Use of *Tivicay* in Pediatric Patients

Summary

- IMPAACT P1093 is a Phase 1/2, open-label, dose-finding, multi-cohort study evaluating the pharmacokinetics (PK), efficacy, safety, and tolerability of *Tivicay* (dolutegravir [DTG]) in HIV-1–infected infants, children, and adolescents ages ≥4 weeks - <18 years.[1] Eligible patients were either ART-naïve or antiretroviral (ART)-experienced, integrase strand transfer inhibitor (INSTI)-naïve, and received ≥1 fully-active drug as part of optimized background therapy (OBT). The dispersible tablet (DT) was specifically studied in three cohorts that included patients aged 4 weeks to < 6 years old.
    - Favorable antiviral activity (< 400 c/mL and < 50 c/mL) was demonstrated through Week 24 in the Proposed Dose (PD) Efficacy Population (N = 58) for patients taking DTG + OBT. Sustained antiviral activity was maintained through Week 48 in the PD Efficacy Population (N = 24). The results through Week 48 came from the ≥ 35 kg weight band from Cohorts 1 and IIA who received DTG 50 mg film-coated tablets.
    - The safety profile of DTG in pediatric populations was similar to the adult DTG studies, including the incidence of the most common adverse events. No new safety issues were identified compared to those seen with the adult DTG studies.
- The ODYSSEY Study is an open-label, randomized, non-inferiority trial evaluating the safety and efficacy of DTG-based anti-retroviral therapy (ART) compared to standard of care (SOC) in 792 HIV-infected children (age < 18 years).[2,3]
    - At Week 96, 47 (14%) in the DTG arm and 75 (22%) in the SOC arm met the primary endpoint of virological or clinical failure in the pooled analysis (-8% [-13.5% to -2.6%]; *P* = 0.004). DTG was found to be superior to SOC at Week 96 based on a 10% non-inferiority (NI) margin.[2]
- Results from the PK sub-studies of ODYSSEY, assessing either the film-coated DTG 50 mg tablet or the 5 mg dispersible tablet, have shown similar PK results among various pediatric weight bands compared to adult standards. Further safety and efficacy evaluations are ongoing.[4-6]
- Important Safety Information and Boxed Warning can be found in the Prescribing Information and can also be accessed from the Our HIV Medicines section of viivhealthcare.com/us.

To access additional scientific information related to ViiV Healthcare medicines, visit the ViiV US Medical Portal at viivhcmedinfo.com.

INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT) P1093 STUDY

Background and Study Objectives

IMPAACT P1093 is an ongoing, Phase 1/2, open-label, dose-finding, multi-cohort, multi-center study evaluating the PK, efficacy, safety, and tolerability of DTG in HIV-1–infected infants, children, and adolescents ages ≥4 weeks to <18 years. IMPAACT P1093 is evaluating DTG in both ART-naïve and ART-experienced patients, both prior to starting, and in combination with, OBT.[1] The study population includes five age-defined cohorts. Each cohort is evaluated in two stages, the first of which involves dose-ranging PK analyses and safety evaluations on DTG, to determine the proper weight-based dose for continued study of DTG for the second stage. The second stage of the study evaluates sparse PK,

efficacy, and safety of DTG plus OBT in each cohort. The following age groups are being or have been evaluated:

- Cohort I: 12 - <18 years of age (tablet formulation, Week 48 data reported)[7]
- Cohort IIA: 6 - < 12 years of age (tablet formulation, Week 48 data reported)[8]
- Cohort IIB: 6 - < 12 years of age (granule formulation; this formulation is no longer being studied)
- Cohort III: ≥2 - <6 years of age (dispersible tablet formulation)[9-11]
- Cohort IV: ≥6 months - <2 years of age (dispersible tablet formulation) [9-11]
- Cohort V: ≥4 weeks - <6 months of age (dispersible tablet formulation) [9-11]

The primary study objectives include the following:[1]

- Determination of the dose of DTG that achieves similar exposure observed in ART-naïve adult patients receiving 50 mg once-daily (primary PK endpoint: C_{24h}; secondary endpoint: AUC_{0-24}). Based on pooled PK results from the SPRING-1 and ING111521 studies in ART-naive adults receiving DTG 50 mg once daily, the pre-determined target exposure ranges were AUC_{0-24} 46 mcg*h/mL (range 37 – 134 mcg*h/mL) and C_{24h} 995 ng/mL (range 697 – 2260 ng/mL).
- Evaluate short- and long-term safety and tolerability of DTG and steady state PK with OBT
- Assess the antiviral activity and immunologic response of DTG plus OBT at weeks 24 and 48 (primary virologic endpoint: proportion of patients with HIV-1 RNA <400 copies/mL using the missing/switch/discontinuation = failure [MSDF; FDA "snapshot"] analysis; secondary virologic endpoint: proportion of patients with HIV-1 RNA <50 copies/mL by FDA snapshot analysis)
- Evaluate phenotypic and genotypic changes in HIV-1 in subjects who experience virologic failure

Efficacy Data

Efficacy data is presented for patients who completed a minimum of 24 weeks at the proposed dose (the PD Efficacy Population).[1] While all participants were on DTG, the efficacy results focus on patients who received the final proposed dose. Therefore, the PD Efficacy Population was the primary population of interest for all efficacy endpoints and was defined by all participants who received either the film-coated tablet or the 5 mg dispersible tablet (DT) per the proposed dosing recommendations.[1]

Table 1. Efficacy of DTG Through Week 24 and Week 48[1]

	Week 24 (n = 58)		Week 48 (n = 24)	
	n/N	**% (95% CI)**	**n/N**	**% (95% CI)**
Number of Patients with HIV RNA < 50 c/mL[a]	36/58	62.1 (48.4 - 74.6)	16/24	66.7 (44.7 - 84.4)
Number of Patients with HIV RNA < 400 c/mL	50/58	86.2 (74.6 – 93.9)	18/24	75 (53.3 – 90.2)
	Median (n*)	**(Q1, Q3)**	**Median (n*)**	**(Q1, Q3)**
Change from baseline in CD4+ cell count (cells/mm)	105 (57)	(-93, 338)	149 (23)	(-17, 291)
Change from baseline in CD4+ percent	5.1 (57)	(1, 9.3)	8 (23)	(0, 11)

N = Number of participants in each cohort; n* = Number of participants contributing data. For binary endpoints: n?n with % (95% CI) was reported for each cohort, where n/N = number of responders/number of patients. For continuous endpoints: median changes with the first and third quartiles were reported. Normal distributions were assumed for continuous endpoints. Snapshot algorithm was used in the RNA analyses. Failures include patients with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the Protocol Team, and discontinuation for nontreatment related reasons with the last HIV RNA ≥ 400/50/LLQ c/mL

a Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis

Because of the sequential enrollment strategy and dose finding nature of the study, the number of participants per visit beyond Week 48 is much lower for the PD Efficacy Population. Data beyond Week 48 in the PD Efficacy Population comes from adolescents and older children (6 to <18 years) recruited into Cohorts I and IIA who were more likely to be heavily treatment experienced at Baseline and who were likely to be at risk for lower treatment adherence. Beyond Week 48 the small number of participants in Cohort IIA (N=5), maintained their antiviral response (HIV-1 RNA <50 c/mL) achieved at Week 48 (80%). However, the response rate for adolescents (Cohort I) continued to decline from Week 60 onward to the end of study (Week 192). An analysis of the adolescent cohort concluded adherence to study medication was problematic for this patient population and impacted their efficacy over time.[1]

In comparison, data beyond Week 48 for the All-Treated (AT) Efficacy Population included those participants mentioned above and younger children receiving granule and DT formulations at lower DTG doses/exposure. While numbers are quite small, and no formal analysis was performed, better efficacy over time was observed in younger children receiving a DTG based regimen.[1]

Virologic failure occurred in 37.9% of patients at Week 24 and 33.3% of patients at Week 48. See Table 2.

Table 2: Study Outcomes Based on Plasma HIV-1 RNA < 50 c/mL (PD Efficacy Population, Snapshot Analysis)[1]

	Week 24 (n = 58) n (%)	Week 48 (n = 24) n (%)
Virologic Success[a]	36 (62.1)	16 (66.7)
Virologic Failure[b]	22 (37.9)	8 (33.3)
Data in Window not below Threshold	22 (37.9)	6 (25)
Discontinued While Not Below Threshold	0	2 (8.3)
No Virologic Data	0	0

Note: n (%) = Number (percent) of participants in each subcategory. Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to > 50 c/mL in this analysis.

a. Virologic success was defined as plasma HIV-1 RNA <50 c/mL; Snapshot algorithm was used in HIV-1 RNA analysis.

b. Failures include participants with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the protocol team, and discontinuation for nontreatment related reasons with the last HIV RNA □50 c/mL

Long Term Safety and Efficacy Data

Sixteen of the 23 patients in Cohort I remained on the study for ≥ 144 weeks, with a median (range) follow up of 153 weeks (range, 55-93 weeks).[10] The median DTG exposure was 147 weeks (40, 194).

Ten patients (43%) achieved HIV RNA <400 copies/mL (95% CI: 23.2, 65.5) and eight (35%) patients had a HIV RNA viral load <50 copies/mL (95% CI: 16.4, 57.3) at 144 weeks. Eight patients meeting confirmed virologic failure criteria underwent HIV genotypic drug resistance testing; one had evidence of integrase strand transfer inhibitor (INSTI) drug resistance with E138E/K/T, S147G, and R263K at week 192. Five patients experienced Grade 3 adverse events and three had Grade 3 laboratory abnormalities; however, none were drug related. No treatment discontinuations occurred due to adverse events.[10]

Protocol Defined Virologic Failure (PDVF)

PDVF criteria was met in 25% of patients (36/142) through the interim cut-off date of February 14, 2019.[1] PDVF was observed across all age cohorts, weight bands, and formulations. For the 36 cases of virologic failure, 18/36 (50%) occurred in children and adolescents ≥ 6 years, 6/36 (17%) in children 2 to < 6 years, and 12/36 (33%) in children < 2 years of age. Genotypes were available on or near the

PDVF timepoint for 22 of the 36 patients (61%). Evidence of treatment-emergent resistance-associated INSTI substitutions were observed in 8/36 (22%) of patients at PDVF: T66I, n=1; L74M, L74I, n=2; E92E/Q, n=1; G118R, G118G/R, n=5; E138E/K, n=1; R263K/R, n=1; E157Q, n=1. A single INSTI associated secondary substitution (E157Q or L74I) emerged in 2 patients; six patients had on study emergence the rare INSTI-associated substitutions G118R or R263K.

Safety Data

Overall, no new safety issues were reported in pediatric patients and the nature of the adverse events (AEs) was comparable to the safety profile of DTG established with the adult population.[1] Overall, serious AEs (SAEs) and ≥3 Grade AEs occurred more frequently in patients weighing < 14 kg. SAEs were reported in 15 patients through Week 24, most often from the Infections and Infestations and Immune System disorders system organ class. One additional SAE was reported between Week 24 and 48. The observed higher frequency of SAEs and ≥3 Grade AEs in younger/lighter infants from P1093 is similar to the overall picture in a similar study (IMPAACT 1066), a PK and dose-finding study of raltegravir in participants from 4 weeks of age.[12] This observation most likely reflects the background increased morbidity/mortality due to diarrhea and pneumonia in children <2 years of age in low and middle-income countries (LMIC).[13] The most common AEs reported through Week 24 in the all-treated population taking the DT formulation were cough (13%), diarrhea (19%), nasal congestion (13%), and gastroenteritis (19%). No AEs led to discontinuation or study withdrawal. Three patients died during the study; none were considered study drug related.

Additional Information

Further analyses of the IMPAACT P1093 studies are available.[14-16] Additionally, characterization of virologic failure in the P1093 study was conducted to assess the impact of observed INSTI resistance substitutions on DTG susceptibility.[17,18]

THE ODYSSEY STUDY

The ODYSSEY Study is a Phase 3, open-label, randomized, non-inferiority trial evaluating the safety and efficacy of DTG-based anti-retroviral therapy (ART) compared to standard of care (SOC) in 792 HIV-infected children (age < 18 years) starting first line ART (ODYSSEY A, n=383) or switching to second line ART (ODYSSEY B, n=409).[2,3]

The primary outcome was time to virological or clinical failure by week 96:[2]

Virological failure:

- Insufficient virological response < 1 log drop at week 24 (or viral load ≥ 50 copies/mL at week 24 in patients with viral load at baseline < 500 copies/mL) with antiretroviral therapy switch for viral failure

or

- Confirmed (x2) viral load ≥ 400 copies/mL at any time after week 36

Clinical failure:

- Any new or recurrent severe WHO 3 or WHO 4 event
- Death due to any cause

Table 3. Baseline Characteristics[3]

Characteristics	All groups (N=792)
Median age (years)	11.4
Female gender	49%
WHO stage 3/4	28%
CD4% < 15%	31%
African	89%

Table 4. ART Regimens[3]

	ODYSSEY A (N=383)		ODYSSEY B (N=409)	
Arm	DTG (n=189)	SOC (n=194)	DTG (n=203)	SOC (n=206)
3rd Agent	DTG	NNRTI (81%) bPI (19%) INSTI (1%)	DTG	NNRTI (3%) bPI (96%) INSTI (1%)
NRTI	ABC+3TC (83%) TDF+XTC (16%)[a] ZDV+3TC (1%)		ABC+3TC (54%) TDF+XTC (25%)[a] ZDV+3TC (20%)	

[a] 1 ODYSSEY A SOC and 1 ODYSSEY B SOC participant initiated TAF+FTC

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; NRTI = nucleoside reverse transcriptase inhibitor; SOC = standard of care; XTC = lamivudine or emtricitabine; ZDV = zidovudine; bPI = boosted protease inhibitor; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor

Efficacy Results

At Week 96, 47 patients (14%) in the DTG arm and 75 patients (22%) in the SOC met the primary endpoint of virological or clinical failure in the pooled analysis (-8% [-13.5% to -2.6%]; *P* = 0.004). DTG was found to be superior to SOC at Week 96 based on a 10% non-inferiority (NI) margin.

Table 5. Proportion with virological or clinical failure at Week 96[2]

	DTG virological/clinical failure	SOC virological/clinical failure	Treatment difference
Total (ODYSSEY A + ODYSSEY B)	47 (14%)	75 (22%)	-8% [-13.5% to -2.6%]; *P* = 0.004[a]
ODYSSEY A	15 (10%)	34 (23%)	-12.5% [-20.6% to -4.3%]; *P* = 0.003[b]
ODYSSEY B	32 (17%)	41 (21%)	-4.6% [-11.8% to 2.7%]; *P* = 0.22[c]

[a] 10% NI margin [b] 12% NI margin [c] 12% NI margin

Following the primary endpoint, participants in Africa and Thailand (n=683) consented to extended follow-up for up to 3-years, during which time they were switched to DTG following their national guidelines. At Week 192, 76 (20%) in the DTG arm and 129 (34%) SOC patients experienced treatment failure (-13.3% [-19.2,-6.5]; *P*<0.001).[3] Thirteen percent of SOC patients had switched to DTG, without prior treatment failure before Week 192.

By the end of follow-up (median 5.5 years [IQR 4.5 – 6.0], 309 of SOC arm had switched to DTG (99% of those completing the extended follow-up).[3] Ninety-three percent of participants with VL less than 400 copies/mL pre-switch to DTG, remained suppressed post-switch.

Safety

Table 6. Adverse Events by Week 192 (Intention-to-Treat)[3]

	DTG (n = 392)	SOC (n = 400)	*P*- value[a]
Adverse Events (AEs) ≥ Grade 3	157	192	0.1
Serious AEs[b]	85	66	0.98
ART-modifying AEs	8	24	0.008

[a] Comparing number of patients with at least 1 event; [b] 82% of serious AEs were hospital admissions

ART = antiretroviral therapy; DTG = dolutegravir; SOC = standard of care.

ODYSSEY sub-studies

WB-PK1 Sub-study

- WB-PK1:[4] The PK of DTG in children in weight bands 3 - <25 kg
  - 3 - < 14 kg: (Lower WB PK-1) Dispersible DTG formulation
  - 14 - < 25 kg (Part 1): Film-coated DTG formulation
  - 14 - <25 kg (Part 2): Dispersible and film-coated formulation (increased dose)

The PK of DTG 5 mg dispersible tablets in children weighing 6 - <20 kg was evaluated in 28 children from South Africa, Uganda and Zimbabwe.[4] Patients were dosed using WHO weight bands: 6 - <10 kg, DTG 15 mg; 10 - <14 kg, DTG 20 mg; 14 - < 20 kg, DTG 25 mg once daily. In children weighing 10 - < 20 kg, C_{trough} values were comparable to children who weighed 20 - < 40 kg and adults who received DTG 50 mg once daily. Children weighing 14 - < 20 kg also exhibited bioavailability data similar to adults. There was higher PK variability in the lower weight band group (6 - < 10 kg); further data is forthcoming on children who weigh 3 - < 10 kg.

The safety and PK of DTG 30 mg (using 5 mg dispersible tablets) and DTG 50 mg in children weighing 20 - <25 kg was assessed.[5] PK sampling was conducted at baseline, and 1, 2, 3, 4, 6, and 24 hours in fasted children after ingesting DTG 50 mg or six 5-mg dispersible DTG tablets (30 mg total). The C_{trough} and AUC_{0-24h} PK values for the DTG 50 mg and the DTG 30 mg doses were similar; however, the C_{max} for both doses was higher than the adult reference values.

WB-PK2 Sub-study

ODYSSEY sub-study WB-PK2 was a crossover pharmacokinetic study of DTG in 28 children from Uganda and Zimbabwe weighing 25 - < 40 kg with dose change to the adult 50 mg dose of DTG once daily.[6] Children were switched from currently approved pediatric DTG doses (DTG 25 mg for weight range 25 - < 30 kg [n=18], DTG 35 mg for weight ranges 30 - < 40 kg [n=10]) to the adult 50 mg dose once daily to simplify DTG administration. Pharmacokinetic sampling (hours 0, 1, 2, 3, 4, 6, 24) was taken on the initial doses and after the switch to film-coated DTG 50 mg. Study participants were followed for 30 weeks (range 12-30). The pediatric PK results (including C_{trough}, C_{max}, $AUC_{0-24\ h*mg/L}$,) were comparable to the adult PK reference parameters for both weight ranges. Adverse events were reported in three participants: Grade 4 cryptococcal meningitis, Grade 3 asymptomatic anemia, and Grade 3 neutropenia.

INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT) 1026 STUDY

The IMPAACT 1026 study is an ongoing, non-randomized, open-label, multi-center, Phase 4 study to evaluate the pharmacokinetics of antiretrovirals, including dolutegravir, during pregnancy and post-partum.[19] Enrolled participants (n=29) were taking dolutegravir 50 mg once daily. Infant samples were collected at 2–10 hours, 18–28 hours, 36–72 hours, and 5–9 days post-delivery. Twenty-nine infants were delivered alive, with data available for 23 at delivery and 22 during the washout period (2 hours - 9 days post-delivery).

Table 7. Pharmacokinetics of Dolutegravir in Neonates Exposed During Maternal Use of Dolutegravir[19]

PK Parameter	Median (IQR)	n
At Delivery (n=23)		
Cord Blood (mcg/mL)	1.67 (1.17 – 2.00)	19
Maternal Plasma (mcg/mL)	1.24 (0.57 – 1.68)	23
Cord Blood/Maternal Plasma Ratio	1.25 (1.07 – 1.40)	18
Infant Washout Samples After Delivery (n=22)		
C_{max} (mcg/mL)	1.64 (1.31–2.38)	18
$T_{1/2}$ (hour)*	32.8 (25.9–35.9)	16
Concentration (2–10 hours, mcg/mL)	1.73 (1.33 – 2.41)	17
Concentration (18–28 hours, mcg/mL)	1.53 (1.04 – 1.91)	18
Concentration (36–72 hours, mcg/mL)	1.00 (0.66 – 1.65)	17
Concentration (5–9 days, mcg/mL)	0.06 (0.04 – 0.14)	17

PK=pharmacokinetics; IQR=interquartile range; C_{max}=maximum plasma concentration; T_{max}=time to maximum concentration; $T_{1/2}$=elimination half life

* excluding one breast fed infant for whom half-life could not be reliably calculated

ADDITIONAL INFORMATION

Other studies have assessed pharmacokinetic profiles DTG in pediatric patients to determine dose optimization and have evaluated the safety and efficacy of DTG in various age ranges of pediatric patients.[20-24]

This information is scientific and non-promotional in nature and is not intended for further distribution.

The described use of this product has not been approved by the FDA; therefore, no conclusions should be drawn about the safety or efficacy of this product. This information is not intended to offer recommendations for using this product in a manner inconsistent with its approved labeling. Please consult the Prescribing Information. For ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877-844-8872.

Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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