CLINICAL REVIEW

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Priority or Standard	Priority
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Division / Office	CDER/OND/OAP/DAVP
Reviewer Name	Mark Needles, M.D.
Review Completion Date	05/13/2016
Established Name	Dolutegravir
Trade Name	TIVICAY®
Therapeutic Class	Integrase Strand Transfer Inhibitor (INSTI)
Applicant	ViiV Healthcare Company
Formulation	Tablet, 10 mg, 25 mg, and 50 mg
Dosing Regimen	~1 mg/kg once daily across 2 weight bands: 30 to <40 kg: 35 mg ≥40 kg: 50 mg Increase the weight-based dose to twice daily when certain UGT1A or CYP3A inducers are coadministered: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin, or carbamazepine.
Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents
Intended Population	Pediatric patients weighing at least 30 kg

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is the opinion of this clinical reviewer that the data from Study ING112578 (P1093) support approval of TIVICAY® (dolutegravir, DTG) for treatment of HIV-1 infection in [redacted] integrase strand transfer inhibitor (INSTI)-naïve pediatric patients weighing at least 30 kg. [redacted] Pediatric patients weighing ≥30 kg had exposures from the proposed DTG dosages that were similar to the observed exposures from the approved adult dose. This submission included limited pharmacokinetic data from pediatric patients 6 to <12 years old and weighing less than 30 kg. Lower exposures were noted from the doses administered to this population, and additional pharmacokinetic data will be needed to determine optimal dose(s) for HIV-1 infected pediatric patients weighing less than 30 kg.

1.2 Risk Benefit Assessment

One Phase 1/2 trial, ING112578 (P1093), support the efficacy of dolutegravir for the treatment of HIV-1 infection in pediatric patients [redacted] weighing ≥30 kg. Children ≥6 to <12 year old administered the proposed DTG dose of ~1 mg/kg QD across weights bands ≥30 kg achieved comparable exposures (AUC_{24} and C_{24h}) as observed in adults administered the 50 mg QD dose. [redacted] Lower exposures were observed in children weighing < 30kg who were administered DTG on a weight-based dosing regimen; and limited pharmacokinetic data was collected from this subset during P1093.

DTG treatment in combination with optimized background therapy resulted in virologic suppression (HIV-1 RNA <50 copies/mL) in both children ≥6 to <12 years old and adolescents ≥12 to <18 years old. The proportion of children and adolescents who achieved virologic suppression was comparable at Week 24; and most of the adolescents continued to remain virologically suppressed at Week 48, compared to Week 24.Evaluation of the efficacy outcome based on weight-bands was conducted because dosing recommendations are being provided for pediatric patients weighing at least 30 kg. Across both cohorts, 71% (17/24) of subjects in the ≥40 kg weight-band and 55% (6/11) of subjects in the 30 to <40 kg weight-band achieved virologic suppression at Week 24. The majority of subjects in the adolescent cohort weighed ≥40 kg (19 of 23) and of the 19, 63% were virologically suppressed at Week 48. The small sample sizes in each Cohort and weight-band may confound findings from the sub-group analysis.

Trial P1093 also support the safety and tolerability of DTG for the treatment of HIV-1 infection in children ≥6 to <12 years old (Week 24 safety data) and adolescents ≥12 to <18 years old (Week 48 safety data). Most of the adverse events reported in P1093 were non-serious, mild or moderate in severity, and self-limited. No serious adverse events or ≥Grade 3 events were reported as at least possibly related to DTG treatment and no adverse events led to permanent discontinuation of the study drug. Overall, the adverse reaction profile in children was similar to that for adults and supports the overall favorable benefit risk assessment for this population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Postmarket Risk Evaluation and Mitigation Strategy (REMS) will not be required. The applicant will continue to submit Periodic Adverse Drug Experience Reports (PAERs) and Development Safety Update Reports (DSURs) for review.

1.4 Recommendations for Postmarket Requirements and Commitments

(b) (4) (PMR) 2078-1 which required a pharmacokinetics, safety, and antiviral activity study in HIV-1 infected INSTI-naïve, pediatric patients 4 weeks to less than 12 years of age. (b) (4)

(b) (4)

(b) (4)

(b) (4)

The status of P1093 is ongoing

(b) (4)

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PMR 2078-2 was issued in the original August 12, 2013 approval letter for DTG and required a pharmacokinetics, safety, and antiviral activity study in HIV-1 infected pediatric patients 2 to <18 years old, who are INSTI-experienced with certain INSTI associated resistance substitutions or clinically suspected INSTI resistance. (b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

Dolutegravir is an HIV integrase strand transfer inhibitor (INSTI). The drug inhibits the catalytic activity of HIV integrase, an enzyme required for HIV-1 replication and responsible for viral genome integration into the host genome. Dolutegravir is currently approved for the treatment of HIV-1 infection in adults and adolescents ages 12 years and older. The approved dose is 50 mg once daily for treatment-naïve or treatment-experienced, INSTI-naïve adults and adolescents aged 12 years and older and weighing at least 40 kg. A 50 mg twice daily dose is recommended in this population when co-administered with certain UGT1A/CYP3A inducers, including efavirenz,

fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin, and carbamazepine. There is also a 50 mg twice daily dose approved for adults who are treatment-experienced, INSTI-experienced.

Established Name:	Dolutegravir
Trade Name:	Tivicay™
Pharmacological Class:	Integrase strand transfer inhibitor
Proposed indication (under review):	Doutegravir in combination with other antiretroviral agents indicated for the treatment of HIV-1 infection in (b) (4)
Dosage form:	10 mg, 25 mg, and 50 mg tablets
Proposed Dosing Regimen (under review):	Pediatric: treatment-naïve or treatment-experienced, INSTI-naïve (b) (4) (b) (4) 35 mg once daily: if weight 30 to <40 kg 50 mg once daily: if weight ≥40 kg Increase the weight-based dose to twice daily when certain UGT1A or CYP3A inducers are coadministered: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin, or carbamazepine.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.2-1 summarizes the approved antiretroviral therapies (ARTs) approved for the treatment of HIV-1 infection. Most of antiretroviral drugs are approved at least in some age cohort of pediatric patients.

Table 2.2-1: Drugs Approved for the treatment of HIV-1 infection

Drug Class	Generic Name	Trade Name
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Abacavir (ABC)	Ziagen®
	Didanosine (ddI)	Videx®
	Emtricitabine (FTC)	Emtriva®
	Lamivudine (3TC)	Epivir®
	Stravudine (d4T)	Zerit®
	Tenofovir alafenamide (TAF)	See fixed dosed combinations
	Tenofovir disoproxil fumarate (TDF)	Viread®
	Zidovudine (AZT)	Retrovir®
Non-nucleoside reverse transcriptase inhibitors	Delavirdine (DLV)	Rescriptor®
	Efavirenz (EFV)	Sustiva®

Drug Class	Generic Name	Trade Name
(NNRTIs)	Etravirine (ETR)	Intelence®
	Nevirapine (NVP)	Viramune®
	Rilpivirine (RPV)	Edurant®
Protease inhibitors (PIs)	Atazanavir (ATV)	Reyataz®
	Amprenavir (APV)	Agenerase®
	Darunavir (DRV)	Prezista®
	Fosamprenavir (FPV)	Lexiva®
	Indinavir (IDV)	Crixivan®
	Lopinavir/Ritonavir (LPV/r)	Kaletra®
	Nelfinavir (NFV)	Viracept®
	Saquinavir (SQV)	Invirase®
	Tipranavir (TPV)	Aptivus®
Fusion/Entry Inhibitor	Enfuvirtide (T-20)	Fuzeon®
CCR5 receptor antagonist	Maraviroc (MVC)	Seizentry®
Integrase Inhibitor	Dolutegravir (DTG)	Tivicay®
	Elvitegravir (EVG)	Vitekta®
	Raltegravir (RAL)	Isentress®
Pharmacokinetic Enhancers	Cobicistat (COBI)	Tybost®
	Ritonavir (RTV)	Norvir®
Fixed Dosed Combination	ABC and 3TC	Epzicom®
	ABC, 3TC, and AZT	Trizivir®
	ABC, 3TC, and DTG	Triumeq®
	EVG, COBI, FTC, and TAF	Genvoya®
	EVG, COBI, FTC, and TDF	Stribild®
	FTC and TAF	Descovy®
	FTC, RPV, and TAF	Odefsey®
	FTC, RPV, and TDF	Complera®
	FTC and TDF	Truvada®
	EFV, FTC, and TDF	Atripla®
	3TC and AZT	Combivir®
	3TC and RAL	Dutrebis®
	ATV and COBI	Evotaz®
	DRV and COBI	Prezcobix®

2.3 Availability of Proposed Active Ingredient in the United States

Dolutegravir (Tivicay®) was approved in the United States on August 12, 2013. The original approval included a pediatric indication for treatment-naïve or treatment-experienced, INSTI-naïve adolescents 12 years and older and weighing at least 40 kg. Triumeq® is a fixed dosed combination drug containing dolutegravir and received approval in the United States for adult on August 22, 2014.

2.4 Important Safety Issues With Consideration to Related Drugs

Raltegravir, elvitegravir, and dolutegravir are currently the only drugs in the INSTI drug class to receive approval for the treatment of HIV-1 infection. Raltegravir (Isentress®) was the first INSTI drug to receive approval and was followed by the approval of elvitegravir in a fixed dose combination drug (Stribild®). Since then, elvitegravir (Vitekta®) and fixed dose combination drugs containing either raltegravir (Dutrebis®) or elvitegravir (Genvoya®) have been approved. Overlapping toxicities have been reported between the various INSTIs. Reports of hypersensitivity reactions, rashes, and liver enzyme elevations have been noted with raltegravir and dolutegravir use. Raltegravir is also associated with the development of serious rashes, including Stevens-Johnson Syndrome and toxic epidermal necrolysis. Psychiatric events including suicidal ideation and depression have been noted with raltegravir, elvitegravir, and dolutegravir use. Both raltegravir and dolutegravir are associated with serum creatinine kinase elevations. Cases of rhabdomyolysis have also been reported for raltegravir. Proximal renal tubulopathy was reported in the Stribild clinical trials, but cases were thought to be related to the tenofovir and cobicistat components, and not elvitegravir. Dolutegravir decreases tubular secretion of creatinine and causes small increases in serum creatinine; however, the drug is not thought to affect glomerular filtration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Study ING112578 (P1093) is an ongoing study being conducted in collaboration with the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), together with the National Institute of Allergy and Infectious Diseases (NIAID). The study is designed to fulfill the PREA PMR requirement 2078-1. A Type B, Pre-sNDA meeting was scheduled to take place on July 7, 2015. This meeting was cancelled after the applicant received sufficient preliminary comments from the Agency in regards to the format and content of the sNDA.

2.6 Other Relevant Background Information

Treatment of HIV disease is monitored by surrogate markers (HIV RNA viral load and CD4 count) and ARTs have shown to lower HIV RNA, improve CD4 counts, and improve clinical outcome in both adult and pediatric subjects. For this reason, the treatment recommendations for both adults and pediatrics are very similar (see Working Group on Antiretroviral Agents in HIV-1 infected Adults and Adolescents. January 28, 2016 1-227 and see Working Group on Antiretroviral Agents in Pediatric HIV Infection. March 1, 2016 1-334 Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf and at https://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf, respectively).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submission were adequate. This reviewer reviewed the datasets and the applicant's analyses were verified.

3.2 Compliance with Good Clinical Practices

The clinical trial was conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects before any study-related procedures.

3.3 Financial Disclosures

Please see section 9.4 for the Clinical Investigator Financial Disclosure Form

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Currently, the 50 mg tablet is the only approved dolutegravir formulation. The applicant presented new chemistry, manufacturing and control (CMC) data in this pediatric submission to support the introduction of 10 mg and 25 mg tablet formulations. Refer to CMC reviewers by Dr. Shrikant Pagay.

4.2 Clinical Microbiology

Treatment-emergent integrase resistance-associated mutations were noted in one subject during P1093. An emergent R263R/K was detected alone at the virologic failure visit in this subject. The subject remained on DTG-containing regimen for another 2 years with uncontrolled HIV-1 RNA viremia. Subsequent resistance results from this subject noted presence of additional INSTI resistance-associated mutations. Please refer to the clinical virology review by Dr. Lisa Naeger for further details. No changes to the microbiology section of the label were proposed.

4.3 Preclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology studies were submitted with the current sNDA. Please refer to the original NDA review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dolutegravir is an integrase strand transfer inhibitor (INSTI). It is a potent, low nanomolar inhibitor of HIV-1 integrase enzyme by binding to integrase active sites and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration. Viral integration is an essential step in HIV-1 replication.

4.4.2 Pharmacokinetics

Intensive and sparse pharmacokinetic samples were collected from adolescents ages 12 to <18 years (Cohort I) and children ages 6 to <12 years (Cohort IIA) during P1093. The intensive pharmacokinetic data was provided from all 10 subjects enrolled in Cohort I Stage 1 and all 11 subjects enrolled in Cohort IIA Stage 1. Sparse pharmacokinetic data was provided for all 23 subjects in Cohort I but only for 13 of the 23 subjects in Cohort IIA. The DTG exposures (AUC_{24} and C_{24h}) in pediatric patients) weighing ≥30 kg were comparable to those observed in adults. (b) (4)

See Section 6.1.4 for intensive pharmacokinetic results during P1093. Please refer to Clinical Pharmacology review by Dr. Su-Young Choi for complete details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

One Phase I/II study was included in this submission and described in Table 5.1-1. The current submission provided the full Week 48 and Week 24 clinical study reports for Cohort I (≥12 to <18 years old) and Cohort IIA (≥6 to <12 years old), respectively.

Table 5.1-1: Listing of Clinical Trials Relevant to this NDA

Study Identify	Primary Objectives	Study Design	Treatment Details (Dosage Regime; Route; Duration)	Treatment Groups	#Enrolled	#Treated	No. of Subjects with ≥24 week data	No. of Subjects with ≥48 week data
NG112578 P1093)	To select a DTG dose for chronic dosing in infants, children, and adolescents that achieves similar exposures to the DTG adult dose and to evaluate safety, tolerability, and steady-state PK of DTG in combination with OBT	Phase 1/2, multicenter, open-label, non-comparative, intensive PK and safety study Enrolling HIV-1 infected pediatric patients ≥4 weeks to <18 years old	DTG ~1mg/kg once daily across 4 weight bands, maximum dose 50 mg[a]; oral, tablets (10mg, 25mg, 50mg); 48 weeks	*Cohort I:* Adolescents ≥12 to <18 years old *Cohort IIA:* Children ≥6 to <12 years old	*Cohort I*: 23 Stage 1 [n=10] Stage 2 [n=13] *Cohort IIA*: 23 Stage 1 [n=11] Stage 2 [n=12]	*Cohort I*: 23 50mg QD [n=19] 35mg QD [n=4] *Cohort IIA*: 23 50mg QD [n=5] 35mg QD [n=6] 35mg BID [n=1] 25mg QD	*Cohort I:* 23 *Cohort* IIA: 22	*Cohort I:* 21 *Cohort IIA:* 16

						[n=8] 20mg QD [n=3]		

[a] Weight-based DTG dosing assignments were as follows: 50 mg QD if weight ≥40 kg, 35 mg QD if weight 30 to <40 kg, 25 mg QD if weight 20 to <30 kg, and 20 mg QD if weight 15 to <20 kg. It was recommended that the dose of DTG be increased to twice daily if certain UGT1A or CYP3A inducers were coadministered (i.e., rifampin, efavirenz, ritonavir boosted fosamprenavir, or ritonavir boosted tipranavir)

Source: Adapted from clinical study report for P1093.

5.2 Review Strategy

The submitted clinical protocol, study report, and relevant literature were reviewed. The conclusions presented by the applicant were independently corroborated through analyses conducted by the FDA. This reviewer evaluated the trial design, subject demographics, baseline characteristics, subject disposition as well as efficacy and safety data using J-Review®, a statistical analysis software package.

5.3 Discussion of Individual Studies/Clinical Trials

ING112578 (P1093) is the pivotal trial submitted to support approval of DTG for the treatment of HIV-infection in pediatric patients ≥6 years to <18 years of age, and weighing at least 15 kg. P1093 consists of PK, safety, and antiviral response data for DTG in combination with optimized background therapy (OBT). DTG currently has a pediatric indication for patients ≥12 years old and weighing at least 40 kg. Previously submitted Week 24 data from adolescent aged ≥12 to <18 years old was the basis for approval of the existing pediatric indication. This submission provides Week 48 data from adolescents aged 12 to <18 years (Cohort I) and Week 24 data from children aged 6 to <12 years (Cohort IIA).

ING112578 (P1093) is an ongoing Phase 1/2, multi-center, open-label, non-comparative study of DTG use in pediatric subjects. Subjects were enrolled at 17 sites consisting of 14 located in the USA, 2 located in Thailand, and 1 located in South Africa.

The primary objectives of the study included the following for HIV-1 infected infants, children, and adolescents: (1) determine optimal pediatric DTG doses that achieve similar exposure (AUC_{24} and C_{24h}) to the 50 mg QD adult dose, and (2) evaluate safety, tolerability, and steady-state PK of DTG in various pediatric age groups who are ART-experienced, INSTI-naïve. Key secondary objectives for HIV-1 infected infants, children, and adolescents were to evaluate antiviral activity of DTG in combination with OBT at 24 and 48 weeks, and to evaluate the effect on immunologic response from Baseline to 24 and 48 weeks.

Key inclusion criteria were enrollment of HIV-1 infected pediatric subjects ages ≥4 weeks to <18 years old who were ART-experienced, INSTI-naïve. Subjects were required to have an HIV-1 RNA >1000 copies/mL at screening and their planned OBT had to include at least one fully active drug. Study entry criteria also required that subjects be off ART for ≥4 weeks or be on an unchanged, failing ART regimen within 8 to 12 weeks prior to screening. Subjects who received ART to interrupt maternal-infant transmission were considered ART-experienced and eligible for enrollment.

Key exclusion criteria included known resistance to an INSTI, an active AIDS-defining opportunistic infection, known lab toxicities ≥Grade 3 in severity, evidence of

pancreatitis, liver toxicity, known exposure to an INSTI, or any ART-naïve subject. In order to limit PK variability, the use of atazanavir, atazanavir/ritonavir, neviripine, efavirenz, fosamprenavir, fosamprenavir/ritonavir, tipranavir, or tipravnir/ritonavir were not allowed prior to initial intensive PK evaluation but could be added afterward as part of OBT.

The initial weight-based DTG dose was ~1 mg/kg once daily across 4 weight bands, with a maximum daily dose of 50 mg. The initial dosing was selected based upon a comparable dose of 50 mg once daily approved for HIV-1 infected adults. Table 5.3-1 summarizes the initial weight-based dosages administered. It was recommended that the dose of DTG be increased to twice-daily administration if subjects received concomitant rifampin, efavirenz, fosamprenavir/ritonavir, or tipranavir/ritonavir after the intensive PK evaluation.

Table 5.3-1:
Initial Weight-Based DTG Dosages

Weight band	Dose
≥40 kg	50 mg
30 - <40 kg	35 mg
20 - <30 kg	25 mg
15 - <20 kg	20 mg

Source: Adapted from clinical study report for P1093.

P1093 included six age and formulation based cohorts. Enrollment occurred sequentially from oldest to youngest age-group. All subjects in Cohorts I and IIA received DTG tablet formulations (10 mg, 25 mg, and 50 mg strengths) and are the focus of the current pediatric submission. The study is ongoing and subjects in Cohorts IIB through V are expected to receive the pediatric formulation (oral granules for suspension).The six cohorts in P1093 were as follows:

- Cohort I: Adolescents ≥12 to <18 years old (tablet formulation)
- Cohort IIA: Children ≥6 to <12 years old (tablet formulation)
- Cohort IIB: Children ≥6 to <12 years old (oral granules for suspension)
- Cohort III: Children ≥2 to <6 years old (oral granules for suspension)
- Cohort IV: Children ≥6 months to <2 years old (oral granules for suspension)
- Cohort V: Infants ≥4 weeks to <6 months old (oral granules for suspension)

Subjects in each Cohort were enrolled into one of two sequential stages and remained in that stage for the duration of the study. Subjects in Stage 1 had OBT stated immediately after intensive PK samples were collected (between Day 5-10). The purpose of this stage was to collect intensive PK and short-term safety data in order to select a final DTG dose for further study in Stage 2. Intensive PK samples were not collected during Stage 2 as these subjects had OBT and DTG started on the same day (Day 1). The purpose of Stage 2 was to assess long term safety and efficacy (antiviral

activity) of DTG in combination with OBT over a 24 week and 48 week period. Subjects in Stage 1 who were treated exclusively at the final selected DTG dose were also evaluated for long term safety and efficacy for a minimum of 48 weeks.

Enrollment began in the oldest Cohort (i.e., Cohort I, Stage 1) and progressed to the next oldest cohort (i.e., Cohort IIA, Stage 1) if preliminary intensive PK and 4 week safety requirements were met in the preceding Cohort's initial 4 subjects. Additional subjects were enrolled into Stage 2 if the PK and safety criteria were met in the particular Cohort's full Stage 1 group. Table 5.3-2 summarizes the pre-defined pharmacokinetic targets related to the final dose selection for Stage 2. The intensive PK targets were selected based on exposures achieved in adults with the 50 mg QD dose. The safety criteria related to final dose selection included the following: no life-threatening suspected adverse drug reaction (SADR), no Grade 4 event considered probably or definitely attributable to DTG, and no more than 25% of subjects terminated from study drug due to a Grade 3 or higher SADR.

Table 5.3-2:
Protocol-Defined Pharmacokinetic Targets
After Intensive Sampling

	AUC_{24} (µg*h/mL)	**C_{24h} (ng/mL)**
Targets:	46	960
Target Range	37-67	770-2260
Max Lower Limit	25	500
Max Upper Limit	92	-

Source: Adapted from clinical study report for P1093.

The following PK parameters were assessed in P1093: area under the drug plasma concentration profile over time of 24-hour dosing interval (AUC_{24}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), plasma concentration at the end of the 24-hour dosing interval (C_{24h}), plasma concentration observed immediately prior to dosing of 24-hour interval (C_{0h}), minimum plasma concentration (C_{min}), apparent clearance following dosing (CL/F), volume of distribution (V/F), and terminal half-life ($t_{1/2}$). The primary PK endpoint was AUC_{24} and the secondary PK endpoint was C_{24h}. Subjects in Stage 1 had intensive PK samples collected over a single day (between Days 5-10) and at the following time points: pre-dose, 1, 2, 3, 4, 6, 8, and 24 hours after a witnessed dose. Population PK samples were collected from all enrolled subjects (Stage 1 or Stage 2) at Weeks 4, 12, and 24.

Safety assessments for all subjects included monitoring all adverse events (AEs), serious adverse events (SAEs), and laboratory parameters including hematology, fasting lipid profile, and blood chemistry. The primary safety endpoint was toxicity through Week 24 and the secondary safety endpoint was toxicity through ≥Week 48. Toxicity included all clinical/laboratory toxicities ≥Grade 3 severity, termination from treatment due to a suspected adverse drug reaction (SADR), and Death.

Key secondary efficacy assessments included evaluation of virologic outcomes based on HIV-1 RNA values at Week 24 and Week 48. Stage 1 subjects from a particular Cohort were included in the efficacy analyses if treated exclusively at the final dose selected for the Cohort. Virologic outcomes at Week 24 and Week 48 were calculated according to the FDA's Snapshot algorithm or the Missing, Switch or Discontinuation = Failure (MSDF) algorithm.

Cohorts I and IIA each consisted of 23 subjects. Cohort I consisted of 10 subjects in Stage 1 and 13 subjects in Stage 2. Cohort IIA consisted of 11 subjects in Stage 1 and 12 subjects in Stage 2. 7 investigators in the US and 1 investigator in Thailand enrolled all subjects in Cohort I; while, 11 investigators in the US, 2 investigators in Thailand, and 1 investigator in South Africa enrolled all subjects in Cohort IIA. The investigators in the US enrolled 20 subjects (87%) and 16 subjects (70%) into Cohort I and Cohort IIA, respectively. The intensive PK and short- term safety targets were met in the full Stage 1 group; thus, the final DTG dose selected for Stage 2 was the same as initially selected for Stage 1. The final weight-based dosing assignments are summarized in Table 5.3-3 by Cohort and Stage.

Table 5.3-3:
Final Weight-Based DTG Dosing Assignments by Cohort and Stage

Final Weight-based DTG dosages		Cohort I			Cohort IIA			Cohorts I and IIA		
Initial Weight	DTG Dose	Stage 1 N=10 n (%)	Stage 2 N=13 n (%)	Total N=23 n (%)	Stage 1 N=11 n (%)	Stage 2 N=12 n (%)	Total N=23 n (%)	Stage 1 N=21 n (%)	Stage 2 N=25 n (%)	Total N=46 n (%)
≥40 kg	50 mg QD	9 (90)	10 (77)	19 (83)	5 (45)	-	5 (22)	14 (67)	10 (40)	24 (52)
30 to <40 kg	35 mg QD	1 (10)	3 (23)	4 (17)	2 (18)	4 (33)	6 (26)	3 (14)	7 (28)	10 (22)
	35 mg BID	-	-	-	-	1 (8)	1 (4)	-	1 (4)	1 (2)
20 to <30 kg	25 mg QD	-	-	-	4 (36)	4 (33)	8 (35)	4 (19)	4 (16)	8 (17)
15 to <20 kg	20 mg QD	-	-	-	-	3 (25)	3 (13)	-	3 (12)	3 (7)

Source: Adapted from clinical study report for P1093; Clinical reviewer's calculations.

All 46 subjects in Cohort I and Cohort IIA were treated exclusively at the final selected dose (~1 mg/kg once daily across 4 weight bands, and maximum dose of 50 mg). 1 subject from Cohort IIA Stage 2 was administered DTG twice-daily because of concomitant use of efavirenz as part of their OBT. There were 3 subjects in Cohort I (Stage 1, n = 2; Stage 2, n = 1) and 1 subject in Cohort IIA (Stage 1, n = 1) who also

received efavirenz as part of their OBT; however, these subjects did not have their weight-based DTG dose increased to twice-daily.

6 Review of Efficacy

Efficacy Summary

ING112578 (P1093) is an ongoing Phase 1/2, multi-center, open-label, non-comparative study to determine the appropriate dose (and formulations) of DTG for use in pediatric subjects with HIV-1 infection. The goal of the study is to determine pediatric dose(s) that approximates adult exposure (AUC_{24} and C_{24h}) observed at the 50 mg QD dose. The primary and secondary PK endpoints were AUC_{24} and C_{24h}, respectively. Though not a true efficacy study because of the single arm design, extrapolation of efficacy for antiretroviral drugs such as DTG can be made based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). The P1093 trial therefore relies on the pharmacokinetic data to extrapolate efficacy and the clinical efficacy (antiviral activity) data, when available, is presented as supportive data.

Subjects in P1093 were sequentially enrolled into six age and formulation based cohorts, and each cohort consisted of two stages. The subjects enrolled into Stage 1 had intensive PK sampling of DTG administered prior to starting optimized background therapy and the subjects enrolled into either Stage 1 or Stage 2 had sparse PK sampling of DTG administered in combination with OBT. The focus of the current pediatric submission is Week 48 results from Cohort I (adolescents ≥12 to <18 years old) and Week 24 results from Cohort IIA (children ≥6 to <12 years old). Both Cohorts were given the tablet formulation of DTG (10-mg, 25-mg, and 50-mg tablets).

Twenty-three subjects were enrolled into each Cohort. All subjects (Stage 1 and 2) received the same weight-based DTG dose of ~1 mg/kg QD across four weight bands because intensive PK targets (AUC_{24} and C_{24h}) were met during the dose-finding period for each Cohort (full Stage 1 groups). Children weighing ≥30 kg administered the proposed DTG dose of ~1 mg/kg QD achieved exposures within the pre-defined target exposure range; however, lower exposures were observed in the subset of children weighing <30 kg in Cohort IIA.

Based on FDA's snapshot analysis, at Week 24, the proportion of subjects with HIV-1 RNA <50 copies/mL in Cohort I and Cohort IIA were 65% (15/23) and 61% (14/23), respectively. Across both cohorts, the Week 24 efficacy outcome was achieved in 71% (17/24) of subjects in the ≥40 kg weight-band and 55% (6/11) of subjects in the 30 to <40 kg weight-band. At Week 48, the proportion of subjects from Cohort I with HIV-1 RNA <50 copies/mL was 61% (14/23). The majority of subjects in the adolescent cohort

weighed ≥40 kg (19 of 23) and of the 19, 63% were virologically suppressed at Week 48. The CD4 count increased over the 48 week period available from Cohort I and over the 24 week period available from Cohort IIA. The small sample sizes in each Cohort and weight-band may confound findings from the sub-group analysis.

6.1 Indication

DTG is currently indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adult and children aged 12 years and older, and weighing at least 40 kg. The applicant seeks to extend the indication to include dosing information for (b) (4)

6.1.1 Methods

Analysis focused on the steady-state PK analysis in children 6 to <12 years old. The PK data was relied upon to extrapolate efficacy and the clinical efficacy (antiviral activity) data was presented as supportive data. Intensive PK data was collected during Stage 1 and the goal was to determine the pediatric dose with comparable exposures to the 50 mg QD adult dose. AUC_{24} was the primary PK endpoint and C_{24h} was the secondary PK endpoint. Please see Section 5.3 (Table 5.3-2) for the pre-defined pharmacokinetic targets related to final dose selection.

Key secondary efficacy endpoints:
1) HIV-1 RNA <50 copies/mL at Week 24 and Week 48
2) HIV-1 RNA <400 copies/mL at Week 24 and Week 48

Virologic outcomes were based on the measured HIV-1 RNA (c/mL) at Week 24 and Week 48. Suspected Virologic failures were confirmed by repeat HIV-1 RNA measurement at ≥ 1 week to ≤ 4 weeks after the initial measurement.

Virologic failure was defined as occurrence of any of the following:
- confirmed decrease in plasma HIV-1 RNA of <1.0 log_{10} c/mL at or after Week 12 and accompanied with HIV-1 RNA ≥400 c/mL
- confirmed HIV-1 RNA >400 c/mL starting at Week 24 or beyond

Virologic failures also included subjects that had ≥1 new ARV(s) added to their OBT before the time points of interest (Week 24 or Week 48). Subjects with missing HIV-1 RNA data at Week 24 (Day 127 to 210) or at Week 48 (Day 295 to 378) were not classified as Virologic successes. Depending on the reason for the missing data, these subjects were classified as either No Virologic Data or Virologic failures. The former group, No Virologic Data, consisted of subjects who were off the study drug due to an adverse event (AE) or for other reasons while virologically suppressed. The subjects

who were off the study drug for other reasons while not virologically suppressed were classified as Virologic failures.

Immunologic parameters (CD4 counts and percent), genotypic and phenotypic measures of resistance at baseline and at virologic failure, and disease progression measured by change in CDC category were additional efficacy evaluations. Additional information related to the study design for P1093 can be found in Section 5.3.1.

6.1.2 Demographics

Table 6.1.2-1 summarizes the demographic characteristics for Cohort I and Cohort IIA. A total of 24 subjects were enrolled into each Cohort. Cohort I consisted of 5 males (22%) and 18 females (78%). There were 16 males (70%) and 7 females (30%) in Cohort IIA. The mean ages were 14.8 years (range 12.2 to 17.8 years) and 9.4 years (range 6.2 to 11.9 years) for Cohort I and Cohort IIA, respectively. Subjects weighing ≥30 kg accounted for 100% and 52.2% of the total population in Cohort I and Cohort IIA, respectively.

Table 6.1.2-1: Demographics

Demographics	Cohort I N=23	Cohort IIA N=23	Cohorts I and IIA N=46
Sex, n (%)			
Male	5 (22)	16 (70)	21 (46)
Female	18 (78)	7 (30)	25 (54)
Age (years)			
Mean (SD)	14.8 (1.9)	9.4 (2.0)	12.1 (3.3)
Median	15.2	10.2	12.0
Min, max	12.2, 17.8	6.2, 11.9	6.2, 17.8
Weight (kg)			
Mean (SD)	55.1 (15.6)	30.1 (10.4)	42.6 (18.2)
Median	52.2	30.0	40.0
Min, max	33.0, 91.0	17.6, 53.5	17.6, 91.0
Weight Bands, n (%)			
≥40 kg	19 (83)	5 (22)	24 (52)
30 - <40 kg	4 (17)	7 (30)	11 (24)
20 - <30 kg	0	8 (35)	8 (17)
15 - <20 kg	0	3 (13)	3 (7)
Ethnicity, n (%)			
Hispanic or Latino	6 (26)	6 (26)	12 (26)
Not Hispanic/Latino	17 (74)	13 (57)	30 (65)
Unknown	0	4 (17)	4 (9)
Race, n (%)			
Black or African American	12 (52)	12 (52)	24 (52)
White	8 (35)	4 (17)	12 (26)
Asian	3 (13)	3 (13)	6 (13)

Other[a]	0	4 (17)	4 (9)

[a] Other includes the following races: Native Hawaiian/other Pacific Islander, More than one race, or Unknown.
Source: Adapted from clinical study report for P1093, Tables 7 and 8; Clinical reviewer's calculations.

As summarized in Table 6.1.2-1, Cohort I had a greater proportion of females and Cohort IIA had a greater proportion of males enrolled. Demographic characteristics were well-balanced across ethnicity and race.

Baseline Characteristics
Table 6.1.2-2 summarizes the baseline characteristics for subjects in each Cohort. The proportion of subjects with a Baseline HIV-1 RNA of ≤100,000 copies/mL was 91% (21/23) for Cohort I and 52% (12/23) for Cohort IIA. 48% (11/23) of the subjects in Cohort I and 74% (17/23) of the subjects in Cohort IIA had a baseline CD4 count ≥500 cells/mm^3. At Baseline, there were 9 subjects (39%) in Cohort I and 6 subjects (26%) in Cohort IIA who were classified as CDC Category C or HIV Stage 3.

Table 6.1.2-2:
Baseline Characteristics by Cohort

	Cohort I N=23	**Cohort IIA N=23**	**Cohorts I and IIA N=46**
Baseline HIV-1 RNA (copies/mL) Mean (SD) Median Range	40,206 (59,167) 17,996 1,168-243,765	653,074 (2,067,120) 96,892 890-10,000,000	346,640 (1,478,755) 38,258 890-10,000,000
Baseline HIV-1 RNA, n (%) ≤5,000 >5,000 - ≤50,000 >50,000 – ≤100,000 >100,000	 2 (9) 17 (74) 2 (9) 2 (9)	 4 (17) 5 (22) 3 (13) 11 (48)	 6 (13) 22 (48) 5 (11) 13 (28)
Baseline CD4 count (cells/mm^3) Mean (SD) Median Range	527 (285) 466 11-1,025	621 (376) 645 9-1,700	574 (333) 639 9-1,700
Baseline CD4 Count, n (%) <200 200 - <500 ≥500	 2 (9) 10 (43) 11 (48)	 4 (17) 2 (9) 17 (74)	 6 (13) 12 (26) 28 (61)
CDC Category C or HIV Stage 3, n (%)	9 (39)	6 (26)	15 (33)

Source: Adapted from clinical study report for P1093, Tables 7 and 8; Clinical reviewer's calculations.

The mean/median HIV-1 RNA and CD4 counts were greater in Cohort IIA compared to Cohort I; while, Cohort I had a greater proportion of subjects classified as CDC Category C or HIV Stage 3. Overall, most of the subjects enrolled into Cohort I and Cohort IIA had a baseline HIV-1 RNA ≤100,000 copies/mL, had a baseline CD4 count ≥500, and were not CDC Category C or HIV Stage 3.

Historical ARV Use

All of the HIV-1 infected subjects in P1093 were treatment-experienced, INSTI naïve. Table 6.1.2-2 summarizes the prior ARVs used by the subjects enrolled into each Cohort.

Table 6.1.2-3: Historical ARV Use

Prior ARV use	Cohort I N=23 n (%)	Cohort IIA N=23 n (%)	Cohorts I and IIA N=46 n (%)
Prior NRTI use	23 (100)	18 (78)	41 (89)
Prior NNRTI use	12 (52)	11 (48)	23 (50)
Prior PI use	18 (78)	14 (61)	32 (70)
Prior T-20 use	1 (4)	0	1 (2)
Prior CCR5 use	1 (4)	0	1 (2)

Source: Adapted from clinical study report for P1093, Tables 10 and 12.

Most of the subjects in Cohort I and Cohort IIA had history of NRTI use prior to enrollment. None had prior INSTI use.

6.1.3 Subject Disposition

10 subjects (43%) in Cohort I and 19 subjects (83%) in Cohort IIA remain on the study drug at the time of this submission. The most frequent reason for discontinuation was "unable to attend clinic visits" and this reason was noted for 13% of the subjects across Cohorts I and IIA. Table 6.1.3-1 summarizes the subject disposition for each Cohort in P1093.

Table 6.1.3-1: Subject Disposition by Cohort (All Available Data as of February 14, 2015)

Population	Cohort I N=23 n (%)	Cohort IIA N=23 n (%)	Cohorts I and IIA N=46 n (%)
Ongoing at time of report	10 (43)	19 (83)	29 (63)
Completed Week 24	23 (100)	22 (96)	45 (98)

Completed Week 48	21 (91)	16 (70)	37 (80)
Off Study Drug	13 (57)	4 (17)	17 (37)
Unable to attend clinic visits	5 (22)	1 (4)	6 (13)
Non-adherent	4 (17)	1 (4)	5 (11)
Lost to Follow-up	1 (4)	1 (4)	2 (4)
Completed Treatment	1 (4)	0	1 (2)
Protocol Defined Clinical Event[a]	0	1 (4)	1 (2)
Pregnancy	1 (4)	0	1 (2)
Other[d]	1 (4)	0	1 (2)

[a] Protocol defined Clinical Event in this case is virologic failure
[b] Other defined as family moved out of state, subject withdrew consent
Source: Adapted from clinical study report for P1093, Table 3.

Two subjects in Cohort I discontinued the study drug prior to the Week 48 Visit and one subject in Cohort IIA discontinued the study drug prior to the Week 24 Visit. The two subjects in Cohort I both withdrew at Week 40 because of non-adherence to treatment. The one subject in Cohort IIA withdrew at Week 12 because they were lost to follow up.

6.1.4 Analysis of Primary Endpoint(s)

Intensive Pharmacokinetic Results
The geometric mean AUC_{24} and C_{24h} from the subjects with intensive PK sampling are summarized in Table 6.1.4-1 by Cohort. The geometric mean AUC_{24} (primary PK endpoint) was 46.0 µg*h/mL (%CV 43.1) and 50.5 µg*h/mL (%CV 63.9) for Cohort I Stage 1 and for Cohort IIA Stage 1, respectively. The geometric mean C_{24h} (secondary PK endpoint) was 902.2 ng/mL (%CV 58.6) and 926.1 ng/mL (%CV 89.3) for Cohort I Stage 1 and for Cohort IIA Stage 1, respectively.

The pharmacokinetic results were also evaluated based on weight, given the proposed dosing is relying on weight-bands. Only 4 subjects weighing <30 kg had intensive PK data collected. All 4 subjects were from Cohort IIA Stage 1, weighed 20 to <30 kg, and received the 25 mg once daily dose of DTG. These subjects had a geometric mean AUC_{24} and C_{24h} of 34.1 µg*h/mL (%CV 45.9) and 515.3 ng/mL (%CV 43.7), respectively. This submission did not contain intensive PK data from subjects weighing 15 to <20 kg or given the 20 mg once daily dose of DTG.

Table 6.1.4-1: Intensive Pharmacokinetic Results

	N	Mean Age (range)	Mean Weight (range)	Mean Dose mg/kg (range)	Geometric Mean AUC_{24} µg*h/mL (%CV)	Geometric Mean C_{24h} ng/mL (%CV)
Cohort						
I	10	14.6 yr (12.2 – 17.8)	57.3 kg (37.7 – 91.0)	0.9 (0.5 – 1.1)	46.0 (43.1%)	902.2 (58.6%)
IIA	11	9.9 yr	34.9 kg	1.1	50.5	926.1

		(6.7 – 11.9)	(21.4 – 53.5)	(0.9 – 1.3)	(63.9%)	(89.3%)
Weight Band						
≥40 Kg	14	13.5 yr (10.4 – 17.8)	54.7 kg (39.7 – 91.0)	1.0 (0.5 – 1.3)	50.1 (51.8%)	994.5 (64.7%)
30 - <40 kg	3	11.4 yr (10.2 – 12.2)	34.3 kg (32.4 – 37.7)	1.0 (0.9 – 1.1)	64.6 (63.7%)	1329.6 (92.3%)
20 - <30 kg	4	8.0 yr (6.7 – 9.3)	22.2 kg (21.4 – 24.5)	1.1 (1.0 – 1.2)	34.1 (45.9%)	515.3 (43.7%)

Source: Adapted from clinical study report for P1093; Clinical reviewer's calculations.

The intensive pharmacokinetic data from this submission is sufficient to support DTG dosing (~1 mg/kg QD) for pediatric patients weighing at least 30 kg. As summarized in Table 6.1.4-1, the AUC_{24} and C_{24h} from subjects with intensive PK sampling in Cohort I Stage 1 and Cohort IIA Stage 1 were within the pre-defined target ranges for both PK parameters (target range 37 - 67 µg*h/mL for AUC_{24} and target range 770 – 2260 ng/mL for C_{24h}). In contrast, there is insufficient data to support DTG dosing for pediatric patients weighing less than 30 kg. Lower exposures were noted among the 4 subjects weighing <30 kg, and the geometric mean AUC_{24} and C_{24h} in these subjects were below the pre-defined target ranges. Please see the Clinical Pharmacology review by Dr. Su-Young Choi for complete details.

6.1.5 Analysis of Secondary Endpoints(s)

Efficacy Analysis at Week 24

Table 6.1.5-1 summarizes the results from the applicant's efficacy analysis of virologic outcomes at Week 24. Results are summarized by Cohort. The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 was 65% (15/23) for Cohort I and 61% (14/23) for Cohort IIA. The proportion of subjects with HIV-1 RNA <400 copies/mL at Week 24 was 78% (18/23) in each Cohort. No subject discontinued for lack of efficacy through Week 24; however, 1 subject in Cohort IIA discontinued at Week 12 for other reasons (lost to follow up) while HIV-1 RNA was ≥50 c/mL. There were no subjects in Cohorts I or IIA with missing data. Compared to Cohort IIA, Cohort I had one additional subject classified as a Virologic success (HIV-1 RNA <50 c/mL) at Week 24. Overall, there were similar proportions of Virologic successes at Week 24 in each Cohort.

Table 6.1.5-1: Virologic Outcomes at Week 24 (Snapshot Algorithm)

Virologic Parameter at Week 24	**Cohort I N=23 n (%)**	**Cohort IIA N=23 n (%)**	**Cohorts I and IIA N=46 n (%)**
Virologic success (HIV-1 RNA <50 c/mL)	15 (65)	14 (61)	29 (63)
Virologic failure (HIV-1 RNA ≥50 c/mL)	8 (35)	9 (39)	17 (37)
Data in window not <50 c/mL	8 (35)	8 (35)	16 (35)
Discontinued for other reasons while not <50 c/mL	0	1 (4)	1 (2)

Source: Adapted from clinical study report for P1093, Table 73;

Clinical reviewer's calculations.

Virologic Success at Week 24 by Baseline Category

The proportion of subjects in each Cohort with virologic success (HIV-1 RNA <50 c/mL) at Week 24 is summarized in Table 6.1.5-2 by baseline category. Among subjects with a baseline HIV-1 RNA ≤100,000 c/mL, the proportion of subjects with virologic success at Week 24 was 71% (15/21) in Cohort I and 83% (10/12) in Cohort IIA. For subjects with a baseline HIV-1 RNA >100,000 c/mL, virologic success at Week 24 was noted in 0% (0/2) of subjects in Cohort I and 36% (4/11) of subjects in Cohort IIA. Across both Cohorts, 66% (23/35) of the subjects weighing ≥30 kg were virologic successes; while, 55% (6/11) of the subjects weighing <30 kg were virologic successes.

In each Cohort, the proportion of subjects with virologic success (HIV-1 RNA <50 c/mL) at Week 24 was greater among subjects with a baseline HIV-1 RNA ≤100,000 c/mL compared to those who had a baseline HIV-1 RNA >100,000 c/mL. Across both Cohorts, a greater proportion of virologic successes were noted in subjects weighing 30 to ≥40 kg compared to those weighing 15 to <30 kg. The small sample size of subjects with a baseline HIV-1 RNA >100,000 c/mL or subjects weighing 15 to <30 kg may confound results.

Table 6.1.5-2:
Proportion (%) With HIV-1 RNA <50 c/mL at Week 24 by Baseline Category

Baseline Category	Cohort I N=23	Cohort IIA N=23	Cohorts I and IIA N=46
Baseline HIV-1 RNA			
≤100,000 c/mL	71% (15/21)	83% (10/12)	76% (25/33)
>100,000 c/mL	0 (0/2)	36% (4/11)	31% (4/13)
Weight Band			
≥40 kg	68% (13/19)	80% (4/5)	71% (17/24)
30 - <40 kg	50% (2/4)	57% (4/7)	55% (6/11)
20 - <30 kg	(b) (4)		
15 - <20 kg			

Source: Adapted from clinical study report for P1093; Clinical reviewer's calculations.

Efficacy Analysis at Week 48

Table 6.1.5-3 summarizes the results from the applicant's efficacy analysis of virologic outcomes at Week 48 for Cohort I. The proportion of subjects in Cohort I with HIV-1 RNA <50 and <400 copies/mL at Week 48 were 61% (14/23) and 74% (17/23), respectively. None of the subjects in Cohorts I discontinued for lack of efficacy through Week 48; however, 2 subjects at Week 40 discontinued for other reasons (non-adherence to treatment) while HIV-1 RNA was ≥50 c/mL. There were no subjects in Cohort I with missing data in the Week 48 window due.

After Week 24, one subject from Cohort I was no longer categorized a virologic success (HIV-1 RNA <50 c/mL) at Week 48. Overall, similar proportions of subjects with virologic success were noted at Week 24 and Week 48 in Cohort I.

Table 6.1.5-3: Virologic Outcomes at Week 48 (Snapshot Algorithm)

Virologic Parameter at Week 48	Cohort I N=23 n (%)
Virologic success (HIV-1 RNA <50 c/mL)	14 (61)
Virologic failure (HIV-1 RNA ≥50 c/mL)	9 (39)
Data in window not <50 c/mL	7 (30)
Discontinued for other reasons while not <50 c/mL	2 (9)

Source: Adapted from clinical study report for P1093, Table 74
Clinical reviewer's calculations.

Virologic Success at Week 48 by Baseline Category

The proportion of subjects in Cohort I with virologic success (HIV-1 RNA <50 c/mL) at Week 48 is summarized in Table 6.1.5-4 by baseline category. Among subjects in Cohort I with a baseline HIV-1 RNA ≤100,000 c/mL, the proportion of subjects with virologic success at Week 48 was 67% (14/21). Neither of the 2 subjects in Cohort I with a baseline HIV-1 RNA >100,000 c/mL were classified a virologic success at Week 48. In addition, 63% (12/19) of the subjects weighing ≥40 kg and 50% (2/4) of the subjects weighing 30 to <40 kg achieved virologic suppression at Week 48. None of the subjects in Cohort I weighed <30 kg.

In summary, the proportion of subjects with virologic success (HIV-1 RNA <50 c/mL) at Week 48 was greater among subjects with a baseline HIV-1 RNA ≤100,000 c/mL compared to those who had a baseline HIV-1 RNA >100,000 c/mL. A greater proportion of virologic suppression were also noted among subjects weighing ≥40 kg compared to the subjects weighing 30 to <40 kg. The small sample size of subjects with a baseline HIV-1 RNA >100,000 c/mL or weighing 30 to <40 kg may confound the results.

Table 6.1.5-4:
Proportion (%) With HIV-1 RNA <50 c/mL at Week 48
by Baseline Category

Baseline Category	Cohort I N=23
Baseline HIV-1 RNA	
≤100,000 c/mL	67%(14/21)
>100,000 c/mL	0 (0/2)
Weight Band	
≥40 kg	63%(12/19)
30 - <40 kg	50% (2/4)

Source: Adapted from clinical study report for P1093;

Clinical reviewer's calculations.

6.1.6 Other Endpoints

Immunologic Evaluation:
The change from baseline is also listed at Week 24 for Cohort I and Cohort IIA, and listed at Week 48 for Cohort I. The mean change from baseline in CD4 count for Cohort I was +71 at Week 24 and +79 at Week 48; while, the median change from baseline in CD4 count was +63 at Week 24 and +84 at Week 48. At Week 24, Cohort IIA had a mean and median change from baseline in CD4 count of +213 and +209, respectively. The mean change in CD4 percent at Week 24 was +5% (range -5, +25%) for Cohort I and +9% (range -4, +21%) for Cohort IIA. The median change in CD4 percent at Week 24 was +5% for Cohort I and +8% for Cohort IIA.

A favorable immunological effect was observed through Week 48 in Cohort I and through Week 24 in Cohort IIA. Mean and median changes in CD4 count were positive at Week 24 in each Cohort and positive at Week 48 in Cohort I. The mean and median CD4 counts were greater at Baseline and at Week 24 in Cohort IIA compared to Cohort I. This finding may be due to the younger aged subjects in Cohort IIA as the mean and median changes in CD4 percentage at Week 24 were comparable between the two Cohorts.

Other Evaluations:
Analyses of resistance at baseline and at virologic failure were conducted. Across both Cohorts, one subject from Cohort I had treatment-emergent INSTI resistance (R263R/K mutation) at virologic failure visit (Week 32). Lack of adherence to study treatment was reported during this subject's participation. Other evaluations included analysis of disease progression measured by change in CDC category. At the time of this submission, no new clinical Class C diagnosis or deaths were reported.

6.1.7 Subpopulations

Subgroup analysis of the key secondary efficacy endpoints were conducted for both Cohort I and Cohort IIA. Based on the small sample sizes, no meaningful differences were observed across the following relevant subgroups: sex, race, ethnicity, baseline HIV-1 RNA (copies/mL), and weight band. Please see Section 6.1.5 (Tables 6.1.5-2 and 6.1.5-4) for analysis of key secondary efficacy endpoint by baseline HIV-1 RNA and weight band.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The study was designed to identify the pediatric DTG dose that achieves comparable exposure (AUC_{24} and C_{24h}) as the 50 mg QD adult dose. The applicant suggests the

dose for HIV-1 infected adolescents and children [redacted] (b) (4) be ~1 mg/kg QD, with dosing adjusted by weight bands. The current submission included limited PK data from subjects weighing <30 kg and lower exposures were noted with the doses evaluated in this subset. Please see Table 6.1.8-1 for the FDA's recommended dosing for pediatric patients weighing ≥30 kg.

Table 6.1.8-1:
FDA's Recommended Dose in Pediatric Patients by Body Weight (kg)

Weight range	Dose	Tablets taken
30 - <40 kg	35 mg once daily	One 10 mg tablet AND one 25 mg tablet
≥40 kg	50 mg once daily	One 50 mg tablet

Note: If certain UGT1A or CYP3A inducers are co-administered, then increase the weight-based dose of DTG to twice daily

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The overall treatment effect, as demonstrated by the virologic response and CD4 counts, was persistent to Week 48 in Cohort I. Please see Sections 6.1.5 and 6.1.6 for details.

6.1.10 Additional Efficacy Issues/Analyses

No other analyses were performed.

7 Review of Safety

Safety Summary

One Phase 1/2 trial demonstrated the safety of dolutegravir for the treatment of HIV-1 infection in children ≥6 to <12 years old (Cohort IIA Week 24 safety data) and adolescents ≥12 to <18 years old (Cohort I Week 48 safety data). The majority of treatment emergent adverse events across Cohorts I and IIA were non-serious, mild or moderate in severity, and self-limited. There were no deaths or adverse events leading to withdrawal. Decreased neutrophil count (n = 3) and diarrhea (n = 2) were the only Grade 2 adverse events reported in more than one subject and possibly related to DTG treatment. No serious adverse events or ≥Grade 3 events were considered at least possibly related to DTG treatment. The Grade 3 or 4 laboratory events reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults. Overall, the adverse reaction profile in adolescents and children were similar to that for adults. No new or unexpected toxicities were observed.

7.1 Methods

The Phase 1/2 study, P1093, enrolled HIV-1 infected pediatric subjects who were ART-experienced, INSTI-naïve. Subjects were enrolled into age-defined cohorts sequentially from oldest to youngest. The focus for the current submission is the Week 48 data from Cohort I (adolescents ≥12 to <18 years old) and the Week 24 data from Cohort IIA (≥6 to <12 years old).

All of the subjects enrolled into either Cohort I or Cohort IIA received DTG ~1 mg/kg once daily across 4 weight bands. The dose of DTG was 50 mg once daily for subjects weighing ≥40 kg, the dose 35 mg once daily for subjects weighing 30 to <40 kg, the dose 25 mg once daily for subjects weighing 20 to <30 kg, and the dose 20 mg once daily for subjects weighing 15 to <20 kg. The following safety assessments were performed after treatment on Day 1: adverse events, vital signs, physical examinations, and laboratory evaluations (hematology, chemistries, lipid profiles, urinalysis, urine microalbumin/creatinine ratio, and urine pregnancy tests).

The primary safety endpoint was toxicity through Week 24 and the secondary safety endpoint was toxicity through ≥Week 48. Toxicity included all clinical/laboratory toxicities ≥Grade 3 severity, termination from treatment due to a suspected adverse drug reaction (SADR), and Death. Additional information related to the study design for P1093 can be found in Section 5.3.1.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 7.1.1-1: Summary of Clinical Trials Used to Evaluate Safety

Study Identifier	Study Design	Study Population	Regimen/ Schedule/ Duration	Treatment (N)	Safety assessments
ING112578 (P1093) **Phase 1/2**	Open-label, non-comparative, intensive PK and safety study	HIV-1 infected pediatric patients ≥4 weeks to <18 years and ART-experienced, INSTI-naive	DTG ~1 mg/kg once daily across 4 weight bands, maximum dose 50 mg Follow-up ≥48 weeks	Cohort I (Stage 1 & 2): 23 treated 10 Ongoing Cohort IIA (Stage 1 & 2): 23 treated 19 Ongoing	• Adverse Events • Vital Signs • Physical Exams • Laboratory evaluations[a]

[a] Laboratory evaluations consisted of the following tests: Hematology, Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, LFTs (total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin), Lipid profiles (triglycerides, cholesterol, HDL, and LDL), Urinalysis, Urine microalbumin / creatinine ratio, and Urine pregnancy tests.
Source: Adapted from clinical study report for P1093.

7.1.2 Categorization of Adverse Events

All adverse events were coded using a MedDRA dictionary and received causality assessments from the Investigator. Events were graded by the investigator based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Experience (DAIDS AE Grading Table).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data from across studies other than P1093 was not conducted.

7.2 Adequacy of Safety Assessments

The safety assessments were considered sufficient. DTG is already approved in adults and children ≥12 years of age.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The current submission contains a minimum of 48-Week safety data for 21 subjects (91%) in Cohort I and a minimum of 24-Week safety data for 22 subjects (96%) in Cohort IIA. Two subjects in Cohort I discontinued DTG treatment prior to Week 48, and the reason for withdrawal was non-adherence to treatment in both. One subject in Cohort IIA discontinued DTG treatment prior to Week 24, and the reason for withdrawal was lost to follow up.

All available safety data collected from Cohort I and Cohort IIA through February 14, 2015 is included in the submission. The median extent of exposure to DTG was 1032 days (range 280 to 1355) for Cohort I and 552 days (range 84 to 1226) for Cohort IIA. The mean days of DTG exposure were 924 days for Cohort I and 630 days for Cohort IIA. Table 7.2.1-1 summarizes the duration of exposure to DTG by Cohort.

Table 7.2.1-1: Minimum Duration of Exposure to DTG by Cohort (All Available Data as of February 14, 2015)

Minimum Exposure	Cohort I N=23 n (%)	Cohort IIA N=23 n (%)	Cohorts I and IIA N=46 n (%)
>8 weeks	23 (100)	23 (100)	46 (100)
>12 weeks	23 (100)	22 (96)	45 (98)
>24 weeks	23 (100)	22 (96)	45 (98)
>48 weeks	20 (87)	16 (70)	36 (78)
>96 weeks	18 (78)	10 (43)	28 (61)
>144 weeks	14 (61)	7 (30)	21 (46)

Source: Adapted from clinical study report for P1093, Table 18.

Please see Section 6.1.2 (Tables 6.1.2-1, 6.1.2-2, and 6.1.2-3) for subject demographic information.

7.2.2 Explorations for Dose Response

DTG dosages in P1093 were weight-based. All subjects in Cohort I and Cohort IIA received the tablet formulation (10 mg, 25 mg, and 50 mg tablets) of the drug. The DTG dose of ~1 mg/kg across four weight bands was administered once daily; however, one subject received DTG twice-daily because of concomitant use of efavirenz. The mean weight-based dose was 0.9 mg/kg (range 0.5 – 1.1 mg/kg) and 1.2 mg/kg (range 0.9 - 2.3 mg/kg) for Cohort I and Cohort IIA, respectively. Please see Section 5.3 (Table 5.3-3) for final weight-based dosing assignments by Cohort and Stage.

7.2.3 Special Animal and/or In Vitro Testing

DTG is approved for the treatment of HIV-1 infection in adults and adolescents ≥12 year old and weighing ≥40 kg. No additional animal or *in vitro* testing was therefore conducted for this submission.

7.2.4 Routine Clinical Testing

Routine clinical testing consisted of both clinical and laboratory evaluations. Evaluations occurred at screening, Week 0 (trial entry within 30 days of screening), intensive PK Visit (Day 5-10 for Stage 1), Day 10 (for Stage 2), Weeks 4, 8, 12, 16, 24, 32, 40, and 48. Subjects who discontinued the study early had routine clinical testing at 4 weeks post therapy. After 48 weeks of treatment, subjects who derived benefit from treatment were eligible for long term safety follow up through 3 years and had routine clinical testing every 8 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

Intensive PK assessments were performed on all Stage 1 subjects in Cohort I and Cohort IIA. Sparse PK assessments were performed on all subjects in Cohort I (n=10, Stage 1; n=13, Stage 2) and on 13 subjects in Cohort IIA (n=11, Stage 1; n=2, Stage 2). Please see Clinical Pharmacology review by Dr. Su-Young Choi for full details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profile of DTG was taken into consideration for this submission. The adverse events of special interest included hypersensitivity and rash, psychiatric disorders including suicidality, gastrointestinal disorders, musculoskeletal disorders,

hepatobiliary disorders, and renal disorders. Please see Section 7.3.5 for Submission Specific Primary Safety Concerns.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during P1093.

7.3.2 Nonfatal Serious Adverse Events

Table 7.3.2-1 summarizes all nonfatal serious adverse events reported from Cohort I and Cohort IIA through February 14, 2015. There were 5 subjects from Cohort I and 3 subjects from Cohort IIA who experienced serious clinical events. Cohort I also had 2 subjects with serious laboratory events. Across Cohorts I and IIA, the most common SAE was deep vein thrombosis (4%) and this was reported in 2 subjects from Cohort I. Both events occurred >48 weeks after starting DTG treatment. The other SAEs occurred in no more than one subject (2%) across both Cohorts. None of the SAEs were considered related to DTG treatment, resulted in permanent discontinuation of the study drug, or were responsible for subject withdrawal from the trial.

Table 7.3.2-1:
Nonfatal Serious Adverse Events by Cohort

Preferred Term	Cohort I N=23 n (%)	Cohort IIA N=23 n (%)	Cohorts I and IIA N=46 n (%)
Clinical Serious Adverse Events			
Deep vein thrombosis	2 (9)	0	2 (4)
Abnormal behavior	0	1 (4)	1 (2)
Aggression	0	1 (4)	1 (2)
B-cell lymphoma	1 (4)	0	1 (2)
Depression/Suicide attempt	1 (4)	0	1 (2)
Gastritis/Abdominal pain	1 (4)	0	1 (2)
Herpes simplex/Oral herpes	1 (4)	0	1 (2)
Herpes zoster	1 (4)	0	1 (2)
Lymphadenopathy	1 (4)	0	1 (2)
Pelvic inflammatory disease/Pelvic pain	1 (4)	0	1 (2)
Pneumonia	0	1 (4)	1 (2)
Respiratory distress	0	1 (4)	1 (2)
Laboratory Serious Adverse Events			
Lipase increased	1 (4)	0	1 (2)
Neutrophils decreased	1 (4)	0	1 (2)

Source: Adapted from clinical study report for P1093, Table 35.

Subject 450367 was a 15 year old female enrolled into Cohort I who later experienced Grade 3 deep vein thrombosis at ~108 weeks after starting DTG treatment. This subject had a history of 2 elective orthopedic surgeries within the 3 months leading up to the event. The last orthopedic surgery was performed ~3 weeks prior and both legs remained casted and immobilized at the time deep vein thrombosis was noted. The event resulted in a 1 week hospitalization for anticoagulation therapy and reported as resolved ~9 months later when anticoagulation therapy was discontinued. DTG therapy was continued throughout.

Subject 290163 was a 17 year old female enrolled into Cohort I who later experienced multiple SAEs after starting DTG treatment. After starting the study drug, the subject first experienced Grade 2 herpes simplex infection and then Grade 2 herpes zoster at ~87 weeks and ~103 weeks, respectively. Both events resulted in brief hospitalizations for IV acyclovir and the events resolved. The same subject then experienced Grade 3 lymphadenopathy at ~137 weeks after starting DTG treatment. The subject was afebrile and hospitalized with a 1 day history of an enlarged right inguinal lymph node associated with right leg swelling. Ultrasonography of the right lower extremity was performed and noted findings compatible with a right thigh cellulitis with surrounding mildly prominent lymph nodes. An MRI of lower abdomen and pelvis (without contrast) was also performed and noted a right inguinal mass-like area with surrounding soft tissue cellulitis, mildly enlarged reactive lymph nodes, and a component of myositis involving the right pectineus and right adductor muscles. The hospitalization was for 3 days and the subject underwent a right inguinal lymph node biopsy before being discharged in stable condition. The subject was given a 14 day course of oral doxycycline pending the biopsy results. The pathology from the biopsy later confirmed a diagnosis of large B-cell lymphoma and was reported as Grade 2. The same subject experienced Grade 2 deep vein thrombosis at ~139 week after starting DTG treatment. The subject was hospitalized for 7 days to initiate anticoagulation therapy. The event was reported as resolved 3 months later. DTG treatment was continued throughout all of these events.

Subject 450366 was a 17 year old female enrolled into Cohort I who later experienced Grade 4 depression with suicide attempt at ~119 weeks after starting DTG treatment. This subject was reported to have a long history of mild intermittent situational depression. The case narrative mentions that the subject took themselves to the emergency department and reported taking 6-7 extra antiretroviral pills (DTG 3-4 tablets [50 mg/tablet] and Atripla 3-4 tablets) in a suicide attempt. The subject reported that the suicide attempt occurred that day and was precipitated by an argument with their caregiver. No toxicities were noted and the subject was discharged home. DTG treatment was held after the event and permanently discontinued at the off study visit 5 days later (Week 120 Visit or Day 841). The event was reported as resolved at this visit; however, the subject withdrew from the study because they were no longer able to attend clinic visits (site closed). Of note, the subject was later found to be pregnant a couple of weeks later at a teen clinic. Pregnancy testing had not been performed at the

off study visit on Day 841 and the pregnancy was suspected to have occurred 824 days after starting DTG treatment. Please see Section 7.6.2 for further details.

Subject 8502565 and subject 2010064 were both 15 year old females enrolled into Cohort I who later experienced Grade 3 gastritis with abdominal pain and Grade 3 pelvic inflammatory disease with pelvic pain, respectively. After starting the study drug, gastritis with abdominal pain occurred at ~59 weeks and pelvic inflammatory disease with pelvic pain occurred at ~86 weeks. Both subjects were hospitalized for less than one week, continued DTG treatment throughout, and had their events resolve within 1 month.

Subject 507090 was a 9 year old male enrolled into Cohort IIA who later experienced multiple episodes of Grade 3 abnormal behavior and Grade 3 aggression. The events were responsible for multiple psychiatric hospitalizations starting ~105 weeks after initiating DTG treatment. Of note, the subject had a history of destructive and defiant behavior since age 3-4 years old and a history of ADHD. The case narrative for the subject's initial psychiatric hospitalization lists episodes of physical harm to classmate, sibling, and to dog in the last 1 to 2 years. Six additional psychiatric hospitalizations for worsening behavior and aggression occurred ~114 weeks, ~120 weeks, ~138 weeks, ~148 weeks, ~155 weeks, and ~160 weeks after starting the study drug. Suicidal ideations were noted at the time of his third and fourth hospitalization, but no suicide attempt reported. These hospitalizations took place within approximately 13 months from the first hospitalization. Other stressors were reported during this time period and included peer on peer sexual abuse at school, disclosure of HIV status, and loss of adoptive sibling within the past year. DTG treatment was continued throughout most of these hospitalizations, although there were a few cases where the study drug may have been briefly interrupted. As of 14-Feb-2015, the subject remains on the study drug and continues to display the same behaviors (i.e., running away, breaking things, soiling furniture, stealing money, and threatening to kill sibling).

Subject 450453 was an 11 year old male and subject 820806 was a 7 year old male who were both enrolled into Cohort IIA and later experienced Grade 1 respiratory distress and Grade 3 pneumonia, respectively. Both subjects were briefly hospitalized for approximately 2 days, had DTG treatment continued throughout, and had resolution of their events when discharged. The case of respiratory distress was related to an asthma exacerbation and reported at ~20 weeks after starting DTG treatment. The subject was primarily hospitalized for family education to ensure asthma medication compliance and had normal oxygen saturation on room air when admitted. The case of pneumonia was reported 1 day after starting DTG treatment. The subject was admitted for observation because they had recently been hospitalized for pneumonia and hypersensitivity from dapsone ~1 week prior to starting DTG treatment. A fever without dyspnea or desaturation was noted on admission but no fevers occurred after the one measurement.

Please see Section 7.4.2 for further details regarding the notable laboratory events from P1093. Please see Section 7.7 for further details regarding the serious adverse events reported during the Safety Update Report period.

7.3.3 Dropouts and/or Discontinuations

Please see Section 6.1.3 for information regarding dropouts in P1093.

7.3.4 Significant Adverse Events

Please see Section 7.3.5 for Submission Specific Primary Safety Concerns and Section 7.4.1-1 for Common Adverse Events. No other significant adverse events were identified.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest included rash, psychiatric disorders, gastrointestinal disorders, musculoskeletal disorders, hepatobiliary disorders, and renal disorders. These events are listed in the DTG label and were events of interest in adults during the Phase 3 clinical development program. Hypersensitivity reactions (HSR) and immune reconstitution syndrome (IRIS) are also listed in the DTG label but no cases of HSR or IRIS were reported from Cohorts I or IIA during P1093.

Rash:
Rash was noted in 17 subjects (37%) across both Cohorts during P1093, including 9 cases of rash, 3 cases of rash generalized, 1 case of rash papular, 4 cases of papule, 2 cases of urticaria, 1 case of macule, and 2 cases of skin lesion. There was overlap between cases and some subjects experienced multiple types of rash. 6 cases of skin lesion were reported during P1093, including 1 case of acne, 1 case of cellulitis, 1 case of crusted lesion on neck, 1 case of folliculitis, 1 case of eczema, and 1 case of scalp lesion with rash. This reviewer included only the latter two cases in the pooled rash terms. All rashes were mild or moderate, most were self-limiting, and only one rash of Grade 2 or above considered possibly related to DTG treatment. Subject 690529 from Cohort I was noted to have Grade 2 rash (face and legs) possibly related to DTG treatment and occurring 10 days after starting the study drug. DTG treatment was continued and the event resolved 18 days later. There were no Grade 3 or Grade 4 rashes and no serious skin reactions such as Steven-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme reported in P1093. Similarly, adults administered DTG during the Phase 3 clinical trials reported few serious cases of rash.

Psychiatric Disorders:
There were 7 subjects (15%) across Cohorts I and IIA that experienced psychiatric events during P1093. Among the psychiatric events, depression was the most frequently reported event and included 3 cases of depression and 2 cases of major

depression. There was overlap between cases and some subjects experienced depression and/or major depression. Three of the four subjects with depression had a medical history of depression or other relevant risk factor. The 3 subjects who did not experience depression included flat affect in 1 subject, initial insomnia in 1 subject, and diagnosis of ADHD in 1 subject. No ≥ Grade 2 psychiatric event was considered related to DTG treatment. One subject from each Cohort reported the only Grade 3 or Grade 4 psychiatric events and both were reported as serious psychiatric events. Subject 450366 from Cohort I reported Grade 4 depression and suicide attempt, while subject 507090 from Cohort IIA reported Grade 3 abnormal behavior and aggression. The subject from Cohort I had a long-standing history of mild intermittent situational depression and the subject from Cohort IIA had a history of destructive behaviors since 3 years old. Adults administered DTG during the Phase 3 trials also reported psychiatric disorders including suicide ideation and behaviors. These events also occurred primarily in subjects with pre-existing history of depression or other psychiatric illness. Please see Section 7.3.2 for further details related to the serious psychiatric events in P1093.

Gastrointestinal Disorders:
There were 24 subjects (52%) across Cohorts I and IIA that experienced gastrointestinal events during P1093. Across Cohorts I and IIA, the most frequently reported gastrointestinal events were diarrhea (28%), abdominal pain (20%), vomiting (13%), and nausea (7%). Abdominal pain, diarrhea, nausea, and vomiting were also the four most commonly reported gastrointestinal events reported in the Phase 3 studies in adults. Abdominal pain in P1093 was noted in 9 subjects, including 5 cases of abdominal pain, 3 cases of abdominal pain upper, 1 case abdominal discomfort, 1 case of epigastric discomfort, and 1 case of gastroesophageal reflux disease. There was overlap between cases and some subjects experienced more than one type of abdominal pain. Most episodes were mild or moderate, self-limiting and not considered to be related to DTG treatment. Subject 8502565 from Cohort I reported Grade 3 gastritis and abdominal pain as serious gastrointestinal events. The events were self-limiting and not considered related to DTG treatment. No other serious or ≥Grade 3 gastrointestinal events were reported during P1093. Please see Section 7.3.2 for further details regarding this SAE. No gastrointestinal erosion or ulceration were reported. There were 2 subjects who experienced ≥ Grade 2 gastrointestinal events that were considered possibly related to DTG treatment. Subject 290650 from Cohort I had Grade 2 abdominal pain and Grade 2 diarrhea possibly related to DTG treatment. The events began 1 day after starting DTG treatment and lasted more than a week. Subject 507090 from Cohort IIA had Grade 2 diarrhea considered possibly related to DTG treatment. The event began ~119 weeks after starting DTG treatment and resolved the following day. None of the gastrointestinal events ultimately led to discontinuation of DTG treatment.

Musculoskeletal Disorders:
There were 17 subjects (37%) across Cohorts I and IIA that experienced musculoskeletal events during P1093. 14 of these subjects were from Cohort I and only

3 subjects were from Cohort IIA. None of the events were reported as Grade 3 or Grade 4 and no musculoskeletal event of at least Grade 2 were considered related to DTG treatment. The most frequently reported musculoskeletal events across both Cohorts were muscular pain (20%) and pain in extremity (13%). Muscular pain was reported in 7 subjects, including 4 cases of back pain, 3 cases of musculoskeletal pain, and 2 cases of myalgia. There was overlap between cases and some subjects experienced more than one type of muscular pain. There were no cases of rhabdomyolysis or myositis reported during P1093. On one occasion, Grade 1 creatinine phosphokinase elevation (CK) was noted in subject 400412 from Cohort I. The event was not considered related to DTG treatment and the subject did not have any concomitant musculoskeletal events reported. These findings are compatible with those observed in adults from the Phase 3 clinical trials for DTG. Adults in the Phase 3 clinical trials had few cases of myositis or CK elevations reported.

Hepatobiliary Disorders:
Only one subject in P1093 experienced a clinical event in the hepatobiliary system organ class. Subject 801804 was from Cohort IIA and experienced Grade 1 hepatomegaly starting 112 days after initiating the study drug. No concomitant abnormalities were noted in LFTs (i.e., ALT, AST, bilirubin, or Alkaline phosphatase) and the event was considered not related to DTG treatment. Adults in the initial Phase 3 study for DTG had two serious cases of possible drug-induced liver injury (DILI). The liver chemistry data collected during P1093 is discussed in Section 7.4.2.

Renal Disorders:
No subjects in P1093 experienced renal failure. DTG was not thought to affect glomerular filtration during the Phase 3 clinical trials in adults. The renal laboratory data collected during P1093 is discussed in Section 7.4.2.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

23 subjects (100%) in Cohort I and 22 subjects (96%) in Cohort IIA reported one or more treatment-emergent clinical adverse events. Cough was the most frequently reported clinical adverse event in both Cohort I and Cohort IIA. The next most frequently reported clinical adverse events in Cohort I were oropharyngeal pain (39%), nasal congestion (35%), and diarrhea (35%); while, the next most frequently reported events in Cohort IIA were nasal congestion (30%), rash (30%), skin lesion (22%), and diarrhea (22%). Table 7.4.1-1 summarizes the common clinical adverse events reported by at least 4 subjects in P1093. All of the common clinical adverse events were reported as mild or moderate (Grade 1 or Grade 2).

Table 7.4.1-1: Summary of Common Clinical Adverse Events by Cohort (Incidence ≥ 4 subjects)

Preferred Term	Cohort I N=23 n (%)	Cohort IIA N=23 n (%)	Cohorts I and IIA N=46 n (%)
Clinical Adverse Events			
Cough	14 (61)	12 (52)	26 (57)
Nasal congestion	8 (35)	7 (30)	15 (33)
Diarrhea	8 (35)	5 (22)	13 (28)
Oropharyngeal pain	9 (39)	3 (13)	12 (26)
Lymphadenopathy	7 (30)	4 (17)	11 (24)
Pyrexia	7 (30)	4 (17)	11 (24)
Rhinorrhea	7 (30)	4 (17)	11 (24)
Headache	7 (30)	3 (13)	10 (22)
Rash	2 (9)	7 (30)	9 (20)
Decreased appetite	7 (30)	1 (4)	8 (17)
Pain in extremity	6 (26)	0	6 (13)
Skin lesion	1 (4)	5 (22)	6 (13)
Vomiting	4 (17)	2 (9)	6 (13)
Abdominal pain	5 (22)	0	5 (11)
Dermatitis atopic	1 (4)	4 (17)	5 (11)
Pruritus	1 (4)	4 (17)	5 (11)
Sinus congestion	4 (17)	1 (4)	5 (11)
Back pain	4 (17)	0	4 (9)
Dizziness	4 (17)	0	4 (9)
Fatigue	3 (13)	1 (4)	4 (9)
Papule	2 (9)	2 (9)	4 (9)
Tinea capitis	0	4 (17)	4 (9)
Wheezing	2 (9)	2 (9)	4 (9)

Source: Adapted from clinical study report for P1093, Table 24.

7.4.2 Laboratory Findings

21 subjects (91%) in Cohort I and 22 subjects (96%) in Cohort IIA reported one or more treatment-emergent laboratory adverse events. The most common laboratory events reported in Cohort I were decreased bicarbonate (48%), hypoglycemia (30%), increased ALT (22%), and hyponatremia (22%). The most common laboratory events reported in Cohort IIA were hypoglycemia (48%), decreased bicarbonate (39%), increased AST (26%), and decreased neutrophil count (26%). Most of the laboratory adverse events from Cohorts I and IIA were categorized as mild or moderate and very few events were categorized as serious or ≥ Grade 3. Only 2 subjects (4%) had laboratory events reported as SAEs and only 6 subjects (13%) had laboratory events categorized as Grade 3 or Grade 4. None of the laboratory events reported as SAEs or categorized as ≥ Grade 3 were considered related to DTG treatment or resulted in permanent discontinuation of the study drug. Notable laboratory events including hepatic-related,

renal-related, SAEs, and ≥ Grade 3 events are discussed below. No new safety signals were appreciated in Cohorts I or IIA.

Hepatobiliary Events:
19 subjects (41%) across Cohorts I and IIA experienced hepatic-related laboratory toxicities (i.e., increased total bilirubin, ALT, AST, and/or alkaline phosphatase). 9 of the subjects were from Cohort I and 10 from Cohort IIA. Most hepatic-related laboratory events were Grade 1 or Grade 2, although three subjects had Grade 3 hyperbilirubinemia. There were no hepatic-related toxicities reported as SAEs and no hepatic-related toxicities ≥ Grade 2 that were considered possible related to DTG treatment. Although no significant changes in liver transaminases were observed across Cohorts I and IIA, there were small increases observed in mean total bilirubin. Concomitant use of atazanavir was noted in 8 of the 9 subjects with hyperbiliruinemia, including the 3 subjects with Grade 3 events. These cases were not considered related to DTG treatment as asymptomatic hyperbilirubinemia is listed in the atazanavir label. One subject was noted to have Grade 1 hyperbilirubinemia associated with Grade 1 elevated AST, but no other subjects with hyperbilirubinemia had concomitant elevations in ALT, AST, and/or alkaline phosphatase. No cases fulfilled criteria for Hy's law of drug-induced liver injury. Table 7.4.2-1 summarizes all hepatobiliary events by worst grade toxicities reported across Cohorts I and IIA.

Table 7.4.2-1: Hepatobiliary Events by Worst Grade Toxicities

	Grade in Cohorts I and IIA			Total Number Subjects in Cohorts I and IIA with Event N=46 n (%)
	1 n (%)	2 n (%)	3 n (%)	
Total Bilirubin increased	3 (7)	3 (7)	3 (7)	9 (20)
Abnormal Indirect Bilirubin	-	-	-	9 (20)
Abnormal Direct Bilirubin	-	-	-	4 (9)
ALT increased	6 (13)	3 (7)	0	9 (20)
AST increased	8 (17)	1 (2)	0	9 (20)
Alk Phos increased	3 (7)	1 (2)	0	4 (9)

Source: Adapted from clinical study report for P1093, Table 25.

Renal Events:
As mentioned in Section 7.3.5, there were no cases of renal failure reported across Cohorts I and IIA. There was one subject (subject 450527) who had multiple episodes of increased serum creatinine after initiating the study drug (baseline creatinine 0.68 mg/dL). The subject was from Cohort I and had Grade 1 serum creatinine elevations at Weeks 8, 12, and 24. The elevated serum creatinine values at these visits were between 1.01 – 1.03 mg/dL (reference range upper limit 0.9 mg/dL) and no abnormal

serum creatinine result was reported at Week 16. No associated proteinuria, hematuria, or abnormal urine albumin/creatinine ratio were noted in this subject and the events were not considered related to DTG treatment. This subject continued the study drug throughout and a normal creatinine level was noted at Week 48.

The mean and median serum creatinine levels are summarized in Table 7.4.2-2 by Cohort and Visit. Changes in the mean serum creatinine at Weeks 4, 24, and 48 compared to the mean baseline are also listed. Overtime, small non-progressive changes in serum creatinine were observed for Cohorts I and IIA. These changes were likely due to decreased tubular secretion of creatinine because the median urine albumin/creatinine ratios from Cohorts I and IIA remained stable over time. There were also no subjects who developed macroalbuminuria (ratio >300 µg/mg). Small non-progressive changes in serum creatinine were also observed in adults during the Phase 3 trials for DTG. Similarly, DTG is not thought to affect glomerular filtration.

Table 7.4.2-2: Change in Serum Creatinine (mg/dL) Compared to Baseline

Cohort	Timepoint	N	Mean	Median	Min	Max
Cohort I	Baseline	23	0.58	0.58	0.40	0.90
	Week 4	22	0.65	0.60	0.40	0.95
	Change from Baseline		+0.07	+0.09	-0.10	+0.27
	Week 24	23	0.73	0.70	0.51	1.03
	Change from Baseline		+0.15	+0.16	-0.07	+0.35
	Week 48	22	0.68	0.69	0.46	1.00
	Change from Baseline		+0.12	+0.10	-0.10	+0.40
Cohort IIA	Baseline	21	0.42	0.44	0.17	0.78
	Week 4	20	0.49	0.51	0.21	0.70
	Change from Baseline		+0.06	+0.05	-0.26	+0.29
	Week 24	19	0.52	0.50	0.24	0.75
	Change from Baseline		+0.11	+0.10	-0.02	+0.27
	Week 48	14	0.53	0.52	0.41	0.72
	Change from Baseline		+0.09	+0.09	-0.03	+0.24
Cohorts I and IIA	Baseline	44	0.51	0.50	0.17	0.90
	Week 4	42	0.50	0.58	0.21	0.95
	Change from Baseline		+0.07	+0.08	-0.26	+0.35
	Week 24	42	0.63	0.63	0.24	1.03
	Change from Baseline		+0.13	+0.13	-0.07	+0.35
	Week 48	36	0.62	0.6	0.41	1.00
	Change from Baseline		+0.11	+0.10	-0.10	+0.40

Source: Adapted from clinical study report for P1093, Tables 44 and 45; Clinical reviewer's calculations.

Two subjects across Cohorts I and IIA did have multiple episodes of proteinuria and/or hematuria after starting DTG. Subject 8503340 from Cohort I had persistent hematuria by Week 24 and persistent proteinuria by Week 48. This subject had Grade 1 hematuria without proteinuria at Week 8, then Grade 1 proteinuria associated with Grade 1

hematuria at Week 24, and finally Grade 2 proteinuria without hematuria at Week 48. The events were not considered related to DTG treatment because the subject had an abnormal urine albumin/creatinine ratio at baseline (265.5 µg/mg) and decreased by Week 48. Subject 8503732 from Cohort I had persistent proteinuria by Week 24 and no hematuria. This subject had Grade 1 proteinuria at both Weeks 8 and 24. The event was considered possibly related to DTG treatment because the subject had a normal urine albumin/creatinine ratio at baseline. This subject did not have hematuria or an abnormal urine albumin/creatinine ratio at any visit. No urinalysis results were available after Week 48 or after Week 24 from subject 8503340 and subject 8503732, respectively.

Other Laboratory Events:
Table 7.4.2-3 summarizes the notable laboratory events including hypoglycemia, neutropenia, anemia, lipase increased, and WBC decreased which are noted in the DTG label. Most of these events were mild or moderate. 4 subjects, all from Cohort I, had ≥ Grade 2 laboratory events that were considered possibly related to DTG treatment (neutropenia n=3; hypoglycemia n=1). All four events were categorized as Grade 2, occurred by Week 24, and resolved. DTG was also continued throughout these events. A more detailed discussion of the frequency of neutropenia and elevated lipase is included below as these were the only two laboratory events reported as SAEs. No new safety signal was appreciated in Cohort I or IIA.

Table 7.4.2-3: Other Selected Laboratory Events by Worst Grade Toxicities

	Grade in Cohorts I and IIA				Total Number Subjects in Cohorts I and IIA with Event N=46 n (%)
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	
Hypoglycemia	12 (26)	6 (13)	0	0	18 (39)
Neutrophils decreased	5 (11)	3 (7)	1 (2)	1 (2)	10 (22)
Hemoglobin decreased	5 (11)	1 (2)	0	0	6 (13)
Lipase increased	2 (4)	0	1 (2)	0	3 (7)
WBC decreased	0	1 (2)	1 (2)	0	2 (4)

Source: Adapted from clinical study report for P1093, Table 25.

Ten subjects (22%) across Cohorts I and IIA experienced neutropenia. Most of the events were mild or moderate, though 2 subjects experienced ≥ Grade 3 neutropenia and 1 of these was reported as a SAE. The SAE related to neutropenia was reported in subject 506495. This subject was a 12 year old female enrolled into Cohort I who was later noted to have Grade 4 neutropenia on days 673, 755, and 1014. The lowest absolute neutrophil count (ANC) value was 100 µL and occurred at days 755 and 1014.

The same subject also had Grade 3 decreased white blood cell count (WBC) of 1300 µL at day 1014, although that event was not reported as a SAE. No changes were made to the study drug and no repeat labs were available before the data cut-off date. The decreased ANC and WBC were not considered related to the study drug as this subject had Grade 1 decreased ANC (1168 µL) and Grade 1 decreased WBC (2500 µL) at Week 0. This subject was also taking trimethoprim/sulfamethoxazole and then dapsone which may have contributed to these events. Though not reported as a SAE, subject 8502592 from Cohort IIA experienced Grade 3 decreased ANC at day 427 (720 µL) and the events was not considered related to DTG treatment. The subject had a history of Grade 1 neutropenia at study entry and noted at multiple visits after Week 0.

Three subjects (7%) across Cohort I and IIA experienced elevated lipase. Most of the events were mild or moderate, though 1 subject experienced Grade 3 elevated lipase and was reported as a SAE. Subject 8500394 was a 16 year old male enrolled into Cohort I who later experienced Grade 3 elevated lipase at day 344 (261 IU/L) and day 347 (268 IU/L). The subject was otherwise asymptomatic with no reports of clinical adverse events related to pancreatitis (i.e., abdominal pain, nausea, vomiting, etc). The study drug was temporarily held for 4 days and the event was considered not related to DTG treatment. Subsequent lipase level noted resolution of the event.

7.4.3 Vital Signs

Vital signs were collected at screening (within 30 days prior to study entry), at study entry, and at regular follow-up visits for all subjects. The applicant and this reviewer did not note any clinically meaningful changes in diastolic or systolic blood pressure, respiratory or pulse rates, or temperature.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in P1093. Please refer to the original NDA review for details of cardiovascular evaluations.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted in this pediatric submission. Please refer to the original NDA submission for adult information.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

DTG dosing in P1093 was based on 4 weight-bands and no safety concerns were noted between the doses utilized.

7.5.2 Time Dependency for Adverse Events

An exploration of time dependency for adverse events was not conducted.

7.5.3 Drug-Demographic Interactions

No drug-drug interaction studies were submitted with this application.

7.5.4 Drug-Disease Interactions

A review of adverse events by subpopulation categorized by CDC Category C or HIV Stage 3 revealed no safety concerns.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were submitted with this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Large B-cell Lymphoma was diagnosed in one subject (290163) after an inguinal lymph node biopsy was performed ~32 months after starting DTG treatment. Please see Section 7.3.2 for further details regarding this serious event. No other neoplasms were reported during the study period from Cohorts I or IIA.

7.6.2 Human Reproduction and Pregnancy Data

Two pregnancies, both from Cohort I, were reported during the study period. The pregnancy in subject 450366 was suspected to have occurred 824 days after starting DTG treatment. The subject at Day 841 had already been off the study drug because she was unable to attend clinic visits (site closed). The pregnancy was estimated to be 5 weeks when confirmed at Day 855. Subject 400805 was noted to be pregnant at Day 1064 and the pregnancy was suspected to be within the first trimester. It was also reported that the subject was non-compliant with ARV therapy for the past 2 months. Subject 400805 permanently discontinued the study drug on Day 1064 because of pregnancy; however, she had DTG continued by private prescription throughout the

pregnancy. Both pregnancies resulted in live full-term births with no apparent congenital abnormalities.

One additional pregnancy occurred during the Safety Update Report period. This pregnancy was reported in subject 506495 at Day 1300 and the pregnancy suspected to be within the first trimester. The subject had the study drug permanently discontinued on Day 1301 because of pregnancy and had an uncomplicated elective abortion approximately 1 week after being taken off the study drug. Please see Section 7.7 for additional information regarding the pregnancy reported during the Safety Update Report period.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant did not conduct a formal assessment on the effects of DTG on growth and development. One Cohort IIA subject experienced growth retardation of Grade 1 severity at Week 60. At subsequent visits through Week 144, this subject's growth increased steadily without crossing major percentile lines (per 2000 CDC Growth Charts for the United States). No specific adverse event profile has been identified which would have major impact on growth of pediatric subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable. Please refer to original NDA review.

7.7 Additional Submissions / Safety Issues

Safety Update Report

The 60 day Safety Update Reported (SUR) was submitted by the applicant on February 05, 2016. The SUR included additional safety data collected between 14-Feb-2015 to 15-Jan-2016 for Cohorts I and IIA from P1093. There were no additional subjects enrolled into either Cohort and no new studies of DTG initiated in pediatrics.

The median days of DTG exposure increased from 1032 days to 1198 days for Cohort I and increased from 552 days to 842 days for Cohort IIA during the SUR period. 2 subjects (9%) in Cohort I and 15 subjects (65%) in Cohort IIA remain on the study drug at the time of this submission. The most frequent reason for discontinuation in each Cohort was "completed treatment." No deaths or adverse events leading to withdrawal were reported. Table 6.1.3-1 summarizes the subject disposition for each Cohort as of January 15, 2016.

Table 7.7-1: Subject Disposition by Cohort (All Available Data as of January 15, 2016)

Population	Cohort I N=23	Cohort IIA N=23	Cohorts I and IIA

	n (%)	n (%)	N=46 n (%)
Ongoing at time of report	2 (9)	15 (65)	17 (37)
Completed Week 48	21 (91)	21 (91)	42 (91)
Off Study Drug	21 (91)	8 (35)	29 (63)
Completed Treatment	6 (26)	3 (13)	9 (20)
Non-adherent	6 (26)	1 (4)	7 (15)
Unable to attend clinic visits	5 (22)	2 (9)	7 (15)
Pregnancy	2 (9)	0	2 (4)
Lost to Follow-up	1 (4)	1 (4)	2 (4)
Protocol Defined Clinical Event[a]	0	1 (4)	1 (2)
Other[b]	1 (4)	0	1 (2)

[a] Protocol defined Clinical Event in this case is virologic failure
[b] Other defined as family moved out of state, subject withdrew consent
Source: Adapted from 60-Day SUR submitted 02/05/16, Table 1.

Four subjects reported a total of 4 SAEs during the SUR period. The 4 SAEs included 1 case of sinusitis, 1 case of pelvic inflammatory disease, 1 case of abscess limb, and 1 case of abnormal behavior. None of the events were considered related to the study drug or responsible for discontinuation of DTG. One subject did have pregnancy diagnosed concurrently and was taken off the study drug because of pregnancy. The 4 SAEs and 1 new pregnancy that occurred during the SUR period are summarized below. No other new SAEs, Grade 3 or 4 events, or pregnancies were reported during the SUR period.

Subject 506495 was 12 year old female enrolled into Cohort I who later experienced Grade 3 sinusitis at ~185 weeks after starting DTG treatment. The subject was hospitalized for an unknown period of time and the event reported as resolved 2 weeks later. DTG treatment was permanently discontinued on Day 1301 as the subject was also noted to be pregnant when admitted for sinusitis. No associated pregnancy complications were reported and the exposure to DTG was during the first trimester of pregnancy. The subject had an uncomplicated elective abortion approximately 1 week after discontinuing the study drug. Of note, the same subject was noted to have Grade 4 neutropenia reported as a SAE prior to the SUR period. Further details can be found in Section 7.4.2. During the SUR period, persistent Grade 4 neutropenia (ANC 200 µL) was noted at day 1135 and then Grade 2-3 events by day 1300.

Subject 8502565 was a 15 year old female enrolled into Cohort I who later experienced Grade 3 pelvic inflammatory disease with abdominal pain and vaginal discharge at ~179 weeks after starting DTG treatment. The subject was hospitalized for IV antibiotics and then discharged 2 days later on oral antibiotics. DTG treatment was continued throughout and the event resolved within 1 week. Of note, the same subject had experienced an SAE prior to the SUR period (gastritis with abdominal pain) and further details can be found in Section 7.3.2.

Subject 2010055 was an 11 year old male enrolled into Cohort IIA who later experienced Grade 3 abscess limb at ~165 weeks after starting DTG treatment. The subject had an abscess in the right foot and required surgical drainage and antibiotic therapy. The subject was not hospitalized for the event, but did require daily wound care at a community health center. DTG treatment was continued throughout and the event resolved.

Subject 507090 was a 9 year old male enrolled into Cohort IIA who later experienced Grade 3 abnormal behavior at ~179 weeks after starting DTG treatment. The subject was hospitalized because of violent behaviors and suicidal ideation. This subject had experienced multiple episodes of abnormal behavior and aggression reported as SAEs before the SUR period (See Section 7.3.2). The hospitalization lasted 1 week and the study drug was not discontinued. He was transferred to a Behavioral treatment facility ~1 month after being discharged due to ongoing behavioral difficulties and anticipated to stay for 90 days.

8 Postmarket Experience

DAVP and OSE monitor post-marketing AEs continuously and specific events are reviewed as needed.

9 Appendices

9.1 Literature Review/References

An independent literature review did not produce any additional significant information regarding DTG.

9.2 Labeling Recommendations

Labeling language is still under discussion at the time this review was finalized. Below are some of preliminary proposed modifications to the clinically-relevant sections of the label.

1 INDICATIONS and USAGE

TIVICAY® is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

2 DOSAGE AND ADMINISTRATION

2.2 Pediatric Patients

Treatment-naïve or Treatment-experienced INSTI-naïve

The recommended dose of TIVICAY in pediatric patients weighing at least 30 kg is provided in Table 2.

Table 2. Dosing Recommendations for TIVICAY in Pediatric Patients (b) (4)

Body Weight (kg)	Daily Dose[a] (Number of Tablets per Dose when Different Strength(s) are Required)
30 to less than 40	35 mg once daily (One 25-mg tablet and one 10-mg tablet)
40 or greater	50 mg once daily

[a] If certain UGT1A or CYP3A inducers are co-administered, then increase the weight-base dose of TIVICAY to twice daily [*see Drug Interactions (7.3) for relevant inducers*].

Safety and efficacy of TIVICAY have not been established in pediatric patients (b) (4) who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir).

6 ADVERSE REACTIONS

(b) (4) **Clinical Trials Experience in Pediatric Subjects**

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)].*

The adverse reaction profile was similar to that for adults. Grade 2 ADRs reported by more than one subject were decreased neutrophil count (n = 3) and diarrhea (n = 2). There were no Grade 3 or 4 drug-related ADRs reported. No ADRs led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults.

Updates to the Drug Interactions section of the label are also proposed, including the table in Section 7.3 of drugs where alterations in the dose of TIVICAY may be recommended. Specifically, comments are added for pediatric patients to increase the weight-based dose of TIVICAY to twice daily if there is concomitant use of efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin, or carbamazepine.

Proposed modifications to the Use in Specific Populations and the Clinical Studies sections of the label include updated pediatric information. The following are the proposed modifications for these sections of the label:

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and efficacy of TIVICAY have not been established in pediatric patients (b) (4) weighing less than 30 kg, or in any pediatric patients who are INSTI-experienced (b) (4)

The safety, virologic, and immunologic responses in subjects who received TIVICAY were evaluated in 46 treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

(b) (4)

Frequency, type, and severity of adverse drug reactions (b) (4) pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.2)]*.

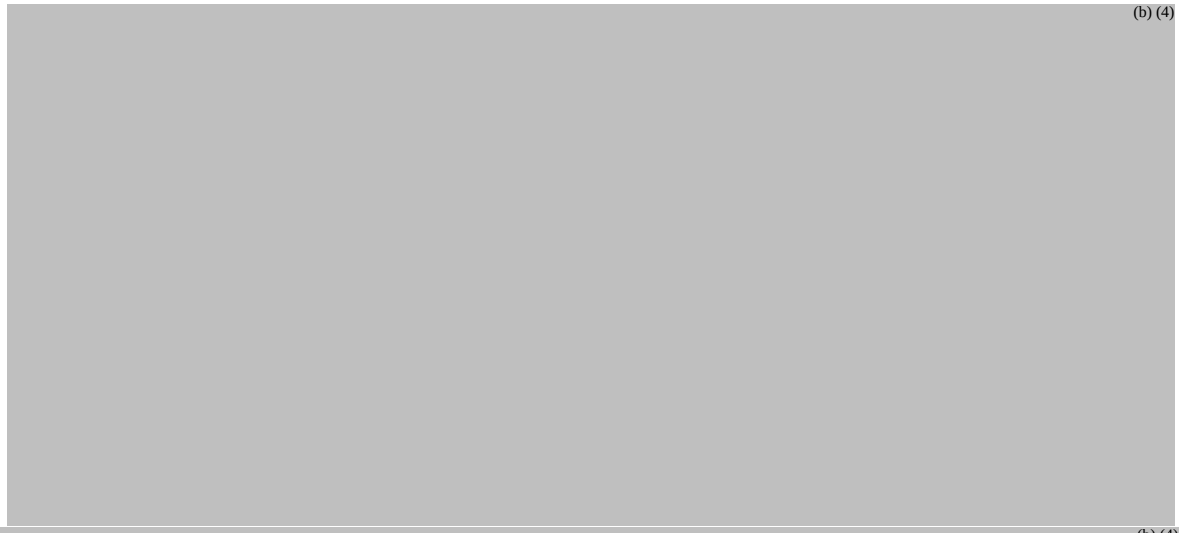
14 CLINICAL STUDIES

14.2 Pediatric Subjects

IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY in combination treatment regimens in HIV–1-infected infants, children, and adolescents. Subjects were stratified by age (b) (4), enrolling adolescents first (Cohort 1: aged 12 to less than 18 years) and then younger children (Cohort 2A: aged 6 to less than 12 years). (b) (4)

These 46 subjects had a mean age of 12 years (range: 6 to 17), were 54% female and 52% black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies per mL, median CD4+ cell count was 639 cells per mm^3 (range: 9 to 1,700), and median CD4+% was 23% (range: 1% to 44%). Overall, 39% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 33% had a CDC HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI (50%) or 1 PI (70%).

(b) (4)



(b) (4)

9.3 Advisory Committee Meeting

Not applicable.

9.4 Clinical Investigator Financial Disclosure

Application Number: 204790

Submission Date(s): 12/09/2015

Applicant: ViiV Healthcare Company

Product: Dolutegravir

Reviewer: Mark Needles, M.D.

Date of Review: 05/13/2016

Covered Clinical Study (Name and/or Number): ING112578 (P1093)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 123		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: ____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 109		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant submitted information related to financial interest/arrangements from the investigators in ING112578 (P1093). Clinical investigators were certified regarding the absence of financial interests and arrangements following requirements in 21 CFR 54.4(a)(1). 14 sub-investigators from 7 sites were not certified because updated equity interest, proprietary interest information and /or information about payments of other

1 See [web address].

sorts could not be obtained despite due diligence. This lack of information is not likely to affect the overall results.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK S NEEDLES
05/13/2016

YODIT BELEW
05/13/2016