to all subjects in each specific country; OR
- Until subjects are no longer deriving benefit; OR
- Until clinical development of DTG is terminated.

11.0 PUBLICATION OF RESEARCH FINDINGS

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

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood borne 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 and Prevention.

All infectious specimens will be transported in compliance with Federal Regulations and the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g. Federal Express or Airborne) for specific instructions and to the ACTN Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and ACTN Instruction for Overnight Shipments documents at:

http://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx
13.0 REFERENCES


## APPENDIX IA

### SCHEDULE OF EVALUATIONS

**Cohorts I, II, IIB, III and III-DT - STAGE I**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Entry(^{12}) Day 0</th>
<th>Intensive PK visit: Day 5-10</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
<th>Virologic Failure(^{13})</th>
<th>2 Wks Post Switch Visit(^{14})</th>
<th>Next Scheduled Visit after Post Switch Visit(^{15})</th>
<th>Premature /DC of Study Drug/ On study(^{16})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Windows</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±1wk</td>
<td>±1wk</td>
<td>±1wk</td>
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<td>±2wk</td>
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<td>- 1wk</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL EVALUATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
</tr>
<tr>
<td>History and Physical exam (^2)</td>
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<tr>
<td>Adherence Questionnaire</td>
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<tr>
<td>CDC Classification</td>
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<tr>
<td>Palatability Assessment</td>
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<tr>
<th>LABORATORY EVALUATIONS</th>
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<tr>
<td>Hematology</td>
</tr>
<tr>
<td>Chemistries (^4)</td>
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<tr>
<td>Lipid profiles (^5)</td>
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<tr>
<td>PBMCs / plasma for storage (includes integrase resistance sample)</td>
</tr>
<tr>
<td>Urinalysis</td>
</tr>
<tr>
<td>Microalbumin/creatinine ratio - urine(^6)</td>
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<tr>
<td>Pregnancy test(^7)</td>
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<tr>
<td>Virology</td>
</tr>
<tr>
<td>HIV-1 RNA PCR</td>
</tr>
<tr>
<td>Genotyping</td>
</tr>
<tr>
<td>Phenotyping (^8)</td>
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<tr>
<td>Immunology</td>
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<tr>
<td>Lymphocyte subsets (^9)</td>
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<thead>
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<th>Pharmacokinetic studies</th>
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<tr>
<td>STAGE I - Intensive PK (^10)</td>
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<tr>
<td>STAGE I - Population PK (^11)</td>
</tr>
<tr>
<td>Total Blood Volumes (mL)(^19)</td>
</tr>
</tbody>
</table>
Appendix IA Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. For information on Tanner Staging assessment, see P1093 MOPs.

4. Electrolytes (sodium, potassium, and HCO₃⁻), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. “ULN” values reported by the laboratory report for the test, or
   b. “ULN” values routinely used/established by the site, or
   c. “ULN” values as per the Harriet Lane Handbook (e.g. the current “ULN” for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of “ULN”, when not reported by your laboratory.

5. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours.

   After a subject has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

6. M/C ratio – microalbumin / creatinine ratio (mcg/mg creatinine)

7. Pregnancy test (urine or serum beta hCG) must be performed on all females of childbearing potential within 72 hours prior to enrollment. Subsequent tests should be performed at each visit. If a blood test is performed, collect 1.0 mL in a red top serum tube.

8. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the team.

9. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

10. The pharmacokinetic evaluation should be scheduled so that witnessed dosing of dolutegravir is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Subjects should have been compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be rescheduled.

   • ≥6 hours PRIOR to dosing – subjects 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 – subjects may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)

From ≥4 hours POST dose onwards – subjects may eat and drink without restriction

For subjects who vomit within 4 hours after dosing; PK must be cancelled and may be rescheduled. Blood samples (0.5 per sample) will be collected at the following time points: pre-dose, 1, 2, 3, 4, 6, 8 and 24 hours post dosing. The 24 hour sample must be collected prior to the next dose. To allow for some flexibility, the 8-hour sample can be collected with a window of 7-9 hours post-dose and the 24 hour sample with a window of 22-26 hours. US sites will ship intensive PK samples in real time to UAB; all non-US sites will ship PK samples in real time to BRI repository for a ‘pass-through’ (see LPC for instructions).

11. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. Subjects will have 2 blood sample collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood sample will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and 26 hours post-dose. Samples to be collected and shipped as described in the LPC. For sample collection timepoints for the ‘Two Weeks Post Switch Visit’ and ‘Next Scheduled Visit after Post Switch Visit’ refer to footnotes 14 and 15 below. For subjects on BID dosing refer to the study MOP for sampling time points.

12. Entry must occur within 30 days of screening.

13. If a subject is experiencing virologic failure (as defined in Section 6.2.5) at any of these points, a visit to confirm failure should be conducted at least one week and within four weeks later

14. For Subjects who switch from granules for suspension to dispersible tablets this visit should be targeted for 2 weeks after initiating dispersible tablets. If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.

Population PK sampling will be done in subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ collect 2 blood samples (0.5 mL per sample): pre-dose and 2-4 hours post dose.

15. For subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ at the next regularly scheduled visit; collect 2 blood samples (0.5 mL per sample) two hours apart between 12 and 26 hours post-dose.

16. Subjects, who discontinue study drug early, should remain on study and follow Appendix IF.

17. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the Laboratory Processing Chart (LPC) for additional details.

18. Only if not done at virologic failure.

19. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain subjects. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.
## APPENDIX IB
### SCHEDULE OF EVALUATIONS
#### Cohorts I, II, III and III-DT - STAGE II

<table>
<thead>
<tr>
<th></th>
<th>Screening&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Entry&lt;sup&gt;11&lt;/sup&gt; Day 0</th>
<th>Day 10</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
<th>Virologic failure&lt;sup&gt;12&lt;/sup&gt;</th>
<th>2 Weeks Post Switch Visit&lt;sup&gt;13&lt;/sup&gt;</th>
<th>Next Scheduled Visit after Post Switch Visit&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Premature DC of Study Drug/On study&lt;sup&gt;15&lt;/sup&gt;</th>
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<td><strong>Visit Windows</strong></td>
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<td>1wk +4 wks</td>
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<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
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<td>Informed Consent</td>
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<tr>
<td>History and Physical exam&lt;sup&gt;2&lt;/sup&gt;</td>
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TOTAL BLOOD VOLUMES (mL)<sup>18</sup>
Appendix IB Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. For information on Tanner assessment, see P1093 MOPs.

4. Chemistries will be performed at all visits. Electrolytes (sodium, potassium, and HCO3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   
   d. "ULN” values reported by the laboratory report for the test, or
   e. “ULN” values routinely used/established by the site, or
   f. "ULN” values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

5. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a subject has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

6. M/C ratio – microalbumin / creatinine ratio

7. Pregnancy test (urine or serum beta hCG) must be performed on all females of childbearing potential within 72 hours prior to enrollment. Subsequent tests should be performed at each visit. If a blood test is performed, collect 1.0 mL in a red top serum tube.

8. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the team.

9. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

10. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. All subjects will have 2 blood sample collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood sample will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and 26 hours post-dose. Samples to be batched and shipped as described in the Laboratory Processing Chart (LPC). For sample collection timepoints for the ‘Two Weeks Post Switch Visit’ and ‘Next Scheduled Visit after Post Switch Visit’ refer to footnotes 13 and 14 below. For subjects on BID dosing refer to the study MOP for sampling time points.

11. Entry must occur within 30 days of screening.
12. If a subject is experiencing virologic failure (as defined in Section 6.2.5) at any of these points, a visit to confirm failure should be conducted at least one week and within four weeks later.

13. For Subjects who switch from granules for suspension to dispersible tablets this visit should be targeted for 2 weeks after initiating dispersible tablets. If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.

Population PK sampling will be done in subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ collect 2 blood samples: pre-dose and 2-4 hours post dose.

14. For subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ at the next regularly scheduled visit; collect 2 blood samples two hours apart between 12 and 26 hours post-dose.

15. Subjects, who discontinue study drug early, should remain on study and follow Appendix IF.

16. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the Laboratory Processing Chart (LPC) for additional details.

17. Only if not done at virologic failure.

18. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain subjects. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.
## APPENDIX IC

**SCHEDULE OF EVALUATIONS**

**Cohorts IV, IV-DT, V and V-DT – STAGE I**

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<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
<th>Virologic failure&lt;sup&gt;11&lt;/sup&gt;</th>
<th>2 Weeks Post Switch Visit&lt;sup&gt;12&lt;/sup&gt;</th>
<th>Next Scheduled Visit after Post Switch Visit&lt;sup&gt;13&lt;/sup&gt;</th>
<th>Premature DC of Study Drug/On Study&lt;sup&gt;14&lt;/sup&gt;</th>
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<td>±1wk</td>
<td>±1wk</td>
<td>±1wk</td>
<td>±2wk</td>
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<td>±2wk</td>
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### CLINICAL EVALUATIONS

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### LABORATORY EVALUATIONS

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**TOTAL BLOOD VOLUMES (mL):**

- 10.5 mL
- 8.5 mL
- 5.5 mL
- 4.5 mL
- 6.0 mL
- 4.5 mL
- 12 mL
- 5.5 mL
- 5.5 mL
- 11 mL
- 14 mL
- 4 mL
- 1 mL
- 9.5 mL
Appendix IC – Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. Electrolytes (sodium, potassium, and HCO₃), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. “ULN” values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all subjects in the study, using the same source all the way through the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

4. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a subject has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

5. M/C ratio – microalbumin / creatinine ratio

6. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the team.

7. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

8. The pharmacokinetic evaluation should be scheduled so that witnessed dosing of dolutegravir is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Subjects should have been compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be rescheduled.

   Subjects should not ingest breastmilk, formula or any other high fat food/liquid) for 2 hours prior to and 1 hour after dosing on the intensive PK day. Water and other fluids (i.e. apple/orange juice and oral rehydration solution) can be taken at any time. Subjects may consume a light meal of their choice four hours after dosing on the intensive PK day. For subjects who vomit within 4 hours after dosing; PK must be cancelled and may be rescheduled. Blood samples (0.5mL per sample) will be collected at the following time points: pre-dose, 1, 2, 3, 4, 6, 8 and 24 hours post dosing. The 24 hour sample must be collected prior to the next dose. To allow for some flexibility, the 8-hour sample can be collected with a window of 7-9 hours post-dose and the 24 hour sample with a window of 22-26 hours. US sites will ship intensive PK samples in real time to UAB; all non-US sites will ship PK samples in real time to BRI repository for a ‘pass-through’ (see Laboratory Processing Chart (LPC).

9. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. All subjects will have 2 blood samples collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood sample will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and
26 hours post-dose. Samples to be batched and shipped as described in the LPC. For sample collection timepoints for the ‘Two Weeks Post Switch Visit’ and ‘Next Scheduled Visit after Post Switch Visit’ refer to footnotes 13 and 14 below. For subjects on BID dosing refer to the study MOP for sampling time points.

10. Entry must occur within 30 days of screening

11. If a subject is experiencing virologic failure (as defined in Section 6.2.5) at any of these points, a visit to confirm failure should be conducted at least one week later, and within four weeks.

12. For Subjects who switch from granules for suspension to dispersible tablets this visit should be targeted for 2 weeks after initiating dispersible tablets. If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.

   Population PK sampling will be done in subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ collect 2 blood samples: pre-dose and 2-4 hours post dose.

13. For subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ at the next regularly scheduled visit; collect 2 blood samples two hours apart between 12 and 26 hours post-dose.

14. Subjects, who discontinue study drug early, should remain on study and follow Appendix IF.

15. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the Laboratory Processing Chart (LPC) for additional details.

16. Only if not done at virologic failure.

17. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain subjects. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.
### APPENDIX ID

**SCHEDULE OF EVALUATIONS**

**Cohorts IV, IV-DT, V, and V-DT – STAGE II**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Entry</th>
<th>Day 10</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
<th>Virologic failure</th>
<th>2 Weeks Post Switch Visit</th>
<th>Next Scheduled Visit after Post Switch Visit</th>
<th>Premature DC of Study Drug/On study</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>-</td>
<td>±2 wk</td>
<td>±2 wk</td>
<td>±2 wk</td>
<td>±2 wk</td>
<td>±2 wk</td>
<td>±2 wk</td>
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<td>±2 wk</td>
<td>±2 wk</td>
<td>±2 wk</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

#### CLINICAL EVALUATIONS

- **Informed Consent**: X
- **History and Physical exam**: X
- **Adherence Questionnaire**: X
- **CDC Classification**: X
- **Palatability Assessment**: X

#### LABORATORY EVALUATIONS

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Chemistries</th>
<th>Lipid profiles</th>
<th>PBMCs / plasma for storage (includes integrase resistance)</th>
<th>Uralysis</th>
<th>Microalbumin/creatinine ratio assay - urine</th>
<th>Virology</th>
<th>Immunology</th>
<th>Pharmacokinetic studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
<td>5.0 mL</td>
<td>X</td>
<td>X</td>
<td>HIV-1 RNA PCR</td>
<td>Genotyping</td>
<td>Phenotyping</td>
</tr>
<tr>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
<td>4.5mL</td>
<td>X</td>
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</tr>
<tr>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
<td>4.5mL</td>
<td>X</td>
<td>X</td>
<td>3mL</td>
<td>2mL</td>
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</tr>
<tr>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
<td>4.5mL</td>
<td>X</td>
<td>X</td>
<td>3mL</td>
<td>2mL</td>
<td>2mL</td>
</tr>
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<td>4.5mL</td>
<td>X</td>
<td>X</td>
<td>3mL</td>
<td>2mL</td>
<td>2mL</td>
</tr>
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</table>

**STAGE II - Population PK**

| TOTAL BLOOD VOLUMES (mL) | 10.5 mL | 10.5 mL | 4.5mL | 4.5mL | 6mL | 4.5mL | 12mL | 5.5mL | 5.5mL | 11mL | 14mL | 4mL | 1mL | 9.5mL |

**SCHEDULE OF EVALUATIONS**

<table>
<thead>
<tr>
<th>Visit Windows</th>
<th>Screening</th>
<th>Day 0</th>
<th>Day 10</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 48</th>
<th>Virologic failure</th>
<th>2 Weeks Post Switch Visit</th>
<th>Next Scheduled Visit after Post Switch Visit</th>
<th>Premature DC of Study Drug/On study</th>
</tr>
</thead>
<tbody>
<tr>
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<td>±3 days</td>
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<td>±1 wk</td>
<td>±1 wk</td>
<td>±1 wk</td>
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<td>±1 wk</td>
<td>±1 wk</td>
<td>±1 wk</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Appendix ID – Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. Blood Chemistries will be performed at all visits. Electrolytes (sodium, potassium, and HCO₃), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. “ULN” values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

Sites must be consistent with the way toxicities are evaluated for all subjects in the study, using the same source all the way through the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

4. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a subject has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

5. M/C ratio – microalbumin / creatinine ratio

6. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the team.

7. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

8. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. All subjects will have 2 blood samples collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood samples will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and 26 hours post-dose. Samples to be batched and shipped as described in the LPC. For sample collection timepoints for the ‘Two Weeks Post Switch Visit’ and ‘Next Scheduled Visit after Post Switch Visit’ refer to footnotes 11 and 12 below. For subjects on BID dosing refer to the study MOP for sampling time points.

9. Entry must occur within 30 days of screening

10. If a subject is experiencing virologic failure (as defined in Section 6.2.5) at any of these points, a visit to confirm failure should be conducted at least one week later, and within four weeks.

11. For Subjects who switch from granules for suspension to dispersible tablets this visit should be targeted for 2 weeks after initiating dispersible tablets. If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.
Population PK sampling will be done in subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ collect 2 blood samples (0.5 mL per sample): pre-dose and 2-4 hours post dose.

12. For subjects who have completed at least 24 weeks of follow-up at the time of the ‘Two Weeks Post Switch Visit’ at the next regularly scheduled visit; collect 2 blood samples (0.5 mL per sample) two hours apart between 12 and 26 hours post-dose.

13. Subjects, who discontinue study drug early, should remain on study and follow Appendix IF.

14. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the LPC for additional details.

15. Only if not done at virologic failure.

16. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain subjects. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.
APPENDIX IE
SCHEDULE OF EVALUATIONS

Long-term Safety Follow-up for Subjects who Continue to Receive Dolutegravir (study-provided or locally)

<table>
<thead>
<tr>
<th>Visit Windows</th>
<th>Every 12 Weeks [Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, 168,180, and 192]</th>
<th>Every 48 Weeks [Weeks 96, 144 and 192 (End of Study Visit)]</th>
<th>Virologic failure$^6$</th>
<th>2 Weeks Post Switch Visit$^7$</th>
<th>Next Scheduled Visit after Post Switch Visit$^8$</th>
<th>Premature Discontinuation of Study Drug/On Study*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL EVALUATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History and Physical$^1$</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Adherence Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palatability Assessment</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LABORATORY EVALUATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA PCR</td>
<td>3mL</td>
<td>3mL</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PBMCs/plasma for storage</td>
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<td></td>
<td></td>
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</tr>
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<td>Genotyping</td>
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<td>2mL$^3$</td>
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<tr>
<td>TOTAL BLOOD VOLUME$^9$</td>
<td>3mL</td>
<td>3mL</td>
<td>13.5mL</td>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
</tr>
</tbody>
</table>

* See Appendix IF for subjects who prematurely discontinue dolutegravir
Appendix IE - Footnotes:

1. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and any HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.
2. If determined by the protocol team genotyping may be done at a frequency ≥24 weeks post virologic failure if HIV-1 RNA is >400 c/mL
3. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the Laboratory Processing Chart (LPC) for additional details.
4. Only if not done at virologic failure.
5. Pregnancy testing, after the initial 48 weeks of study treatment, should be determined as per local practice. If pregnancy occurs, it is an event that should be captured on the CRFs.
6. If a subject is experiencing virologic failure (as defined in Section 6.2.5), a visit to confirm virologic failure should be conducted at least one week and within four weeks later.
7. For Subjects who switch from granules for suspension to dispersible tablets this visit should be targeted for 2 weeks after initiating dispersible tablets. If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated. Collect 2 population PK blood samples (0.5 mL per sample): pre-dose and 2-4 hours post dose. For subjects on BID dosing refer to the study MOP for sampling time points
8. For Subjects who switch from granules for suspension to dispersible tablets at the next regularly scheduled visit after the two-week switch visit; collect 2 population PK blood samples (0.5mL per sample) two hours apart between 12 and 26 hours post-dose. For subjects on BID dosing refer to the study MOP for sampling time points
9. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain subjects. For insufficient blood draws, priorities are as follows: pharmacokinetic studies; HIV-1 RNA; genotyping; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.
APPENDIX IF
SCHEDULE OF EVALUATIONS
Subjects who Prematurely Discontinue Dolutegravir

Subjects who continue dolutegravir will be followed as per Appendix IE

<table>
<thead>
<tr>
<th>Visit Windows</th>
<th>4 Week Follow-Up Visit(^2)</th>
<th>Every 3 months until resolved (if applicable)(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical(^1)</td>
<td>±2wks</td>
<td>±4wks</td>
</tr>
</tbody>
</table>

Appendix IF - Footnotes:

1. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and any HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

2. This follow up visit should be performed 4 weeks after the subject’s last exposure to dolutegravir.

3. Subjects who are pregnant or who have a drug related adverse event that has not resolved within 3 months of stopping study drug, should come back to clinic every 3 months for follow-up until the AE is resolved or the mother delivers the baby. Study required tests are an interim history and physical exam at these visits. If sites perform safety tests at these visits as a result of standard of care, sites should document all results in the case report forms. If the subject discontinues for any reason other than pregnancy or drug related AE, no other visit after the 4 week visit is required.
### APPENDIX IG

**SCHEDULE OF EVALUATIONS**

**Subjects who Start Rifampin as Part of Treatment for Active Tuberculosis**

<table>
<thead>
<tr>
<th>Visit Windows</th>
<th>Day 1 of rifampin therapy ¹</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Every 8 weeks until end of rifampin therapy</th>
<th>Virologic failure ¹⁰</th>
<th>Premature Discontinuation of Study Drug/On study ¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>±1wk</td>
<td>±1wk</td>
<td>±1wk</td>
<td>±2wk</td>
<td></td>
<td>±2wk</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

**CLINICAL EVALUATIONS**

<table>
<thead>
<tr>
<th></th>
<th>History and Physical exam ²</th>
<th>Adherence Questionnaire</th>
<th></th>
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<tbody>
<tr>
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<td>X</td>
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<td>X</td>
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</table>

**LABORATORY EVALUATIONS**

<table>
<thead>
<tr>
<th></th>
<th>Hematology</th>
<th>Chemistries³</th>
<th>Lipid profiles⁴</th>
<th>Microalbumin/creatinine ratio assay – urine⁵</th>
<th>PBMCs / plasma for storage</th>
<th>Pregnancy test⁶</th>
<th>Virology</th>
<th>HIV-1 RNA PCR</th>
<th>Immunology</th>
<th>Lymphocyte subsets⁷</th>
<th>Pharmacokinetics</th>
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<tbody>
<tr>
<td></td>
<td>1mL</td>
<td>1mL</td>
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<td>X</td>
<td></td>
<td>X</td>
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<td>1mL</td>
<td>TOTAL BLOOD VOLUMES (mL)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>6mL</td>
<td>6mL</td>
</tr>
</tbody>
</table>

**NOTE:** Subjects who are diagnosed with active tuberculosis while taking dolutegravir as part of P1093, will have their medications changed as per Section 6.1.8 and should be followed as per Appendix IG. It is estimated the subject will be on anti-TB treatment for approximately 24 weeks. Upon discontinuation of the rifampin containing anti-TB therapy, the subject’s dolutegravir dose will revert back to once daily administration. The subject should complete the remainder of the first 48 weeks of dolutegravir therapy on their original schedule of evaluations, or if they have completed 48 weeks of dolutegravir therapy, they should move to long-term follow-up (Appendix IE). For example, if the subject was at week 16 when they were started on rifampin, and they complete 24 weeks of rifampin therapy, they would then go back to week 40 of their original SOE.
Appendix IG Footnotes:

1. Subjects who are already enrolled in P1093 and become exposed to TB, and subsequently require an anti-TB treatment that includes the use of rifampin, may be allowed to continue in the study if their ART options are compatible with co-administration of rifampin. Continuation requires the approval of the Protocol Team (impaact.teamp1093@fstrf.org).

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. Chemistries will be performed at all visits. Electrolytes (sodium, potassium, and HCO₃), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all subjects in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

4. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a subject has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

5. M/C ratio – microalbumin / creatinine ratio

6. Pregnancy test (urine preferably) must be performed on all females of childbearing potential at each visit. If a serum beta hCG test is performed, collect 1.0 mL in a red top serum tube.

7. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

8. The pharmacokinetic evaluation should be scheduled so that witnessed dosing of dolutegravir is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Subjects should have been compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be re-scheduled. For subjects who vomit within 4 hours after dosing; PK must be cancelled and may be rescheduled. Blood samples (0.5 mL per sample) will be collected at the following time points: pre-dose, and at 1, 2, 3, 4, 6, 8, and 12 hours post-dose. To allow for some flexibility, the 8-hour sample can be collected with a window of 7-9 hours post-dose and the 12 hour sample with a window of 11-13 hours. US sites will ship intensive PK
samples in real time to UAB; all non-US sites will ship PK samples in real time to BRI repository for a ‘pass-through’ (see LPC for instructions). See dosing and fasting instructions for Cohorts I-III and Cohorts IV-V, below.

**Instructions for Cohorts I-III:**

- ≥6 hours PRIOR to dosing – subjects 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 – subjects may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)
- From ≥4 hours POST dose onwards – subjects may eat and drink without restriction

**Instructions for Cohorts IV-V:**

Subjects should not ingest breastmilk, formula or any other high fat food/liquid) for 2 hours prior to and 1 hour after dosing on the intensive PK day. Water and other fluids (i.e. apple/orange juice and oral rehydration solution) can be taken at any time.

9. All subjects will have 2 blood samples (0.5mL per sample) collected at weeks 4 and 12: pre-dose and 8-14 hours post dose. Samples to be batched and shipped as described in the LPC.

10. If a subject is experiencing virologic failure (as defined in Section 6.2.5) at any of these points, a visit to confirm failure should be conducted at least one week and within four weeks later.

11. Subjects who discontinue study drug (dolutegravir) early are required to come back to clinic four weeks after stopping study drug or after resolution of any adverse event.

12. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain subjects. For insufficient blood draws, priorities are as follows: pharmacokinetic studies; HIV-1 RNA; genotyping; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.
APPENDIX II
Sample Consent Form For Subjects Enrolling in STAGE ONE

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS
GROUP (IMPAACT)

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

Subjects Enrolling in STAGE ONE
P1093 Version 4.0, dated 13 April 2016

SHORT TITLE FOR THE STUDY: Safety and PK of dolutegravir in HIV-1 Infected Children

INTRODUCTION
You are/your child is being asked to take part in this research study because you have /your child has the
Human Immunodeficiency Virus (HIV), which is the virus that causes AIDS, and because the drugs
currently available may not keep the amount of HIV in your / your child’s blood low enough or may
cause side effects too difficult to deal with. This study is sponsored by the National Institutes of Health
(NIH). 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 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 are free to ask questions about this study at any time. If you agree to/agree to allow
your child 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?
This study is being done to study a new antiretroviral HIV medication called dolutegravir. This drug is a
type of medicine called an integrase inhibitor. Integrase inhibitors work by blocking integrase, a protein
that HIV needs to enter human cells and make more copies of itself. The study will help find the best
amount or dose of dolutegravir for infants, children and teenagers, when it is taken on its own as well as
with other antiretroviral medications. This study will also find out the safety of using this medication in
infants, children and adolescents and if there are any side effects from the medication. Dolutegravir has
been tested in adults and children. The study drug (dolutegravir) is approved for use in children 12 years
and older by the FDA [and/or local regulatory authorities].

WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE IS IN THIS STUDY?
If you decide to (allow your child to) enroll in this study, you / your child will be asked to come to the
clinic at least 10 times over 48 weeks and then every 12 weeks until the end of the study. You / your child
will be given dolutegravir and you / your child will be asked to take it once or twice a day for the entire
study, in addition to your / your child’s regular HIV medicines. Dolutegravir is available in 3 different
formulations: 1) a film-coated tablet which cannot be crushed or dissolved, 2.) a liquid suspension and, 3)
a tablet that can be dissolved in water. . If you are/your child is 12 up to 18 years old, you/your child will
take the film-coated tablet formulation of dolutegravir. If your child is older than 4 weeks of age to less
than 12 years of age your child will receive the liquid or dissolvable tablets. You will be given
instructions on how to give dolutegravir to your child and how to store the dolutegravir. If your child is
between 6 to less than 12 years of age and was prescribed the liquid or dissolvable tablets of dolutegravir
he/she may be allowed to switch to the film-coated tablet formulation at a later time. The study staff will let you know when your child can switch and if you request to do so.

Although the study will provide you/your child with dolutegravir, other antiretrovirals will not be provided by the study.

This study will be done in two parts – Stage one and Stage two. Stage one will enable the doctors to find the right dose of study drug for you/your child and then will keep you on that dose to look for any side effects that you/your child might experience. In Stage two the doctors will know the right dose to put you/your child on and will look at any side effects that you / your child might experience as well as how well the drug is controlling your HIV infection. You/your child will be enrolled into either Stage one or Stage two, depending on when you/your child enroll and your age / the age of your child. This consent form is for Stage one.

In this study there are 6 cohorts – Cohort 1 will enroll adolescents aged 12 to less than 18 years of age and Cohorts 2A and 2B will enroll children aged 6 to 12 years of age. Subjects who have had their 18th birthday by the entry visit will not be enrolled into the study. Cohort 3 will enroll children from 2 to less than 6 years of age. Cohort 4 will enroll children aged 6 months to less than 2 years of age. Cohort 5 will enroll infants from 4 weeks to less than 6 months of age.

**Screening:**
If you are interested in taking part / allowing your child to enroll in this study, we will see if you are / your child is eligible for the study:

- We will ask your / your child’s medical history including questions about your /your child’s health and what symptoms, medications, and illnesses you have/your child has had.

- We will do a physical exam including height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate). Doses may be modified based on the results of the weight.

- We will take a little more than 2 teaspoons (11mL) of blood, to check for the following:
  - The amount of HIV in the blood,
  - The amount of cholesterol and triglycerides (types of fat) in the blood,
  - How well your immune system, liver and kidneys are working,
  - Other routine tests.

You will be given the results of these tests.

We will also ask you/your child to provide a urine sample for routine tests. Girls and women who can have a baby will also be asked to provide a urine or blood sample to test for pregnancy. If you are / your child is engaged in sexual activity that could lead to pregnancy, you / your child will be asked to take birth control precautions (ways to prevent pregnancy) throughout the study period.

**On Study:**
If you are/your child is eligible for this study, you/your child will come to the clinic at least 10 times in about 1 year to complete Stage I. Most of the visits will last about 1-2 hours. More visits will be needed if
the amount of study drug in your blood is too low or too high and your dose needs to be adjusted. You/your child will come to the clinic for the first study visit within 30 days of the screening visit.

- At each visit, a medical history will be taken and you/your child will have a physical exam. At the enrollment visit and at the week 48 visit, you/your child’s stage of sexual development will be determined. For girls/women, this will be done by looking at how developed the breasts are. For boys/men, this will be done by measuring the size of the testes.

- We will draw blood at each visit. Depending upon your/your child’s age, between 1- 4 teaspoons (5-17 mLs) of blood will be drawn at these visits; you will be informed of results of routine blood tests. Some of the blood drawn will be stored and tested to find out how your/your child’s immune system is affected by the study drug. This testing will be done after the study is over, and you will not be given the results of these tests.

- A palatability assessment will be done at Day 10, Week 4 and Week 24 to find out what you/your child thinks about the taste of the study drug.

- You/your child will be asked to come to the clinic to have blood drawn 8 times over 24 hours during one visit, approximately 5-10 days after you / your child started taking the study medication. This visit is known as an ‘intensive PK visit’. Depending on your/your child’s age, up to 9 mLs (about 2 teaspoons) of blood will be drawn at this visit and you will be asked to withhold certain liquids and food. The study staff will give you instructions about this. These blood tests are done to measure the amount of study drug in your/your child’s blood. If these tests show that the amount of study drug in your/your child’s blood is not enough or is too high, you/your child will be asked to take a different dose and return to the clinic within 7 days for blood to be drawn again 8 times over 24 hours. A small plastic catheter (a needle that is placed in a vein for an extended period of time, so that blood can be drawn multiple times, without having to stick you with a needle several times) will be placed in your/your child’s arm to draw these blood samples. The needle will stay in place until all of the blood samples are drawn.

If you are/your child is 2 to less than 18 years old and having intensive PKs done, the following guidelines are in place regarding eating and drinking around the intensive PK visit.

- ≥6 hours PRIOR to taking your medication – you/your child may eat and drink without restriction
- ≥4 to <6 hours PRIOR to taking your medication – milk, apple/orange juice and water may be consumed; No food
- <4 hours PRIOR to taking your medication – water ONLY
- From dosing to <2 hours AFTER taking your medication – apple/orange juice and water may be consumed; No food
- From ≥2 to <4 hours AFTER taking your medication – you may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)
- From ≥4 hours AFTER taking your medication onwards – you may eat and drink without restriction

If your child is 4 weeks to less than 2 years old and having intensive PKs done, the following guidelines are in place regarding eating and drinking around the intensive PK visit.
• No breastmilk, formula or any other high fat food/liquid for 2 hours prior to and 1 hour after dosing on the intensive PK day.
• Water and other fluids (i.e. apple/orange juice and oral rehydration solution) can be taken at any time.

• You will have extra blood draws at three visits (week 4, week 12 and week 24). At weeks 4 and 24, you will have two blood draws. At week 12 you will only have one blood draw. The amount of blood drawn at the different study visits will be less than 1 teaspoon (0.5-1mL) depending on your /your child’s age.

• If the amount of HIV virus in your/your child’s blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood. If the level of HIV virus in your blood is still too high, your study doctor may ask you to stop taking the study medicine and to come back to the clinic for another visit. As part of this visit, you/your child will have an interim medical history, physical exam and approximately 3 teaspoons of blood (14-16.5mL) will be drawn for testing and storage.

• If you/your child experiences a severe liver reaction or inflammation while on the study, you/your child may be asked to come back to clinic to have less than one teaspoon of blood (2mL) drawn to check the level of dolutegravir in the blood. Additional testing as part of routine assessments for liver inflammation (e.g. checking for viruses that cause liver inflammation) may be performed as well.

Long Term Follow-Up
After you have been on study drug for approximately 48 weeks, you will enter the long term follow-up phase of the study. You will be asked to come back into clinic every 12 weeks (every 3 months) for 3 years. If the drug is not commercially available in your country after three years, it will continue to be provided to you/your child but will no longer be provided through the study. Most visits will last about 30 mins.

• At each visit, a medical history will be taken and you/your child will have a physical exam. You will also be asked if you have missed taking any of your medications.

• We will draw less than 1 teaspoon of blood (3-4mL) at each visit. You will be informed of results of routine blood tests.

• As before, if the amount of HIV virus in your/your child’s blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood (see above).

You/your child must continue to take your/his/her anti-HIV medications during the study as prescribed by your/your child’s HIV care provider. If your/your child’s HIV care provider changes your/your child’s anti-HIV medications during the study, you/your child can still take the study drug. You/your child will be asked questions about taking your/his/her anti-HIV medications and the times you take/he/she takes them and if you have/he/she has missed any medications.

If you/your child can become pregnant, you/your child must have a pregnancy test before you enter/she enters this study. If you are/your child is pregnant, you/your child can not be in the study. If you think you/if your child thinks she may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you/your child about your/her choices. You/your child will be tested at each visit during the study. If you are/your child is pregnant, you/your child will not be allowed to continue on the study drug, but will continue to come in for study visits until your baby is born.
Blood & Urine Samples
Some of your / your child’s blood and urine samples will be shipped out of the country to the USA for specialized tests. These tests will tell the doctors how much study drug is in your / your child’s blood and if the study drug is causing any changes in your kidneys.

[For Participants Receiving Granules for suspension only]

[If your child is receiving the liquid he/she will need to switch to the dissolvable tablet. The study staff will inform you when your child will need to switch. This is because the company will not be making the (granule) liquid form of dolutegravir any longer. The study staff will provide instructions on how to dispense the dissolvable tablet and on the day you are scheduled to come to the clinic to begin taking the dissolvable tablets you will be asked to not give the (granule) liquid dose to your child. The first dose of the dissolvable tablet will be given in the clinic. You will be asked to come back to the clinic about 2 weeks later and will have a palatability assessment and blood drawn to confirm the level of HIV in your child’s blood. If you have been on the study for more than 24 weeks at each of these visits, blood samples will be drawn at two separate times. The amount of blood drawn will be less than 1 teaspoon (0.5 -1mL)].

WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE BECOMES INFECTED WITH TUBERCULOSIS WHILE ON THIS STUDY?
If you become/your child becomes exposed to Tuberculosis (TB) while on study and requires anti-TB treatment that includes Rifampin you/your child will have to increase the dose of dolutegravir from once a day to twice a day while taking Rifampin. After you/your child complete(s) treatment with Rifampin, you/your child will go back to taking the dolutegravir once a day depending on what other medications you/your child is taking.

You/your child will also be required to return for at least five additional follow-up visits after starting Rifampin.

- At each of these visits, a medical history will be taken and you/your child will have a physical exam and a pregnancy test. We will draw approximately 1-3 teaspoons of blood to look at the following:
  - The amount of HIV, cholesterol and triglycerides (types of fat) in your blood
  - How well your immune system, liver and kidneys are working, as well as other routine tests

- At each visit you will be asked whether you are taking your medication as instructed.

- You/your child will be asked to come to the clinic to have blood drawn 8 times over 12 hours during one visit, approximately 5-10 days after you/ your child started taking anti-TB medication. For this visit, you/your child will be asked to fast for 6 hours before your daily dose of study medication.

- The study staff will give you more instructions about this. Depending on your/your child’s age, up to 13mL (about 3 teaspoons) of blood will be drawn at this visit.

- You will have extra blood draws at two visits. At weeks 4 and 12, you will have two blood draws - blood will be drawn once before you take dolutegravir and about 12 hours later. The amount of blood drawn at the different study visits will be less than 1 teaspoon (1mL) depending on your /your child’s age.
OTHER INFORMATION
The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 160 children and adolescents will take part in this study

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?
You/your child is enrolling in Stage I of the study, and so will be in the study for at least 48 weeks, depending on how long it takes to find out the correct dose of study drug for children/adolescents in your/your child’s age group.

After we have found the correct dose of medication for you/your child, you/your child will stay in the study for at least 48 weeks. After that time you/your child will enter the long term safety follow-up phase of the study. During this time, you / your child will continue to take study-provided dolutegravir and will be asked to come to clinic every 12 weeks until the drug is available to you from another source, such as your local pharmacy.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THE STUDY DRUG / THIS STUDY EARLY?
The study doctor may need to take you/your child off the study drug early, without your permission, if:

- Continuing the study drug may be harmful to you / your child
- You become / your child becomes pregnant while on study
- If you elect not to attend repeat PK evaluations as part of the study

The study doctor may need to take you/your child off the study early, without your permission, if:

- If you elect not to participate in the intensive PK evaluations as part of the study
- You are/ your child is not able to attend the study visits as required by the study
- You need / your child needs a treatment that you / your child may not take while on the study
- You are / your child is not able to take the study drug as required by the study
- The study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office of Human Research Protections (OHRP), other country specific governmental agencies, IMPAACT, the drug company supporting this study (GSK), or the site’s Institutional Review Board (IRB) or Ethics Committee (EC). An IRB or EC is a committee that watches over the safety and rights of research subjects

If your doctor wants you / your child to stop taking the study drug, you/your child will be asked to return to the clinic once more, four weeks after your last dose of dolutegravir, to make sure you are/your child is continuing to do well. This visit will include a history and physical exam, a blood draw and a review of your medical records.

IF MY CHILD HAS TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICINE, OR ONCE I LEAVE THE STUDY, HOW WOULD THE STUDY MEDICINE BE PROVIDED?
During the study:
If you / your child must permanently stop taking study-provided dolutegravir before your/your child’s study participation is over, the study staff will discuss other options that may be of benefit to you/your child.

After the study:
Once you / your child leaves the study, if you/they are gaining benefit from the study-provided drug, this drug may continue to be provided until it is available to you in your country, but there is no guarantee. Study clinicians will work to ensure that you/your child continue to receive appropriate care and treatment outside of the study.

WHAT ARE THE RISKS OF THE STUDY?
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 additional study drug side effects please ask the medical staff at your site.

Possible Risks Associated with dolutegravir

Dolutegravir has been given to 2,836 HIV-infected subjects and 760 healthy adults in Phase I to Phase IIIb clinical trials as of 16 July 2015. The following side effects have been seen with dolutegravir:

<table>
<thead>
<tr>
<th>Very Common (could affect more than 1 to 10 in every 100 people)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea or feeling sick</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Diarrhea or loose stools</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common (could affect between 1 in 1000 and 1 in 100 people)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold symptoms like runny nose and sore throat; cough; flu</td>
</tr>
<tr>
<td>Dizziness or feeling light headed</td>
</tr>
<tr>
<td>Trouble sleeping; abnormal dreams</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Feeling tired</td>
</tr>
<tr>
<td>High temperature</td>
</tr>
<tr>
<td>Pain in the stomach; vomiting</td>
</tr>
<tr>
<td>Changes in kidney, liver and muscle blood tests</td>
</tr>
<tr>
<td>Ocular icterus (yellowing of the whites of the eyes)</td>
</tr>
<tr>
<td>Itching (pruritus)</td>
</tr>
<tr>
<td>Feelings of deep sadness and unworthiness (depression)</td>
</tr>
<tr>
<td>Flatulence (gas or wind)</td>
</tr>
<tr>
<td>Increase in the level of liver enzymes</td>
</tr>
<tr>
<td>Increase in the level of enzymes produced in the muscles (creatinine phosphokinase)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncommon (could affect less than 1 in 1,000 people)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Inflammation of the liver (hepatitis)</td>
</tr>
<tr>
<td>An inflammatory condition which may develop as the immune system becomes stronger (immune reconstitution syndrome or ‘IRIS’ (see below)</td>
</tr>
</tbody>
</table>


Suicidal thoughts and behaviors (mainly in patients who have had depression or mental health problems before)

Most of the side effects listed above have been mild or moderate, and have not generally stopped HIV-infected patients treated with DTG from getting on with their lives as normal.

Other side effects that may show up in blood tests:

- An increase in bilirubin (a pigment produced from the breakdown of red blood cells) in the blood,
- An increase in the level of enzymes produced in the kidneys.

In a GlaxoSmithKline study of HIV-infected adults receiving HIV treatment for the first time, known as SPRING-2, one person who was receiving dolutegravir and abacavir/lamivudine had an allergic reaction with liver inflammation within the first 2 weeks of taking study medications. Symptoms included fever, rash, joint aches and jaundice (yellowing of the skin and/or eyes). If you/your child develop these symptoms at any time on this study, contact your/your child’s study doctor immediately.

In one animal study, gastric erosion (irritation of the stomach lining) was seen. This finding has not been seen in adults in studies to date. However, if you or your child feels heartburn or stomach pain or has vomiting, please contact your/your child’s study doctor.

Mental illness

Some people with HIV infection occasionally have feelings of depression or may have thoughts of hurting or killing themselves (committing suicide). A small number of people being treated with integrase inhibitors for HIV infection, including dolutegravir, have had suicidal thoughts and behaviors, particularly patients with a prior history of depression or mental health illness. HIV infected patients taking integrase inhibitors including dolutegravir have also reported depression.

Tell the study doctor if you/your child have a history of mental illness. If you/your child have thoughts of hurting or killing yourself or have any other unusual or distressing thoughts or feelings at any time during the study, you/your child should tell the study staff or go to the nearest hospital immediately.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

The use of potent antiretroviral drug combinations 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
Other Risks

There is the risk of serious and/or life threatening side effects when non-study medications are taken with study drugs. For your/your child’s safety, you must tell your/your child’s HIV care provider and the study doctor or nurse about all medications you take/your child takes before the start of this study and also before starting any new medications while you are/your child is on the study. In addition, you must tell the study doctor or nurse before you enroll/enrolling your child in any other clinical trials while on this study.

The use of highly active HIV medications may also be associated with altered fat metabolism including increased triglycerides (fatty acid in the blood) and/or increased cholesterol.

Other side effects besides those listed and side effects from taking these drugs together may occur. If any unusual symptoms or changes happen, you should call your/your child’s doctor immediately. It is also important that while participating in the study, you do not/your child does not take any other prescription drugs or over-the-counter medications without first talking to your/your child’s doctor or study nurse.

Blood Drawing and Heparin Lock Risks:
Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur when a needle enters the body.

ARE THERE RISKS RELATED TO PREGNANCY?
It is not known if the drug or drug combinations in this study harm fetuses. Tests in pregnant animals do show some risk to the mother. If you are/your child is having sex that could lead to pregnancy, you/your child must agree not to become pregnant.

Because of the risk involved, you and your partner, or your child and their partner must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until two weeks 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)

All birth control methods listed above except condoms do not reduce the risk of giving HIV to someone else. HIV-infected individuals should use a birth control method that includes condoms to keep from giving HIV to someone else.

If you/your child can become pregnant, you/she must have a pregnancy test before entering this study. If you are / your child is pregnant, you/she cannot be in the study. If you think you/your child may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you about your/your child’s choices. You/your child will be tested again during the study if it is possible that you/she may be pregnant.

If you are /your child becomes pregnant while on study, you/she will not be allowed to continue on the study drug but will be asked to remain on study and come in for study visits as planned in case of safety concerns and so that the doctors can follow your/her pregnancy until your / your child’s baby is born.
ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
If you / your child take(s) part in this study, the amount of HIV in your / your child’s body may go down and your / your child’s immune system may become stronger, but no guarantee can be made. You / your child 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 HAVE BESIDES THIS STUDY?
Instead of being in this study you have the choice of:

- Treatment with prescription drugs available to you / your child
- Treatment with other experimental drugs, if you / your child qualify(ies)
- No treatment (NOT recommended)

Please talk to your doctor about these and other choices available to you / your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?
(For US Sites Only)
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 / your child’s records include the U.S. Food and Drug Administration, the Office of Human Research Protections (OHRP), the site IRB / EC (insert name of site IRB/EC), the National Institutes of Health, study staff, study monitors, drug companies supporting the 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.

(For sites outside the U.S.)
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name of identify you personally.

Your records may be reviewed by the Ministry of Public Health in your country, the FDA, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB/EC, study staff, study monitors and the drug companies supporting this study.

WHAT ARE THE COSTS TO ME / MY CHILD?
There are no costs to you / your child for study drugs, study visits or study procedures. However, taking part in this study may lead to added costs to you and your insurance company if medical complications
arise or if your doctor decides extra tests are needed. In some cases it is possible that your insurance company will not pay for these costs because you/your child are taking part in a research study.

**WILL I RECEIVE ANY PAYMENT?**
You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

**WHAT HAPPENS IF I AM/ MY CHILD IS INJURED?**
If you are/your child is injured as a result of being in this study, you/your child will be given immediate treatment for your/his/her 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/your child’s legal rights by signing this consent form.

**WHAT ARE MY / MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?**
Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

**WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?**
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), Ethics Committee (EC) or other organization appropriate for the site
- Telephone number of above
**SIGNATURE PAGE**

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>Subject’s Name (print)</th>
<th>Subject’s Signature and Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject’s Legal Guardian (print) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
</tr>
<tr>
<td>Second Guardian (print) (If required)</td>
<td>Second Guardian’s Signature and Date</td>
</tr>
</tbody>
</table>
APPENDIX III
Sample Consent Form For Subjects Enrolling in STAGE TWO

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

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

Subjects Enrolling in STAGE TWO
P1093 Version 4.0, dated 13 April 2016

SHORT TITLE FOR THE STUDY: Safety and PK of dolutegravir in HIV-1 Infected Children

INTRODUCTION
You are/your child is being asked to take part in this research study because you have /your child has the Human Immunodeficiency Virus (HIV), which is the virus that causes AIDS, and because the drugs currently available may not keep the amount of HIV in your / your child’s blood low enough or may cause side effects too difficult to deal with. This study is sponsored by the National Institutes of Health (NIH). 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 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 are free to ask questions about this study at any time. If you agree to/agree to allow your child 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?
This study is being done to study a new antiretroviral HIV medication called dolutegravir. This drug is a type of medicine called an integrase inhibitor. Integrase inhibitors work by blocking integrase, a protein that HIV needs to enter human cells and make more copies of itself. The study will help find the best amount or dose of dolutegravir for infants, children and teenagers, when it is taken on its own as well as with other antiretroviral medications. This study will also find out the safety of using this medication in infants, children and adolescents and if there are any side effects from the medication. Dolutegravir has been tested before in adults and children. The study drug (dolutegravir) is approved for use in children 12 years and older by the FDA [and/or local regulatory authorities].

WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE IS IN THIS STUDY?
If you decide to (allow your child to) enroll in this study, you / your child will be asked to come to the clinic at least 10 times over 48 weeks and then every 12 weeks until the end of the study. You / your child will be given dolutegravir and you / your child will be asked to take it once or twice a day for the entire study, in addition to your / your child’s regular HIV medicines. Dolutegravir is available in three different formulations: 1) a film-coated tablet that cannot be crushed or dissolved, 2) a liquid suspension and 3) a tablet that can be dissolved in water. If you are/your child is 12 up to 18 years old, you/your child will take the film-coated tablet formulation of dolutegravir.
If your child is older than 4 weeks of age to less than 12 years of age your child will receive the liquid or dissolvable tablets. You will be given instructions on how to give dolutegravir to your child. If your child is between 6 to less than 12 years of age and was prescribed the liquid or dissolvable tablet tablets of dolutegravir he/she may be allowed to switch to the film-coated tablet formulation, at a later time. The study staff will let you know when your child can switch, if you request to do so.

Although the study will provide you/your child with dolutegravir, other antiretrovirals will not be provided by the study.

This study will be done in two parts – Stage One and Stage Two. Stage One will enable the doctors to find the right dose of study drug for you/your child and then will keep you on that dose to look for any side effects that you/your child might experience. In Stage Two the doctors will know the right dose to put you/your child on and will look at any side effects that you / your child might experience as well as how well the drug is controlling your HIV infection. You/your child will be enrolled into Stage One or Stage Two, depending on when you enroll /your child enrolls and your age / the age of your child. This consent form is for Stage Two.

In this study there are 6 cohorts – Cohort 1 will enroll adolescents aged 12 to less than 18 years of age and Cohorts 2A and 2B will enroll children aged 6 to 12 years of age. Subjects who have had their 18th birthday by the entry visit will not be enrolled into the study. Cohort 3 will enroll children from 2 to less than 6 years of age. Cohort 4 will enroll children aged 6 months to less than 2 years of age. Cohort 5 will enroll infants from 4 weeks to less than 6 months of age.

Screening:
If you are interested in taking part / allowing your child to enroll in this study, we will see if you are / your child is eligible for the study:

- We will ask your / your child’s medical history including questions about your /your child’s health and what symptoms, medications, and illnesses you have/your child has had.

- We will do a physical exam including height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate). Doses may be modified based on the results of the weight.

- We will take about 3 teaspoons (11 mLs) of blood, to check for the following:
  - The amount of HIV in the blood,
  - The amount of cholesterol and triglycerides (types of fat) in the blood,
  - How well your immune system, liver and kidneys are working,
  - Other routine tests.

You will be given the results of these tests. We will also ask you to provide a urine sample for routine tests. Girls and women of childbearing age will also be asked to provide a urine or blood sample to test for pregnancy. If you are / your child is engaged in sexual activity that could lead to pregnancy, you / your child will be asked to take birth control precautions throughout the study period.

On Study:
If you are/your child is eligible for this study, you/your child will come to the clinic at least 8 times in 48 weeks to complete Stage Two. Most of the visits will last about 1-2 hours. You/your child will come to the clinic for the first study visit within 30 days of the screening visit.

- At each visit, a medical history will be taken and you/your child will have a physical exam. If you are/your child is older than 2 years of age, at the enrollment visit and at the week 48 visit, you/your child’s stage of sexual development will be determined. For girls/women, this will be done by looking at how developed the breasts are. For boys/men, this will be done by measuring the size of the testes. Girls and women of childbearing age will also be asked to provide a urine or blood sample to test for pregnancy at each visit.
- We will draw blood at each visit. Depending upon your/your child’s age, between 1-5 teaspoons (5-17 mLs) of blood will be drawn at these visits. You will be informed of results of routine blood tests. Some of the blood drawn will be stored and tested to find out how your/your child’s immune system is affected by the study drug. This testing will be done after the study is over, and you will not be given the results of these tests.
- A palatability assessment will be done at Day 10, Week 4 and Week 24 to assess what you/your child thinks about the taste of the study drug.
- At two visits (week 4 and week 24), blood samples will be drawn two separate times. At week 12, you will only have one blood draw. The amount of blood drawn at the different study visits will be less than 1 teaspoon (0.5-1mL) depending on your /your child’s age.
- If the amount of HIV virus in your/your child’s blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood. If the level of HIV virus in your blood is still too high, your study doctor may ask you to stop taking the study medicine and to come back to the clinic for another visit. As part of this visit, you/your child will have an interim medical history, physical exam and approximately 4 teaspoons of blood (14-17mL) will be drawn for testing and storage.
- If you/your child experiences a severe liver reaction or inflammation while on the study, you/your child may be asked to come back to clinic to have less than one teaspoon of blood (2mL) drawn to check the level of dolutegravir in the blood. Additional testing as part of routine assessments for liver inflammation (e.g. checking for viruses that cause liver inflammation) may be performed as well.

*Long Term Follow-Up*

After you have been on study drug for approximately 48 weeks, you will enter the long term follow-up phase of the study. You will be asked to come back into clinic every 12 weeks (every 3 months) for 3 years. If the drug is not commercially available in your country after three years, it will continue to be provided to you/your child but will no longer be provided through the study. Most visits will last about 30 minutes.

- At some visits, a medical history will be taken and you/your child will have a physical exam. You will also be asked if you have missed taking any of your medications.
- We will draw less than 1 teaspoon of blood (3-4mL) at some visits. You will be informed of results of routine blood tests.
- As before, if the amount of HIV virus in your/your child’s blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood (see above).
You/your child must continue to take your/his/her anti-HIV medications during the study as prescribed by your/your child’s HIV care provider. If your/your child’s HIV care provider changes your/your child’s anti-HIV medications during the study, you/your child can still take the study drug. You/your child will be asked questions about taking your/his/her anti-HIV medications and the schedule you take/he/she takes them on and if you have/he/she has missed any medications.

If you/your child can become pregnant, you/your child must have a pregnancy test before you enter/she enters this study. If you are/your child is pregnant, you/your child can not be in the study. If you think you/if your child thinks she may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you/your child about your/her choices. You/your child will be tested again during the study if it is possible that you/she may be pregnant. If you are/your child is pregnant, you/your child will not be allowed to continue on the study drug but will be asked to continue to come in for study visits so we can follow you/her until you/your child delivers the baby.

Blood & Urine Samples
Some of your / your child’s blood and urine samples will be shipped out of the country to the US for specialized tests. These tests will tell the doctors how much study drug is in your / your child’s blood and if the study drug is causing any changes in your kidneys.

[For Participants Receiving Granules for suspension only]

[If your child is receiving the (granule) liquid he/she will need to switch to the dissolvable tablet. The study staff will inform you when your child will need to switch. This is because the company will not be making the liquid form of dolutegravir any longer. The study staff will provide instructions on how to dispense the dissolvable tablet and on the day you are scheduled to come to the clinic to begin taking the dissolvable tablets you will be asked to not give the (granule)liquid dose to your child. The first dose of the dissolvable tablet will be given in the clinic. You will be asked to come back to the clinic about 2 weeks later and will have a palatability assessment and blood drawn to confirm the level of HIV in your child’s blood. If you have been on the study for more than 24 weeks at each of these visits, blood samples will be drawn at two separate times. The amount of blood drawn will be less than 1 teaspoon (0.5-1mL) depending on your /your child’s age.]

WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE BECOMES INFECTED WITH TUBERCULOSIS WHILE ON THIS STUDY?
If you become/your child becomes exposed to Tuberculosis (TB) while on study and requires anti-TB treatment that includes Rifampin you/your child will have to increase the dose of dolutegravir from once a day to twice a day while taking Rifampin. After you/your child complete(s) treatment with Rifampin, you/your child may go back to taking the dolutegravir once a day, depending on what other medications you/your child is taking.

You/your child will also be required to return for at least five additional follow-up visits after starting Rifampin.
- At each of these visits, a medical history will be taken and you/your child will have a physical exam and we will draw approximately 1-3 teaspoons of blood to look at the following:
  - The amount of HIV, cholesterol and triglycerides (types of fat) in your blood
  - How well your immune system, liver and kidneys are working, as well as other routine tests
At each visit you will be asked whether you are taking your medication as instructed.

You/your child will be asked to come to the clinic to have blood drawn 8 times over 12 hours during one visit, approximately 5-10 days after you/your child started taking anti-TB medication. For this visit, you/your child will be asked to fast for 6 hours before your daily dose of study medication.

The study staff will give you more instructions about this. Depending on your/your child’s age, up to 13mL (a little more than 4 teaspoons) of blood will be drawn at this visit.

You will have extra blood draws at two visits. At weeks 4 and 12, you will have two blood draws — blood will be drawn once before you take dolutegravir and about 12 hours later. The amount of blood drawn at the different study visits will be less than 1 teaspoon (1mL).

OTHER INFORMATION
The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 160 children and adolescents will take part in this study

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?
By signing this consent form, you are agreeing to/allow your child to participate in Stage II of the study, and so you/your child will be in the study for 48 weeks.

After Stage II is completed, you/your child will enter the long term safety follow-up phase of the study. You/your child will continue to take study provided dolutegravir and will be asked to come to clinic every 12 weeks until the drug is available to you from another source, such as your local pharmacy.

WHY WOULD THE DOCTOR TAKE ME/MY CHILD OFF THE STUDY DRUG/THIS STUDY EARLY?
The study doctor may need to take you/your child off the study drug early, without your permission, if:

- Continuing the study drug may be harmful to you/your child
- You become/your child becomes pregnant while on study
- You are/your child is not able to attend the study visits as required by the study
- You need/your child needs a treatment that you/your child may not take while on the study
- You are/your child is not able to take the study drug as required by the study
- If you elect not to attend repeat PK evaluations as part of the study

The study doctor may need to take you/your child off the study early, without your permission, if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office of Human Research Protections (OHRP), other country specific governmental agencies, IMPAACT, the drug company supporting this study (GSK), or the site’s Institutional Review Board (IRB) or Ethics Committee (EC). An IRB or EC is a committee that watches over the safety and rights of research subjects
If your doctor wants you / your child to stop taking the study drug, you/your child will be asked to return to the clinic once more, four weeks after your last dose of dolutegravir, to make sure you are/your child is continuing to do well. This visit will include a history and physical exam, a blood draw and a review of your medical records.

**IF MY CHILD HAS TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICINE, OR ONCE I LEAVE THE STUDY, HOW WOULD THE STUDY MEDICINE BE PROVIDED?**

**During the study:**
If you / your child must permanently stop taking study-provided dolutegravir before your/your child’s study participation is over, the study staff will discuss other options that may be of benefit to you/your child.

**After the study:**
Once you / your child leaves the study, if you/they are gaining benefit from the study-provided drug, this drug may continue to be provided until it is available to you in your country, but there is no guarantee. Study clinicians will work to ensure that you/your child continue to receive appropriate care and treatment outside of the study.

**WHAT ARE THE RISKS OF THE STUDY?**
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 additional study drug side effects please ask the medical staff at your site.

**Possible Risks Associated with dolutegravir**

Dolutegravir has been given to 2836 HIV-infected subjects and 760 healthy adults in Phase I to IIIb clinical trials as of 16 July 2015.

The following side effects have been seen with dolutegravir:

<table>
<thead>
<tr>
<th>Possible Risks Associated with dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common (could affect more than 1 to 10 in every 100 people)</td>
</tr>
<tr>
<td>Nausea or feeling sick (mild to moderate)</td>
</tr>
<tr>
<td>Headache (mild to moderate)</td>
</tr>
<tr>
<td>Diarrhea or loose stools</td>
</tr>
<tr>
<td>Common (could affect between 1 in 1000 and 1 in 100 people)</td>
</tr>
<tr>
<td>Cold symptoms like runny nose and sore throat; cough; flu</td>
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<tr>
<td>Dizziness or feeling light headed</td>
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<tr>
<td>Trouble sleeping; abnormal dreams</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Feeling tired</td>
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<tr>
<td>High temperature</td>
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<tr>
<td>Pain in the stomach; vomiting</td>
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<tr>
<td>Changes in kidney, liver and muscle blood tests</td>
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<tr>
<td>Ocular icterus (yellowing of the whites of the eyes)</td>
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<tr>
<td>Itching (pruritus)</td>
</tr>
<tr>
<td>Feelings of deep sadness and unworthiness (depression)</td>
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<tr>
<td>Flatulence (gas or wind)</td>
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</tbody>
</table>
Increase in the level of liver enzymes
Increase in the level of enzymes produced in the muscles (creatine phosphokinase)

Uncommon (could affect less than 1 in 1000 people)
Allergic reaction
Inflammation of the liver
An inflammatory condition which may develop as the immune system becomes stronger (immune reconstitution syndrome or ‘IRIS’ (see below)
Suicidal thoughts and behaviors (mainly in patients who have had depression or mental health problems before)

Most of the side effects listed above have been mild or moderate, and have not generally stopped HIV-infected patients treated with DTG from getting on with their lives as normal.

Other side effects that may show up in blood or urine tests:
- An increase in bilirubin (a pigment from the breakdown of red blood cells) in the blood.
- An increase in the level of enzymes produced in the kidney (creatine)

In a GlaxoSmithKline study of HIV-infected adults receiving HIV treatment for the first time, known as SPRING-2, one person who was receiving dolutegravir and abacavir/lamivudine had an allergic reaction with liver inflammation in the first 2 weeks of taking study medications. Symptoms included fever, rash, joint aches and jaundice (yellowing of the skin and/or eyes). If you/your child develop these symptoms at any time on this study, tell your/your child’s study doctor immediately.

In one animal study, gastric erosion (irritation of the stomach lining) was seen. This finding has not been seen in adults in studies to date. However, if you or your child feels heartburn or stomach pain or has vomiting, please contact your/your child’s study doctor.

Mental illness
Some people with HIV infection occasionally have feelings of depression or may have thoughts of hurting or killing themselves (committing suicide). A small number of people being treated with integrase inhibitors for HIV infection, including dolutegravir, have had suicidal thoughts and behaviors, particularly patients with a prior history of depression or mental health illness. HIV infected patients taking integrase inhibitors including dolutegravir have also reported depression.

Tell the study doctor if you/your child have a history of mental illness. If you/your child have thoughts of hurting or killing yourself or have any other unusual or distressing thoughts or feelings at any time during the study, you/your child should tell the study staff or go to the nearest hospital immediately.

Use of Combination Antiretroviral Drugs
Immune Reconstitution Syndrome: In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

The use of potent antiretroviral drug combinations 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

**Other Risks**

There is the risk of serious and/or life threatening side effects when non-study medications are taken with study drugs. For your/your child’s safety, you must tell your/your child’s HIV care provider and the study doctor or nurse about all medications you take/your child takes before the start of this study and also before starting any new medications while you are/your child is on the study. In addition, you must tell the study doctor or nurse before you enroll/enrolling your child in any other clinical trials while on this study.

The use of potent antiretroviral drug combinations may also be associated with altered fat metabolism including elevated triglycerides (fatty acid in the blood) and/or elevated cholesterol.

Other side effects besides those listed and side effects from taking these drugs together may occur. If any unusual symptoms or changes happen, you should call your/your child’s doctor immediately. It is also important that while participating in the study, you do not/your child does not take any other prescription drugs or over-the-counter medications without first talking to your/your child’s doctor or study nurse.

**Blood Drawing and Heparin Lock Risks:**

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the needle enters the body or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

**ARE THERE RISKS RELATED TO PREGNANCY?**

It is not known if the drug or drug combinations in this study harm fetuses. Tests in pregnant animals do show some risk. If you are/your child is having sex that could lead to pregnancy, you/your child must agree not to become pregnant or make a female pregnant.

Because of the risk involved, you and your partner, or your child and their partner, must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until two weeks after stopping the 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)

All birth control methods listed above except condoms do not reduce the risk of giving HIV to someone else. HIV-infected individuals should use a birth control method that includes condoms to keep from giving HIV to someone else.

If you/your child can become pregnant, you/she must have a pregnancy test before entering this study. If you are / your child is pregnant, you/she cannot be in the study. If you think you/your child may be
pregnant at any time during the study, tell the study staff right away. The study staff will talk to you about your/your child’s choices. You/your child will be tested at each visit during the study if it is possible that you/she may be pregnant. If you are /your child is pregnant, you/she will not be allowed to continue on the study drug.

If you are /your child becomes pregnant while on study, you/she will not be allowed to continue on the study drug but will be asked to remain on study and come in for study visits as planned in case of safety concerns and so that the doctors can follow your/her pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
If you /your child take(s) part in this study, the amount of HIV in your / your child’s body may go down and your/your child’s immune system may become stronger, but no guarantee can be made. You/your child 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 HAVE BESIDES THIS STUDY?
Instead of being in this study you have the choice of:
- Treatment with prescription drugs available to you/your child
- Treatment with other experimental drugs, if you/your child qualify(ies)
- No treatment (NOT Recommended)

Please talk to your doctor about these and other choices available to you/your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?
(For U.S. sites only)
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/your child’s records include the U.S. Food and Drug Administration, the Office of Human Research Protections (OHRP), the site IRB /EC (insert name of site IRB/EC), the National Institutes of Health, study staff, study monitors, drug companies supporting the 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.

(For sites outside the U.S.)
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name of identify you personally.
Your records may be reviewed by the Ministry of Public Health in your country, the FDA, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB/EC, study staff, study monitors and the drug companies supporting this study.

**WHAT ARE THE COSTS TO ME / MY CHILD?**
There are no costs to you/your child for study drugs, study visits or study procedures. However, taking part in this study may lead to added costs to you and your insurance company if medical complications arise or if your doctor decides extra tests are needed. In some cases it is possible that your insurance company will not pay for these costs because you/ your child are taking part in a research study.

**WILL I RECEIVE ANY PAYMENT?**
You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

**WHAT HAPPENS IF I AM / MY CHILD IS INJURED?**
If you are / your child is injured as a result of being in this study, you / your child will be given immediate treatment for your/his/her 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/your child’s legal rights by signing this consent form.

**WHAT ARE MY / MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?**
Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

**WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?**
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
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SIGNATURE PAGE

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.

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<tr>
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</tr>
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<tbody>
<tr>
<td>Subject’s Legal Guardian (print) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
</tr>
<tr>
<td>Second Guardian (print) (If required)</td>
<td>Second Guardian’s Signature and Date</td>
</tr>
</tbody>
</table>
APPENDIX IV
Sample Informed Consent Form for Specimen Storage and Future Use

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

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

P1093 Version 4.0, dated 13 April 2016

You have decided to allow your child to join the study named above/You are participating in the study named above. As part of the study, you/your child will have blood drawn and urine collected. After these samples are tested for the study, there may be some samples that are left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether or not to allow the extra samples to be used.

You are free to say yes or no, or to change your mind at any time. Your decision will not affect your/your child’s participation in the study. If you say no, all extra samples will be destroyed.

2. If you agree, your child’s extra samples will be kept in a repository.

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. There is no limit on how long the samples will be kept [sites may insert time limits or additional site-specific requirements here if required by local authorities].

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at your/your child’s genes.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the persons whose samples will be used.

4. There is little risk to you/your child.

When extra samples are used for research, they are labeled with a code number only. To protect your child’s privacy, no names are used. However, information such as age, gender, HIV status, and other
health information may be linked to the samples. Information on which study ARVs you/your child received and you/your child’s immune system responses to the ARVs may also be linked to the samples.

There may be some risks from tests of you/your child’s genes. If others found out the results of these tests, they could treat you badly or unfairly. However, this is almost impossible because the results of these tests will not be in you/your child’s study records and they will not be given to you.

5. **There may be no benefit to you/your child.**

The research done with extra samples is not expected to give any information relevant to your child’s health. The results will not be given to you and will not be part of your study records.

6. **You will not be paid for use of your/your child’s samples.**

There is no cost to you for use of your child’s extra samples. The samples will not be sold and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with you or your child.

7. **Information from research using extra samples may be reviewed by groups that oversee the research.**

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research

The people who do research with the extra samples and the groups listed above are required to make efforts to information private and confidential.

The results of research done with extra samples may be presented publicly or published. However, no presentation or publication will use your/your child’s name or identify your child personally.

8. **If you have any questions, concerns, or problems related to your/your child’s extra samples, use these contacts.**

- If you have questions about use of your/your child’s extra samples, contact: [sites insert name and telephone number of investigator or other study staff].

- If you later change your mind about use of your/your child’s extra samples, contact: [sites insert name and telephone number of investigator or other study staff].

- If you have questions about your/your child’s rights as a research participant, or problems or concerns about how your child is being treated in the study, contact: [sites insert name and telephone number of IRB contact person or other appropriate person/organization].
9. Signatures

If you agree to let your/your child’s extra samples be used, please sign or make your mark below.

________ I allow my/my child’s extra samples to be used for research on HIV, the immune system, and other diseases. I also allow my child’s samples to be used for tests of his or her genes.

________ I allow my/my child’s extra samples to be used for research on HIV, the immune system, and other diseases. I do not allow my child’s samples to be used for tests of his or her genes.

________ I do not allow my/my child’s extra samples to be used for any research.

__________________________________________
Subject’s Name (print)

__________________________________________  __________________________
Parent’s Name (print)  Parent’s Signature  Date
(Or Legal Guardian)

__________________________________________  __________________________
Parent’s Name (print)  Parent’s Signature  Date
(Or Legal Guardian)

__________________________________________  __________________________
Study Staff Conducting  Study Staff Signature  Date
Consent Process Name (print)

__________________________________________  __________________________
Witness Name  Witness Signature  Date
(As appropriate)