CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213983Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 204790.S-025 and 213983 **SDN**: 744 and 000 **DATE REVIEWED:** 03/16/2020

Virology Reviewer: Anamaris M. Colberg-Poley, Ph.D.

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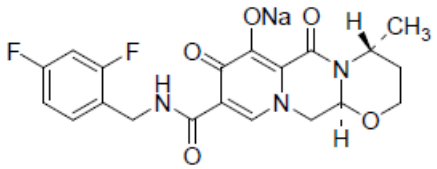
Submissions Reviewed:

SDN	Date Received	Date Assigned
752	01/21/2020	01/17/2020
755	02/07/2020	02/06/2020
758	02/25/2020	02/21/2020

Product Name(s)
Proprietary: TIVICAY®
Non-Proprietary/USAN: dolutegravir, GSK1349572 (DTG sodium salt)

Product Name	Dolutegravir, DTG, TIVICAY®
Chemical Structure	
Chemical Name	Sodium (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Molecular formula	$C_{20}H_{18}F_2N_3NaO_5$
Molecular weight	441.36

Drug category: Antiviral
Indication: Treatment of HIV-1 infection in combination with other antiretroviral agents in adults and in pediatric patients aged at least 4 weeks and weighing at least 3 kg
Dosage Form/Route of administration: Film coated tablets (10, 25, and 50 mg DTG) and dispersible tablets for oral suspension (5 mg of DTG)/oral
Related/Supporting Documents: IND 75382, IND 110847 (IMPAACT P1093), NDA 205551 (DTG/ABC/3TC); NDA 210192 (DTG/RPV); NDA 211994

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Abbreviations

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ARV, antiretroviral; ATV, atazanavir; BL, baseline; DRV, darunavir; DT, dispersible tablet; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; FC, fold change; FTC emtricitabine; HIV-1, human immunodeficiency virus type 1; IMPAACT, international maternal pediatric adolescent AIDS clinical trials; IN, integrase; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; NRTI, (deoxy)nucleoside analogue reverse transcriptase inhibitor; NVP, nevirapine; OBT, optimized background therapy; PK, pharmacokinetic(s); r, ritonavir; RAS, resistance-associated substitution; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate; VF, virologic failure; VL, viral load; WB, weight band

BACKGROUND and SUMMARY

The sponsor submitted NDA 204790.S-025 and NDA 213983.000 in support of dolutegravir (DTG) dosing recommendations for subjects weighing 30 to <40 kg, new dosing recommendations for an expanded pediatric population weighing 14 to <30 kg, and new oral suspension tablet for pediatric population weighing ≥3 kg. The applications were submitted also in response to PMRs 3091-1 and 3091-2.

The sponsor submitted efficacy results from IMPAACT Clinical Study P1093 (ING112578, protocol-amend-4 version 5, NCT01302847) entitled, "Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety and Tolerability and Antiviral Activity of GSK1349572, a Novel Integrase Inhibitor, in Combination Regimens in Human Immunodeficiency Virus Type 1 (HIV-1) Infected Infants, Children and Adolescents" and pharmacokinetic (PK) and safety data from ODYSSEY (PENTA 20, NCT02259127) clinical study "An Open-Label, Multi-Centre, Randomised (1:1), Non-Inferiority, Phase II/III, 96-Week, 2-Arm Clinical Trial to Compare the Efficacy and Toxicity of Dolutegravir Plus 2 Nucleoside Analogue Reverse Transcriptase Inhibitor (NRTI) vs. Standard of Care in HIV-Infected Children Aged <18 Years Who Are Starting First-line Antiretroviral Therapy (ART, ODYSSEY) or Switching to Second-Line ART (ODYSSEY B)" is being conducted by the Paediatric European Network for the Treatment of AIDS (PENTA). The sponsor does not plan to include efficacy data (as agreed during the Type B Pre-sNDA Meeting for these submissions) from ODYSSEY in this submission because the randomized main study is currently ongoing. ViiV Healthcare will submit the final full study results when available.

Post-Marketing Requirements

- **PMR 3091-1:** Conduct a trial to evaluate pediatric pharmacokinetics, safety, and antiviral activity of dolutegravir in HIV-1 infected integrase strand transfer inhibitor-naïve, pediatric subjects weighing less than 15 kg and at least 4 weeks in age. Initial evaluation of DTG exposure must be performed in an initial pharmacokinetic study or sub-study to allow dose selection. Using doses selected based on the pharmacokinetic study/sub-study, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.
  Final Report Submission: 09/30/2020

- **PMR 3091-2:** Conduct a trial to evaluate pediatric pharmacokinetics, safety, and antiviral activity of dolutegravir in HIV-1 infected integrase strand transfer inhibitor-naïve, pediatric subjects weighing 15 kg to less than 30 kg. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or sub-study to allow dose selection. Using doses selected based on the study/sub-study, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.
  Final Report Submission: 12/31/2019

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 204790.S-025 and 213983 **SDN**: 744 and 000 **DATE REVIEWED:** 03/16/2020

Virology Reviewer: Anamaris M. Colberg-Poley, Ph.D.

TIVICAY® (Dolutegravir, DTG) is an HIV-1 integrase (IN) strand transfer inhibitor (INSTI) and is currently indicated in combination with other antiretroviral (ARV) drugs agents for the treatment of HIV-1 infection in adults and in pediatric patients weighing ≥30 kg or with rilpivirine (RPV; an non-nucleoside reverse transcriptase inhibitor, NNRTI) as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL, copies/mL) on a stable ARV regimen for ≥6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral drug.

DTG initially received marketing approval from the FDA on August 12, 2013 for the treatment of HIV-1 infection in combination with other ARV drugs in adults and children aged ≥12 years and weighing ≥40 kg. DTG indication was then expanded to children weighing ≥30 kg on June 09, 2016 (Supplement 8). A new indication was approved on November 21, 2017 (Supplement 14) to use with RPV as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for ≥6 months with no history of treatment failure or known substitutions associated with resistance to either ARV drug. FDA approved the use of DTG (film coated tablets) in pediatric patients ≥6 years old and weighing ≥30 kg for the treatment of HIV-1 infection in combination with other ARV drugs.

Clinical Study Protocol P1093, ING112578

Title: International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) Study P1093: Phase I/II Study, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of GSK1349572, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

Objectives *(protocol-amend-4 version 5, pages 36-37)**:***

Primary Objectives:

1. To select a dose for each formulation of DTG for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily dose in adults
2. To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks
3. To evaluate the steady-state pharmacokinetics (PK) of DTG in combination with optimized background therapy (OBT) in treatment-experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves the targeted C_{24h} and AUC_{0-24} PK parameters in this population

Secondary Objectives:

1. To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks
2. To evaluate the effect on immunologic response from baseline to 24 and 48 weeks
3. To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in participants experiencing virologic failure
4. To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g., age, weight) using intensive and sparse sampling and population PK analysis
5. To determine the extended long term (>48 weeks) safety, tolerability and efficacy of DTG in HIV-1 infected infants, children and adolescents
6. To explore the relationship between DTG exposure and the antiviral activity

7. To evaluate PK, safety and tolerability profile of DTG when dosed by weight bands

Virology Relevant Efficacy Endpoints *(ing112578-report, pages 182, 920-929):*

1. The proportion of subjects with ≥1 $\log_{10}$ drop from baseline (BL) or HIV RNA <400
2. The proportion of subjects with HIV RNA <50 copies/mL through WK24 and WK48
3. The proportion of subjects with HIV RNA <400 copies/mL through WK24 and WK48
4. The proportion of subjects with HIV RNA below the lower limit of quantification

Virology Relevant Inclusion Criteria *(protocol-amend-4, version 5, pages 42-45):*

1. Age: ≥4 weeks to <18 years at study entry
2. Confirmed HIV-1 infection
   - Documentation of HIV-1 infection defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. All test methods should be FDA-approved if available. If FDA-approved methods are not available, test methods should be verified according to good clinical laboratory practice (GCLP) and approved by the IMPAACT central laboratory.
   - Sample #1 may be tested by non-study public or PEPFAR programs. However, both the result and the assay date must be recorded in the participant's chart. Source documentation (patient's medical record/chart, in-country Ministry of Health registers, laboratory results, etc.) must be available if requested.
   - Sample #2 must be performed in a College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory (for US sites) or in a laboratory that operate according to GCLP guidelines and participates in appropriate external quality assurance program (for non-US sites).

Acceptable tests when participants are ≤18 months of age:

- Sample #1 and Sample #2 may be tested using any of the following:
  - One HIV DNA PCR
  - One quantitative HIV RT-PCR (above the limit of detection of the assay)
  - One qualitative HIV RT-PCR
  - One total HIV nucleic acid

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

Acceptable tests when participants are >18 months of age:

- Sample #1 may be tested using any of the following:
  - Two rapid antibody tests from different manufacturers or based on different principles and epitopes
  - One EIA, Western Blot, immunofluorescence, or chemiluminescence
  - One HIV DNA PCR
  - One quantitative HIV RT-PCR (above the limit of detection of the assay)
  - One qualitative HIV RT-PCR
  - One total HIV nucleic acid
- Sample #2 may be tested using any of the following:
  - Rapid antibody test. If this option is used in combination with the two tests for Sample #1, at least one of the three rapid antibody tests for Sample #1 must be FDA approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.

- One enzyme immunoassays (EIA), Western Blot, immunofluorescence, or chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RT-PCR (above the limit of detection of the assay)
- One qualitative HIV RT-PCR
- One total HIV nucleic acid

3. Participants must belong to one of the ARV exposure groups below.
   3.1 ARV-treatment experienced (not including receipt of ARVs as prophylaxis or for prevention of perinatal transmission)
   - Previously took ARVs for treatment, but not currently taking ARVs:
     - Must have been off treatment ≥4 weeks prior to screening

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

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

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

   OR

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

   3.2 ARV treatment-naïve (no exposure to ARVs for treatment; could have received ARVs for prophylaxis or prevention of perinatal transmission)

4. If an infant has received nevirapine (NVP) as prophylaxis to prevent perinatal transmission, he or she must have not received NVP for at least 14 days prior to enrollment into Stage I or II.
5. HIV-1 RNA viral load greater than 1,000 copies/mL of plasma at screening
   Note: For participants enrolling into cohorts IV, IV-dispersible tablet (DT), and V-DT, the HIV RNA test performed at screening may be pending at the time of enrollment. If the screening HIV RNA is ≤1000 copies/mL, the participant should discontinue study drug, per Section 6.9 and be followed per Appendix IF.

6. Optimized background therapy (OBT):
   - Participants who are both ≥2 years of age and ARV-treatment experienced (meeting entry criterion 4.1.3.1) must have available at least one fully active drug for the OBT to enroll. If screening genotype testing is inconclusive, historical genotypes obtained within 1 year of screening will be considered by the Protocol Team for determination of fully active drugs.
   - Participants who are ≥2 years of age and ARV-treatment naïve (meeting entry criterion 4.1.3.2) can enroll if genotype testing has been obtained with results pending.
   - Participants <2 years of age (ARV treatment-experienced or ARV treatment-naïve) can enroll if genotype testing has been obtained with results pending.

Virology Relevant Exclusion Criteria *(protocol-amend-4 version 5, pages 45-48)*

1. Presence of any active AIDS defining opportunistic infection
2. At enrollment, participant <3.0 kg

3. Use of any disallowed medications (Section 4.3.2) at time of screening
4. Known history of exposure to INSTI treatment by the participant or participant's mother prior to delivery/cessation of breast feeding
5. Known resistance to an INSTI
6. Participant has used, or anticipates using, chronic systemic immunosuppressive agents or systemic interferon (e.g., for treatment of HCV infection) within 30 days prior to beginning DTG study drug. Systemic corticosteroids (e.g., prednisone or equivalent up to 2 mg/kg/day) for replacement therapy or short courses (≤30 days) are permitted.
7. Active TB disease and/or requirement for treatment that includes rifampin at the time of the screening visit. However, participants who need rifampin treatment while on DTG will be allowed to continue in P1093 provided the DTG dose is adjusted according to Section 6.1.8.

   Comment not to be communicated to the sponsor: During our analyses of the virological resistance database (HIVVR JMP database), we noticed that columns listed as HIVHIST and PRVARV in the resistance database listed DTG in these columns for some subjects but not others. As subjects with previous INSTI use were to be excluded from this study, we sent an IR to the sponsor (January 31, 2020) asking whether the HIVHIST and PRVARV columns refer to previous ART treatments prior to the enrollment of the subjects in the P1093 clinical study or to medications started with treatment during the P1093 clinical study. In their response (response-to-davp-fda-31jan2020.pdf), the sponsor stated that no subject with prior dosing of any agent in the INSTI drug class, including DTG, was recruited into P1093. We could not verify or test this assertion as the baseline genotypes were not provided for all subjects. Moreover, the known integrase (IN) resistance-associated substitutions (RAS) present in some of the subjects' baseline genotypes (L74I or L74M) polymorphic: L74I occurs in 3% to 30% of viruses from ART-naïve individuals depending on subtype (Rhee et al., 2003, Stanford University HIV Drug Resistance Database). L74M occurs in nearly 10% CRF02-AG (which is present to a minor extent in the U.S.) from ART-naïve individuals (Stanford University HIV Drug Resistance Database). Thus, these IN L74 substitutions cannot be used to document DTG treatment-experience.

Study Design *(Protocol-amend-4.pdf, protocol version 5, pages 37-38):*
P1093 is a Phase I/II multi-center, open-label, non-comparative study of pharmacokinetic (PK) parameters, safety, tolerability, and efficacy of DTG in pediatric populations. Formulations will be evaluated in age-specific cohorts as shown below.

- Cohort I: Adolescents ≥12 to <18 years of age (film-coated tablets)
- Cohort IIA: Children ≥6 to <12 years of age (film-coated tablets)
- Cohort IIB: Children ≥6 to <12 years of age (granules for suspension or dispersible tablets)
- Cohort III: Children ≥2 to <6 years of age (granules for suspension) – closed to enrollment
- Cohort III-DT: Children ≥2 to <6 years of age (dispersible tablets)
- Cohort IV: Children ≥6 months to <2 years (granules for suspension) – closed to enrollment
- Cohort IV-DT: Children ≥6 months to <2 years of age (dispersible tablets)
- Cohort V-DT: Infants >4 weeks to <6 months (dispersible tablets)

Participants receiving the film-coated tablet formulation were initially enrolled sequentially into Cohorts I and IIA. Granules for suspension were introduced in protocol version 3.0. When it subsequently became clear that dispersible tablets (DT) would be commercially available in pediatric formulation, new cohorts for DT were opened in protocol version 4.0. Under this protocol version 5.0, two formulations of DTG (film-coated tablets and DT) will be evaluated; the target enrollment in Stage I was increased to allow for additional examination of PK, safety, and tolerability by weight bands (WBs), including participants from all of Cohorts III-DT, IV-DT, and

V-DT. Additional cohorts and WB groups might be opened or reopened to investigate data gaps or new modifications to dosing, for example, regarding fasting requirements or background regimens.

The fundamental procedure for evaluation of DTG doses remained unchanged through all protocol versions. Each cohort is enrolled in two sequential stages: Stage I and II. (The only exception is Cohort IIB which only enrolled through Stage I). In Stage I, participants undergo intensive PK sampling and are monitored for the safety and tolerability of DTG; to accept or reject a dose, the Protocol Team evaluates PK parameters exposures and 4-week safety and tolerability data. Once a treatment dose has been accepted, enrollment to Stage II begins to complete the cohort. Participants in Stage II will be followed for 48 weeks and evaluated for PK parameters (using population PK methods), safety and tolerability. After study WK48, all Stage I and Stage II participants transition to long-term follow-up and remain on study for approximately three additional years (144 additional weeks of follow-up, for a total of 192 weeks on study). Study drug is provided for the duration of the study. Thereafter, participants are transitioned into care outside of the study.

Protocol-defined Virologic Failure (Protocol-amend-4.pdf, page 59)

Virologic Failure (VF) in this study is defined as:

- A confirmed decrease in HIV RNA of <1.0 $\log_{10}$ at or after WK12 unless the HIV RNA is <400 copies/mL

OR

- A confirmed HIV RNA >400 copies/mL starting at WK24 or beyond on 2 consecutive measurements at least 1 week but no more than 4 weeks apart

Virologic REBOUND in this study is defined as:

- Confirmed >1.0 $\log_{10}$ increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week but no more than 4 weeks apart). For participants who initially achieve VL<400, nadir will be defined as 399 for the purposes of this definition.

  Note: A confirmatory HIV-1 RNA measurement must be performed within 1-4 weeks of the initial suspected failure or rebound.

At the confirmed virologic failure visit, a specimen should be drawn that should be sent for resistance testing (genotyping and phenotyping). Subjects may then, at the discretion of the subject's clinician and with the approval of the protocol team:

- Be taken off study drug and followed as per Appendix IF, 'Long Term Follow up for Subjects who discontinue study provided GSK1349572'. Subjects who refuse to complete P1093 follow up should be offered enrollment in the IMPAACT Long Term Follow-up protocol (P1074);
- Have background therapy re-optimized, with the subject remaining on study drug;

OR

- Continue with no changes made to the current regimen.

Any re-optimization of background therapy that includes experimental drugs must first be approved by the P1093 team, DAIDS Medical Officer and GSK representatives.

FDA VIROLOGIC ANALYSES

According to the sponsor, the all-treated population (n = 159) included pediatric subjects ≥3 months to18 years old in 7 weight bands (≥3-<6 kg, ≥6kg to <10kg, ≥10 to <14 kg, ≥14 to <20kg, ≥20 to >25kg, ≥25 to <35 kg, ≥35kg) (synopsis, page 11-12). The sponsor used the proposed dose population (n = 75) for their analyses of the clinical study and of these, the sponsor included 58 subjects for their virologic outcomes analyses (b) (4) [redacted]. We, therefore, sent an IR (January 13, 2020) to identify the proposed dose

population subjects and the subjects used to calculate virologic outcomes (b) (4). In their response, the sponsor identified the proposed dose population subjects (n = 75) who were treated with the final proposed dose of DTG and the subjects (n = 58), who had WK24 and/or WK48 results and were used to calculate virologic outcomes (b) (4) (m1.11.3 Resp 13Jan2020 IR Q2_Final).

Using the LRNAFIN JMP database, we determined the virologic outcomes of the subjects (n = 58) (b) (4) using <50 copies/mL as the cutoff for success (Table 1). We identified 35 virologic successes at WK24 in the total 58 pediatric subjects with WK24 results. Using <50 copies/mL, the sponsor calculated 36 subjects with successful virological outcomes at WK24 (b) (4). As our virologic outcomes analyses differed by one subject at WK24 (Table 1) and on the total number of subjects included at WK48 outcomes (b) (4), we sent another IR (February 14, 2020) to the sponsor requesting the identities of the virologic successes for WK24 and WK48 timepoints (b) (4) and noted for them that we identified 17 additional subjects, who had received the final proposed dose and had WK48 data in the LRNAFIN JMP database; but, were not included (b) (4) (Table 2; WK 48 discussed below). In their response (response-to-davp-14-feb-2020-comments.pdf), the sponsor identified the viral loads (VLs) used for each subject at the WK24 and WK48 windows for the Snapshot analyses. Our analysis of the WK24 outcomes using LRNAFIN identified the same subjects as those identified by the sponsor as virologic successes at WK24 except for Subject (b) (6) (Table 1). The sponsor used Subject's (b) (6)'s WK28 VL value (VL = 44 copies/mL) instead of the WK24 VL value (VL = 470 copies/mL) used by the FDA analysis. The sponsor's use of WK28 VL classified Subject (b) (6) as a success for the sponsor's analysis; whereas, our use of Subject (b) (6)'s WK24 VL classified the subject as a virologic failure (VF) in the FDA analysis. Nonetheless, as the WK28 value was within their 4-week verification window, we agreed to the sponsor's use of WK28 VL for Subject's (b) (6) in the virologic outcomes analysis of WK24 data (b) (4). Therefore, we agree with the sponsor's virologic outcome results for WK24 using <50 copies/mL (36/58, 62.1%) and <400 copies/mL (50/58, 86.2%) cutoffs.

For the WK48 virologic outcomes, we examined, using the LRNAFIN JMP database, the WK48 VL of the subjects (n = 58) included by the sponsor (b) (4). In addition to the initially proposed n = 24 subjects for WK48 outcomes (b) (4), we found an additional 17 subjects with WK48 VLs (Table 2) who were treated with the final proposed dose for their WB (m1.11.3 Resp 13Jan2020 IR Q2_Final) but were not included (b) (4). In our IR (February 14, 2020), we requested that these subjects' virologic outcomes be included in the WK48 results (b) (4). Their inclusion increased the number of subjects, particularly for the relevant Cohorts III-V, at WK48 from n = 24 to n = 41. The sponsor agreed to our request and incorporated the subjects' virologic outcomes into WK48 results (b) (4) (response-to-davp-14-feb-2020-comments.pdf, Negotiated Label, Section 14.3, Pediatric Subjects, (b) (4)). In addition, the sponsor included one additional subject (Subject (b) (6), Cohort V-DT) who, according to the sponsor, discontinued at Week 40 and thus would be considered as discontinued due to adverse event or death for the snapshot response at WK48. As seen in Table 1, WK48 data, 29 successful subjects had VL values <50 copies/mL, 13 subjects were VFs (VL ≥50 copies/mL) and WK48 data from 16 subjects are missing at WK48. Therefore, we agree with the sponsor's virologic outcome results for WK48 using <50 copies/mL (29/42, 69%) and <400 copies/mL (33/42, 78.6%) cutoffs (Negotiated Label, (b) (4)).

> **Comment not to be communicated to the sponsor:** We note that the sponsor' added subject (Subject (b) (6)) for the WK48 outcomes is not included in their WK24 or WK48 subject listings in either of the relevant sponsor's responses (m1.11.3 Resp 13Jan2020 IR Q2_Final or response-to-davp-14-feb-2020-comments.pdf) and, moreover, Subject (b) (6) is not listed in the LRNAFIN JMP database submitted with this application.

Rather, we conclude that the sponsor is referring to Subject (b) (6) who was in Cohort V-DT, failed at WK12 and was discontinued at WK36 (HIV VL end of treatment = 19,842 copies/mL) based upon the following. Of the subjects listed in Cohort V-DT at WK48 (Subjects (b) (6)), only Subject (b) (6) is listed as discontinued by WK48. Further, in the LRNAFIN JMP database, only Subject (b) (6) of the Cohort V-DT subjects has WK24 VL values (VL = 81,302 copies/mL), lacks the WK48 VL value, and was discontinued between the WK24 and WK48 timeframe.

It is also noteworthy that 12 virologic failure subjects (12/24, 50%) (Subjects (b) (6)) of the total VFs (n = 24) and 9 virologic success subjects (9/38, 23.7%) (Subjects (b) (6)) of the total virologic successes (n = 38) identified at the virology efficacy endpoints (WK24 and/or WK48) using the <50 copies/mL cutoff had DTG listed in their HIVHIST column in the HIVVR database. This high percentage of virologic failure of the subjects with annotated DTG in HIV ART history is inconsistent with the sponsor's assertion that no subject with prior dosing of any agent in the INSTI drug class, including DTG, was recruited into P1093 (response-to-davp-fda-31jan2020.pdf). If DTG treatment-experienced subjects were included in P1093, their anticipated virologic failure is higher than that of DTG treatment-naïve subjects. Therefore, DTG treatment of treatment-naïve subjects is expected to be more efficacious than for treatment-experienced subjects.

Table 1. Virologic outcomes of HIV-1 infected pediatric subjects in Clinical Study P1093 through Week 48 using the Snapshot algorithm (Source: FDA analysis of lrnafin.xpt JMP database)

Subject ID	HIVHIST listed DTG	WK24 HIV-1 VL (c/mL)	VF	WK48 HIV-1 VL (c/mL)	VF	Notes
(b) (6)	√	8,072	Y	57,801	Y	
		<40	N	<40	N	
		<40	N	<40	N	
		<40	N	<40	N	WK192 VL <40 copies/mL
		<40	N	<40	N	Added to Table 17 WK48
	√	470	Y	6,137	Y	WK40 VL = 4,757 copies/mL Sponsor chose WK28 VL= 44 copies/mL, FDA chose WK24 VL= 470 copies/mL, D/C WK40 VL = 4,757 copies/mL
	√	36,223	Y	34,565	Y	
	√	<40	N	<40	N	WK168 VL = 555 copies/mL
	√	<40	N	<40	N	WK144 VL = 12,875 copies/mL
		<40	N	<40	N	
		<40	N	<40	N	
		<40	N	<40	N	WK 138 VL <40 copies/mL
		<40	N	<40	N	WK168 VL <40 copies/mL
		<40	N	<40	N	WK132 VL <40 copies/mL
	√	302	Y	16,126	Y	
	√	<40	N	53	Y	WK192 VL <40 copies/mL

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VIROLOGY REVIEW

NDA: 204790.S-025 and 213983 **SDN**: 744 and 000 **DATE REVIEWED:** 03/16/2020

Virology Reviewer: Anamaris M. Colberg-Poley, Ph.D.

(b) (6)

√	<40	N	<40	N	WK216 VL = 381 copies/mL
√	60	Y	4,524	Y	WK196 VL = 1,029 copies/mL
√	3,240	Y	<40	N	Added to Table 17 WK48
	<40	N	-	M	
	<40	N	-	M	
√	81,302	Y	D/C	Y	WK36 VL = 19,842 copies/mL
	<40	N	<40	N	Added to Table 17 WK48
	<40	N	<40	N	
	<40	N	<40	N	Added to Table 17 WK48
	77	Y	-	M	
	<40	N	<40	N	Added to Table 17 WK48
	195	Y	109	Y	Added to Table 17 WK48
√	<40	N	<40	N	Added to Table 17 WK48
	120	Y	<40	N	Added to Table 17 WK48
√	203	Y	60	Y	Added to Table 17 WK48 Resuppressed
	<40	N	<40	N	Added to Table 17 WK48
√	<40	N	<40	N	Added to Table 17 WK48
√	<40	N	<40	N	Added to Table 17 WK48
	<40	N	<40	N	Added to Table 17 WK48
√	<40	N	-	M	
	139	Y	-	M	
	<40	N	-	M	
	87	Y	-	M	
√	11,259	Y	1,468	Y	Added to Table 17 WK48
√	2,532	Y	4,555	Y	Added to Table 17 WK48
	285	Y	217	Y	WK192 = VL 40 copies/mL
√	<40	N	<40	N	WK192 VL = 5,055 copies/mL
	<40	N	<40	N	
	<40	N	<40	N	WK192 VL <40 copies/mL
√	16,506	Y	D/C	Y	WK40 VL =12,414 copies/mL
	<40	N	<40	N	WK192 VL <40 copies/mL
	58	Y	-	M	
	<40	N	<40	N	Added to Table 17 WK48
√	479	Y	<40	N	Added to Table 17 WK48 Resuppressed
	194	Y	-	M	
	<40	N	-	M	
	54	Y	-	M	
	279	Y	-	M	
	<40	N	-	M	
	49	N	-	M	
	40	N	-	M	WK32 VL = 102 copies/mL
	258	Y	-	M	

Abbreviations: c/mL, copies/mL; D/C, discontinued; M, missing; VF, virologic failure; VL, viral load

Highlights: green, success at WK24/48; red, VF at WK24/48; yellow, data missing

Table 2. P1093 subjects with virologic outcomes at Week 48 in lrnafin.xpt (b) (4) (FDA IR 2.14.2020)

	Subject ID	Cohort	Visit	Viral Load (c/mL)
1.	(b) (6)	Cohort III-DT	WK48	<-999
2.		Cohort III-DT	WK48	<40
3.		Cohort V - DT	WK48	<40
4.		Cohort IV-DT	WK48	<40
5.		Cohort V - DT	WK48	<40
6.		Cohort V - DT	WK48	109
7.		Cohort V - DT	WK48	<-999
8.		Cohort V - DT	WK48	<40
9.		Cohort V - DT	WK48	60
10.		Cohort V - DT	WK48	<-999
11.		Cohort IV-DT	WK48	<40
12.		Cohort IV-DT	WK48	<-999
13.		Cohort V - DT	WK48	<40
14.		Cohort V - DT	WK48	1468
15.		Cohort III-DT	WK48	4555
16.		Cohort III-DT	WK48	<-999
17.		Cohort IV-DT	WK48	<-999

Sources: FDA analyses of lrnafin.xpt JMP database and m1.11.3 Resp 13Jan2020 IR Q2_Final
Abbreviations: c/mL, copies/mL;

FDA analyses of evaluable virologic failures in P1093 through Week 48

In P1093, 11 subjects (11/58, 19%) were identified as meeting FDA virologic failure criteria by WK48 (Table 3). We agree with the sponsor in the identification of 11 evaluable virologic failures (Subjects (b) (6)) through WK48 (Table 3). The documentation of the sponsor's identification of these subjects as virologic failures (VF) is listed for each subject below their ID in Table 3. Of the virologic failure subjects, some were infected with subtype B (n = 5), subtype C (n = 5), and one subject with subtype CRF01_AE. Virologic failure subjects were from each of the cohorts (I, n = 5; IIA, n = 1; III-DT, n = 2; V-DT, n = 3), except for Cohort IV, and all received the proposed final dose of DTG (Table 3). Moreover, treatment of the weight bands (WB) were comparable except for WB 3 to <6kg, which had 30% efficacy at WK24 using the <50 copies/mL cutoff and WB 14 to <20kg at WK48 which only had one subject (Table 4). The time of virologic failure for each subject is highlighted by bold

font in Table 3. Some subjects (Subjects (b) (6)) had viral load (VL) values that increased after initial suppression during DTG treatment and remained elevated, consistent with the possible emergence of resistance-associated substitutions (RASs). In contrast, other virologic failure subjects (Subjects (b) (6)) had confirmed VL values ≥400 and subsequent resuppression and in some cases (Subjects (b) (6)) increased VL values thereafter, suggesting possible non-adherance. Other virologic failure subjects did not suppress their HIV-1 VL values (Subjects (b) (6)) or suppressed at very late times (Subject (b) (6)), indicating non-adherance.

Table 3. Evaluable Pediatric Virologic Failures during DTG treatment in Clinical Study P1093 through Week 48 (Sources: FDA analyses of HIVVR and LRNAFIN databases; Sponsor included subjects in analysis (NDA 204790.S-025, (b) (4) WK24 (n = 58) WK48 (n = 42))

Subject ID	HIV-1 Subtype	Cohort	WB	ART	Time of Failure	VL (c/mL)
(b) (6) ing112578-report, page 263	B	I	WB ≥35kg BL Weight 71 kg	*WK24* DTG 3TC ABC ATV *WK144* DTG 3TC ABC	WK0 WK4 WK8 WK12 **WK16** WK20 WK24 WK32 WK48 WK48	18,228 40 <40 <40 **3,281** 45,986 8,072 <40 48 57,801
(b) (6) ing112578-report, page 264	B	I	WB ≥35kg BL Weight 58 kg	*WK24* DTG DRV/r FTC TDF	WK0 WK4 WK8 WK12 WK16 WK24 WK24 WK28 **WK32** WK40 WK48 WK52	10,902 473 40 <40 <40 470 2,307 44 **2,194** 4,757 6,137 11,220
(b) (6) ing112578-report, page 265	B	I	WB ≥35kg BL Weight 91	*WK24* DTG ATV/r TDF	WK0 WK4 WK8 WK12 WK16 **WK24** WK32 WK40 WK48	32,553 <40 <40 <40 <40 **36,223** 48,872 5,440 34,565
(b) (6) ing112578-report, page 268	B	I	WB ≥35kg BL Weight 84	*WK36/ WK162* DTG	WK0 WK12 WK16 WK20	7,739 96 983 55

				FTC TDF	WK24 **WK32** WK36 WK40 WK48	302 **13,722** 9,778 43,985 16,126
(b) (6) ing112578-report, page 276	B	IIA	WB ≥35kg BL Weight 50	*WK45/ WK159/ WK196* DTG ATV/r FTC TDF	WK0 WK16 WK24 **WK32** WK40 WK45 WK48	202,460 54 60 **68,738** 86,403 5,788 4,524
(b) (6) ing112578-report, page 285	CRF01_AE	III-DT	WB 6 to <10kg BL Weight 9kg	*WK28* DTG 3TC DRV/r EFV	WK0 WK4 **WK8** WK12 WK16 WK24 WK28 WK32 WK40 WK48	846,872 3,861 **79,502** 1,611 6,542 3,240 1,024 1,297 68 <40
(b) (6) ing112578-report, page 296	C	V-DT	WB 3-<6kg BL Weight 4	*WK22/ WK36* DTG 3TC ABC LPV/r	WK0 WK8 **WK12** WK16 WK22 WK24 WK32 WK36	305,468 79,471 **154,091** 122,451 99,362 81,302 119,239 19,842
(b) (6) ing112578-report, page 297	C	V-DT	WB 6 to <10kg	*WK44* DTG 3TC ABC	WK0 WK4 WK12 WK24 WK32 **WK40** WK42 WK44 WK48 WK60 WK72	579514 413 132 203 40 **17,998** 36,685 243 60 <40 <40
(b) (6) ing112578-report, page 298	C	V-DT	WB 3 to <6kg BL Weight 5	*WK32/ WK67/ WK87* DTG 3TC AZT	WK0 WK4 WK8 WK12 **WK16** WK24 WK28 WK32	646,790 44,410 19,104 9,617 **11,245** 11,259 4,274 4,185

					WK40 WK48 WK60	1,730 1,468 1,866
(b) (6) ing112578-report, page 286	C	III-DT	WB: 14 to <20kg BL Weight 14	*WK32* DTG 3TC AZT	WK0 WK4 WK8 WK12 WK16 **WK24** WK28 WK32 WK40 WK48	30,531 <40 <40 242 <40 **2,532** 1,480 5,254 2,105 4,555
(b) (6) ing112578-report, page 273	C	I	PK Dose ≥35 Weight 63	*WK32* DTG DRV/r ETR	WK0 WK4 WK8 WK12 WK16 **WK24** WK32 WK33 WK40	9,906 <40 <40 13,533 52 **16,506** 1,700 <40 12,414

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; c/mL, copies/mL; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; FTC emtricitabine; LPV, lopinavir; PK, pharmaco-kinetics; r, ritonavir; TDF, tenofovir disoproxil fumarate; VF, virologic failure; VL: viral load; WB, weight band
Sponsor's identification of VFs: Clinical Study Report ing112578-report, pages 263-265, 268, 273, 276, 285, 286, 296-298

Table 4. Efficacy Outcomes in P1093 by Cohorts and Weight Bands through Week 48 (Source: FDA analyses of response-to-davp-14-feb-2020-comments.pdf)

		Week 24		Week 48	
Cohort	**WB**	**<50 copies/mL**	**<400 copies/mL**	**<50 copies/mL**	**<400 copies/mL**
I	≥35 kg	14/19 (73.7%)	16/19 (84.2%)	12/19 (63.2%)	14/19 (73.7%)
IIA	≥35 kg	4/5 (80%)	5/5 (100%)	4/5 (80%)	4/5 (80%)
III DT	14-<20 kg	2/4 (50%)	3/4 (75%)	0/1 (0%)	0/1 (0%)
III DT	10-<14 kg	3/3 (100%)	3/3 (100%)	2/2 (100%)	2/2 (100%)
III DT	6-<10 kg	0/1 (0%)	0/1 (0%)	1/1 (100%)	1/1 (100%)
IV DT	6-<10 kg	6/9 (66.7%)	8/9 (88.9%)	4/4 (100%)	4/4 (100%)
V DT	6-<10 kg	4/7 (57.1%)	7/7 (100%)	3/4 (75%)	4/4 (100%)
V DT	3-<6 kg	3/10 (30%)	8/10 (80%)	3/6 (50%)	4/6 (66.7%)
		Week 24		**Week 48**	

		<50 copies/mL	<400 copies/mL	<50 copies/mL	<400 copies/mL
WB	≥35 kg	18/24 (75%)	21/24 (87.5%)	16/24 (66.7%)	18/24 (75%)
WB	14 to <20 kg	2/4 (50%)	3/4 (75%)	0/1 (0%)	0/1 (0%)
WB	10 to <14 kg	3/3 (100%)	3/3 (100%)	2/2 (100%)	2/2 (100%)
WB	6 to <10	10/17 (58.8%)	15/17 (88.2%)	8/9 (88.9%)	9/9 (100%)
WB	3 to <6 kg	3/10 (30%)	8/10 (80%)	3/6 (50%)	4/6 (66.7%)

Abbreviations: DT, dispersible tablet; WB, weight band

FDA Resistance Analyses in Pediatric Clinical Study P-1093

Of the 11 evaluable virologic failures, 10 virologic failure subjects had post-baseline (post-BL) data with 3 of them having emergence of DTG genotypic resistance (Table 5).

Pediatric subjects with emergence of known IN RASs during DTG treatment:

- **Subject** (b) (6) had the emergence of the known IN RAS R263R/K as a mixture combined with the emergence of IN K71K/R substitution by WK36 of DTG treatment. By WK132, IN R263K emerged in combination with two additional emergent known IN RASs, E138E/A/K/T and S147S/G. Four other IN substitutions (A49G, M50V, S119S/R, V201V/I) emerged by WK132 of DTG treatment. By WK 162, E138T and R263K were detected, in combination with IN substitutions A49G, M50V, K71K/R, and V201I; whereas, the known IN RAS S147S/G was not detected at WK162.
  Phenotypic analyses of Subject (b) (6)'s HIV-1 variants showed that the BL variant did not have reduced susceptibility to DTG (FC = 1.2) or raltegravir (RAL, FC = 1.0) and that the WK132 genotype conferred reduced susceptibility to DTG (FC = 5.1) and cross resistance to RAL (1.6-fold). At WK162, similar reduced susceptibility to DTG (FC = 5.2) and cross resistance to RAL (FC = 2.2) was detected.
- **Subject** (b) (6) had the emergence of DTG RAS S153S/A/F/V as a mixture in combination with the emergent IN substitutions T125V, H183H/R, and V260V/I by WK159 of DTG treatment. By WK196, only T125V was detected; the IN RAS S153S/A/F/V as well as IN substitutions, H184H/R and V260V/I, were no longer detected. The sponsor did not provide phenotypic analysis of Subject (b) (6)'s HIV-1 samples.
- **Subject** (b) (6) had the emergence of IN RAS G118R in combination with emergence of IN substitutions 72I/L and T112A by WK32 of DTG treatment. Phenotypic analyses of Subject (b) (6)'s HIV-1 variants at BL showed susceptibility to DTG (FC = 0.6) and RAL (FC = 0.8) and by WK32 showed reduced susceptibility to DTG (FC = 9.8) and cross resistance to RAL (FC = 14).

Pediatric subjects with emergence of IN substitutions during DTG treatment:

- **Subject** (b) (6) had the emergence of IN substitutions E96D and E152K by WK24 of DTG treatment. The sponsor did not provide phenotypic analysis of the HIV-1 samples.
- **Subject** (b) (6) had the emergence of IN substitutions D253E, D278A, S283G, and R284G by WK22 and WK36 of DTG treatment. The sponsor did not provide phenotypic analysis of the HIV-1 samples.
- **Subject** (b) (6) had the emergence of IN substitution R199R/K as a mixture by WK92 of DTG treatment. WK0 phenotypic analyses was missing and WK92 phenotypic analysis showed that the HIV variants were not reduced in susceptibility to DTG (FC = 0.9) and RAL (FC = 0.7).
- **Subject** (b) (6) had the emergence of IN substitutions T218T/I and S255S/N by WK32 of DTG treatment. The sponsor did not provide phenotypic analysis of the HIV-1 samples.

Table 5. Treatment emergence of integrase (IN) resistance-associated substitutions (RASs) and phenotypic resistance in evaluable virologic vailures in Clinical Study P1093 (Sources: FDA analyses of HIVVR, LRNAFIN, PHENOALL, RCHIVDB databases)

Subject ID	ART	Time of Failure	HIV-1 VLs (c/mL)	BL IN RAS	Post-BL IN RAS	Phenotype
(b) (6)	DTG 3TC/ ABC/ ATV	WK24 WK144	8,072 64,139	L74I S230N	WK24/WK144 L74I S230N	
	DTG 3TC/ DRV/r FTC/TDF	WK24	2,307	None	None	
	DTG ATV/r/TDF	WK24 WK24 WK24	36,223 2,492 2,505	None	***E96D*** ***E152K***	
	DTG FTC/TDF	WK36 WK132 WK162	9,778 1,367 1,966	L74L/M	WK36 ***K71K/R*** **R263R/K** WK132 ***A49G*** ***M50V*** ***S119S/R*** **E138E/A/K/T** **S147S/G** ***V201V/I*** **R263K** WK162 ***A49G*** ***M50V*** ***K71K/R*** **E138T** ***V201I*** **R263K**	WK 0 FC DTG 1.2 (RAL 1.0) WK36 FC DTG 1.2 (RAL 1.0) WK137 FC DTG 5.1 (RAL 1.6) WK162 FC DTG 5.2 (RAL 2.2)
	DTG ATV/r/FTC/ TDF	WK159 WK196	<40 1,029	G163A/E	WK159 ***T125V*** **S153S/A/F/V** ***H183H/R*** ***V260V/I*** WK196 ***T125V***	
	DTG 3TC/ DRV/r/ EFV	WK28	1,024	No BL seq	L74I	

(b) (6)	DTG 3TC/ABC/ LPV/r	WK22 WK36	99,362 19,842	None	WK22/WK36 ***D253E*** ***D278A*** ***S283G*** ***R284G***	
	DTG 3TC/ABC	WK0	579,514	L74I	No Post-BL seq	
	DTG 3TC/AZT	WK32 WK65 WK92	4,185 2,003 954	None	WK32/WK65 None emergent WK92 ***R199R/K***	WK0 FC Missing data WK92 FC DTG 0.9 (RAL 0.7)
	DTG 3TC/AZT	WK32	5,254	L74I	***I72I/L*** ***T112A*** **G118R**	WK0 FC DTG 0.6 (RAL 0.8) WK32 FC DTG 9.8 (RAL 14)
	DTG DRV/r/EZR	WK32 WK32	1700 70	None	***T218T/I*** ***S255S/N***	

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; c/mL, copies/mL; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; FC, fold change; FTC emtricitabine; LPV, lopinavir; r, ritonavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate; VF, virologic failure; VL: viral load;
Font: bold, treatment emergent; plain, present at BL and post-BL; italics, not a known IN RAS
Highlights on Subject ID: red: complete agreement for VF of FDA and sponsor; partial: FDA identification of VF
Known IN RASs conferring DTG resistance listed in: DOVATO (DTG/3TC) Label and Rhee et al., 2019, Stanford University HIV Drug Resistance Database, and Wensing et al., 2019

Emergence of HIV-1 RT and PR RASs in evaluable virologic failure subjects in Clinical Study P1093
Of the 11 evaluable virologic failures, 10 virologic failure subjects had post-baseline (post-BL) data with 3 of these subjects had emergence of RT or PR genotypic resistance (Table S1).

Pediatric subjects with emergence of known RT or PR RASs during OBT:

- **Subject** (b) (6) had emergent RT RAS M184V in combination with RT substitution D192D/N as a mixture by WK24 of the OBT containing 3TC and ABC. However, these substitutions were not detected at WK144. K20R and V35I were detected by WK144. No emergent PR RAS were detected by WK24 or WK144 of OBT. The sponsor did not provide phenotypic analyses for susceptibility of these HIV-1 variants to NRTIs, NNRTIs or PIs.
- **Subject** (b) (6), treated with OBT containing 3TC, DRV/r, and EFV, had emergent RT T215T/F/I/S (multi-NRTI resistance) as a mixture in combination with RT M230M/I (NNRTI RAS) by WK28 of OBT. Subject (b) (6) also had emergent PR substitution I63A/T at a known PR RAS position as a mixture by WK28. PR substitution is not known to be associated with resistance to DRV. The sponsor did not provide phenotypic analyses for susceptibility of these HIV-1 variants to NRTIs, NNRTIs or PIs.
- **Subject** (b) (6) had emergent RT RAS T69T/N (multi-NRTI resistance) in combination with RT substitutions R143R/K, A272P, K275R, K277R, Q278H, I293V, P313T, Q334H, G335D by WK96 of OBT containing 3TC and AZT. No RT RASs emerged by WK32, 67, and 87. No PR RAS emerged by WK32, 67, 87, and 96. The sponsor did not provide phenotypic analyses for susceptibility of these HIV-1 variants to NRTIs, NNRTIs or PIs.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 204790.S-025 and 213983 **SDN**: 744 and 000 **DATE REVIEWED:** 03/16/2020

Virology Reviewer: Anamaris M. Colberg-Poley, Ph.D.

Documentation of nonadherence **by evaluable virologic failure subjects in Clinical Study P1093:**
The ing112578-report documented nonadherence of all the evaluable virologic failures in IMPAACT Clinical Study P1093 (Table S2). Independent evidence of the subjects' nonadherence was provided by intensive PK data and the sparse PK data of the evaluable virologic failures (Table 6). Subject (b) (6) had low WK12 sparse PK data; whereas Subjects (b) (6) had low sparse WK4 C_0 data, suggestive of nonadherence. Subject (b) (6) had low sparse WK12 PK data; whereas, Subjects (b) (6) had low sparse WK24 data. Further, Subjects (b) (6) (AUC and C_{24} were low) and (b) (6) (low C_0 value) had low intensive PK data. These PK data are consistent with nonadherence of multiple evaluable virologic failure subjects.

Table 6. Summary of Intensive PK and Sparse PK data from evaluable pediatric virologic failures in Clinical Study P1093

	Days 5 to 10			WK4, WK12, WK24			
Subject	**Intensive PK**	**Result**	**ICH Page**	**Sparse PK**	**Result**	**ICH Page**	**TOF**
(b) (6)	N	NA	NA	Y	**WK12 low**	1259	WK16
	N	NA	NA	Y	**WK4 C_0 low**	1271	WK32
	Y	OK	1311	Y	**WK24 low**	1271	WK24
	N	NA		Y	**WK24 low**	1275	WK32
	Y	OK	1315	Y	OK	1284	WK32
	Y	**AUC and C_{24} low**	1315	Y	OK	1286	WK8
	Y	**C_0 low**, C_{24} OK	1305	Y	**WK24 low**	1257	Non-responder WK24
	Y	OK	1308	Y	OK	1265	WK40
	Y	OK	1312	Y	**W4 C_0 low**	1277	Non-responder WK24
	Y	OK	1313	Y	OK	1278	WK24
	N	NA	NA	Y	**WK4 C_0, WK24 low (no W12 data)**	1291	WK24

Source: ICH Data Listings for ing112578-report
Low PK values highlighted in red font.
Abbreviations: PK, pharmacokinetics

CONCLUSIONS
There is a discrepancy between the exclusion criteria and the JMP database information that the sponsor submitted (i.e., listing of DTG in ART history of some subjects). The sponsor maintains that all the subjects with previous DTG treatment were excluded. We cannot confirm that the subjects are DTG treatment-naïve

using the genotypic data provided. If subjects with previous DTG experience were included, the risk of virologic failure for those DTG treatment-experienced subjects is higher than for DTG treatment-naïve subjects. If DTG treatment-experienced were included in Clinical Study, the efficacy of DTG in treatment-naïve subjects should be higher than found in P1093. We agree with the sponsor's calculations (b) (4). At Week 24 (<50 copies/mL: 36/58, 62.1%; <400 copies/mL: 50/58, 86.2%) and Week 48 (<50 copies/mL: 29/42, 69.0%; <400 copies/mL: <400 copies/mL: 33/42, 78.6%), most pediatric subjects had successful virologic outcomes during DTG treatment. FDA analyses identified 11 evaluable virologic failures (19%) of 58 pediatric subjects through Week 48. Known IN RASs (G118R E138T, S147S/G, S153S/A/F/V, R263K) emerged in three virologic failure subjects during DTG treatment. The causes of virologic failure for the other subjects with no emergence of known IN RAS are less clear. Based upon subject reported nonadherence and intensive PK data and sparse PK data, suboptimal adherence appears to have contributed to virologic failure in some pediatric subjects of Clinical Study P1093.

Reviewer's Signatures

Anamaris M. Colberg Poley, Ph.D.
Clinical Virology Reviewer

Concurrence

Clin.Virol.TL/J. O'Rear, Ph.D.

CC:
HFD-530/N 204790.S-025.744 and N 213983.000
HFD-530/Division File
HFD-530/PM/Akunne

Appendix

Table S1. Emergence of RT RASs and PR RASs in pediatric virologic failure subjects in Clinical Study P1093 (Sources: FDA analyses of HIVVR, LRNAFIN, PHENOALL, RCHIVDB databases and Sponsor's Response (2.21.20) to IR (2.14.2020))

Subject ID	ART	RT RAS	PR RAS
(b) (6)	WK24 DTG 3TC ABC ATV WK144 DTG 3TC ABC	WK24 **M184V** ***D192D/N*** WK144 ***K20R*** ***V35I***	WK24/144 None emergent

(b) (6)

WK24 DTG DRV/r FTC TDF	WK24 None emergent	WK24 None emergent
WK24 DTG ATV/r TDF	WK24 None emergent	WK24 **L63S** ***K70R***
WK36/ WK162 DTG FTC TDF	WK36 ***K173T*** ***G196E*** WK162 ***K122K/E*** ***K173T*** ***G196E*** ***D250E***	WK36/ WK162 **M36M/I**
WK45/ WK159/ WK196 DTG ATV/r FTC TDF	WK45 None emergent WK159/ WK196 ***V35M***	WK45/WK159 None emergent WK196 **L63P/S**
WK28 DTG 3TC DRV/r EFV	WK28 ***G51G/R*** ***G196G/R*** ***T215T/F/I/S*** ***M230M/I***	WK28 **I63A/T**
WK22/WK36 DTG 3TC ABC LPV/r	WK22/WK36 None emergent	WK22/WK36 None emergent
WK44 DTG 3TC ABC	No BL or Post-BL sequence	No BL or Post-BL sequence
WK32 WK67 WK87 WK96 DTG	WK32/WK67/WK87 None emergent WK96 **T69T/N**	WK32/WK67/WK87/WK96 None emergent

	3TC AZT	***R143R/K*** ***A272P*** ***K275R*** ***K277R*** ***Q278H*** ***I293V*** ***P313T*** ***Q334H*** ***G335D***	
(b) (6)	WK32 DTG 3TC AZT	***K102K/R*** ***Q207E***	**I72I/T**
(b) (6)	WK32 DTG DRV/r ETR	None emergent	None emergent

Font: bold, treatment emergent; plain, present at BL and post-BL; italics, not a known RAS

Table S2. Documentation of evaluable virologic failure subjects in Clinical Study P1093

Subject ID	**ART**	Nonadherence **Documentation**
(b) (6)	DTG/3TC/ABC/ATV/	ing112578-report, p. 263 ICH Data Listings, p. 1259
	DTG/DRV/r/FTC/TDF	ing112578-report, p. 264 ICH Data Listings, p. 1271
	DTG/ATV/r/TDF	ing112578-report, p. 265 ICH Data Listings, p. 1271
	DTG/FTC/TDF	ing112578-report, p. 268 ICH Data Listings, p. 1275
	DTG/ATV/r/FTC/TDF	ing112578-report, p. 276 PK data ok
	DTG/3TC/DRV/r/EFV	ing112578-report, p. 285 ICH Data Listings, p. 1315
	DTG/3TC/ABC/LPV/r	ing112578-report, p. 296 ICH Data Listings, p. 1275 and 1305
	DTG/3TC/ABC	ing112578-report, p. 297 PK data ok

(b) (6)		
	DTG/3TC/AZT	ing112578-report, p. 298 ICH Data Listings, p. 1277
	DTG/3TC/AZT	ing112578-report, p. 286 ICH Data Listings, p. 1313
	DTG/DRV/r/ETR	ing112578-report, p. 273 ICH Data Listings, p. 1291

FDA Negotiated Package Insert (NDA 204790.S-025 and NDA 213983.000)

Below is the negotiated label with the sponsor's proposed edits highlighted in yellow with red font. FDA edits are highlighted in blue. Note that only the relevant paragraph of Section 14.3 Pediatric Subjects and (b) (4) are included in this review.

12.1 Mechanism of Action
Dolutegravir is an HIV-1 antiretroviral agent *[see Microbiology (12.4)]*.

12.4 Microbiology
Mechanism of Action
Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture
Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents
The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance
Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to

dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subject who received ~~in the~~ dolutegravir 50-mg once-daily ~~treatment arms~~ in the ~~of~~ treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

Virologically Suppressed Subjects: SWORD-1 and SWORD-2 are identical trials in virologically suppressed subjects receiving 2 NRTIs plus either an INSTI, an NNRTI, or a PI, that switched to dolutegravir plus rilpivirine (n = 513) or remained on their current antiviral regimen (n = 511). Two subjects in each treatment arm had confirmed virologic failure at any time through Week 48. The 2 subjects in the dolutegravir/rilpivirine arm had detectable resistance substitutions at rebound. One subject had the NNRTI-resistance-associated substitution K101K/E with no decreased susceptibility to rilpivirine (fold-change = 1.2) at Week 36, had no INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir (fold-change less than 2), and had HIV-1 RNA less than 50 copies per mL at the withdrawal visit. The other subject had the dolutegravir resistance-associated substitution G193E at baseline (by exploratory HIV proviral DNA archive sequencing) and at Week 24 (by conventional sequencing) without decreased susceptibility to dolutegravir (fold-change = 1.02) at Week 24. No resistance-associated substitutions were observed for the other 2 subjects in the comparative current antiretroviral regimen arm.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI- (elvitegravir or raltegravir) containing regimen. Use of TIVICAY in INSTI-experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of TIVICAY 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

Response by Baseline Genotype

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143R/C/H, Q148H/R/K, and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed in an "as-treated" analysis at Week 48 (n = 175) (Table 11). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions (see Table 11). In addition, a

diminished virologic response of 40% (6 of 15) was observed when the substitution E157Q or K was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Table 11. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Genotype	Week 48 (<50 copies/mL) n = 175 [a]
Overall Response	66% (116/175)
No Q148 substitution[a]	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI-resistance substitution[b]	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutions[b,c]	29% (6/21)

[a] Includes INSTI-resistance substitutions Y143R/C/H and N155H.
[b] INSTI-resistance substitutions included T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. Two additional subjects had baseline genotypes of Q148Q/R plus L74L/I/M (virologic failure) and Q148R plus E138K (responder).
[c] The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 16).

Response by Baseline Phenotype

Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (see Table 12). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Table 12. Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	Response at Week 48 (<50 copies/mL) Subset n = 163
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3- <10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies per mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was T97A. Other frequently emergent INSTI-resistance substitutions included L74M, I or V, E138K or A, G140S, Q148H, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C/H, S147G, V151A, and E157E/Q each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 61-fold (range: 0.75 to 209) for isolates with emergent INSTI-resistance substitutions (n = 33).

Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 49% (19 of 39) of subjects in the Week 48 resistance analysis.

In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8. Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI-resistance categories and the INSTI resistance-associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Cross-Resistance

Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

14.3 Pediatric Subjects

(b) (4)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 204790.S-025 and 213983 **SDN**: 744 and 000 **DATE REVIEWED:** 03/16/2020

Virology Reviewer: Anamaris M. Colberg-Poley, Ph.D.

(b) (4)

[redacted]

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