

## Cross-Discipline Team Leader Memorandum

<b>Date</b>	June 8, 2016
<b>From</b>	Yodit Belew, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Memorandum
<b>NDA/NDA #</b>	204790
<b>Supplement #</b>	S-08 (b) (4)
<b>Applicant</b>	GSK
<b>Date of Submission</b>	December 9, 2015
<b>PDUFA Goal Date</b>	June 9, 2016
<b>Proprietary Name / Established (USAN) names</b>	Tivicay (dolutegravir)
<b>Dosage forms / Strength</b>	New proposed dosage strength tablet: 10mg, 25mg Approved dosage forms: 50 mg tablets
<b>Proposed Indication(s)</b>	Treatment of HIV infection
<b>Recommended:</b>	-Approval for pediatric patients weighing 30 to <40kg [Supplement 08] (b) (4)

This memorandum summarizes several important labeling, regulatory and inspection issues that occurred after the reviews of the pediatric data to NDA 204790 were completed. The first section summarizes the overall PK, safety and efficacy outcomes from trial P1093 in Cohorts I and IIA. The second section addresses the discrepancy between the primary clinical reviewer's efficacy findings and the results included under section 14 of the USPI. Section 3 addresses preliminary findings from the inspection of one of the clinical site by the EMA. Specifically, it discusses the information submitted by the IND holder (NIH, DAIDS), and what actions the review team plans to take. Section 4 and 5 discusses the regulatory actions to be taken as it relates to the sub-populations studied and the PREA PMRs.

### Section 1 – Summary of PK, Safety and Antiviral Activity (Efficacy)

#### Background

Please refer to Drs. Mark Needles and Su-Young Choi's, clinical and clinical pharmacology reviews, respectively, for detailed analyses of the PK, safety and antiviral activity (efficacy) of DTG in INSTI-naïve, treatment-experienced pediatric patients.

Tivicay (dolutegravir, DTG) was approved on August 12, 2013 for the treatment of HIV infection in adults and pediatric patients 12 years and older and weighing at least 40kg. Week 24 results from study P1093 supported the pediatric indication in HIV infected adolescent patients who are treatment-naïve or treatment-experienced, but INSTI naïve.

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<sub>24</sub> and C<sub>24h</sub>) observed at the 50 mg QD dose. Forty-six subjects were enrolled into Cohorts I and IIA. The current submission updates the

adolescent results with Week 48 findings and proposes to extend the indication to

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Specifically, it includes:

- Week 48 data for adolescents  $\geq 12$  to  $< 18$  y/o (Cohort I)
- Week 24 data for children  $\geq 6$  to  $< 12$  y/o (Cohort IIA)
- Population PK analysis from Cohort I and Cohort IIA
- New CMC data for the 10 mg and 25 mg tablet formulations

Although the protocol enrolled subjects into cohorts based on age, the proposed dosing recommendations for patients (b) (4) is based on weight. The following are the weight-bands used during the clinical trial and subjects were dosed according to weight; the goal of dosing was DTG once daily oral dose of approximately 1mg/kg across the 4 weight bands with a maximum dose of 50mg once daily.

**Table 1: DTG Dosing Regimen by Weight**

Weight Band (kg)	DTG dose (mg)
15 to $< 20$	20
20 to $< 30$	25
30 to $< 40$	35
$\geq 40$	50

## Results

### • Pharmacokinetics

Small number of subjects (n=4) were enrolled for intensive pharmacokinetics in the 20 to  $< 30$  kg weight band; based on the small sample size, dolutegravir exposures from pediatric subjects in the 20 to  $< 30$  kg weight band in the intensive PK group were significantly lower as compared to the target exposures (i.e., DTG exposures in adults). In the population pharmacokinetic analyses, three out of seven subjects in this weight band achieved exposures lower than the lower limit of the target exposure (80% of exposures observed in adults). In addition, there is limited sparse PK data (and no intensive PK data) in pediatric subjects weighing 15 to  $< 20$  kg administered the tablet formulation. (b) (4)

### • Antiviral Activity/Efficacy (Partial Extrapolation)

The efficacy results for Cohorts I and IIA were acceptable when evaluating the overall outcome by age. Based on FDA's snapshot analysis, overall, 63% of subjects had HIV RNA  $< 50$ c/mL at Week 24. For Cohort 1 the results were 65% (15/23) and 61% at (14/23) Week 24 and 48, respectively. In Cohort IIA, 61% (14/23) were suppressed at Week 24. Although the efficacy results by age are encouraging, the efficacy outcome by weight would be more appropriate to establish the PK/PD relationship.

Because the protocol was not written to enroll subjects by weight-band criteria, the efficacy analysis based on weight-band is underpowered, thus the interpretation of the results should be with caution. Evaluation of the efficacy outcome based on weight-bands was conducted because dosing recommendations are being provided for pediatric patients (b) (4). Across both cohorts, 71% (17/24) of subjects in the  $\geq 40$  kg weight-band and 55% (6/11) of subjects in the 30 to  $< 40$  kg weight-band

achieved virologic suppression at Week 24. Too few subjects were enrolled in the 20 to <30kg or 15 to <30kg weight-bands.

**Table 2**  
**Proportion (%) With HIV-1 RNA <50 c/mL at Week 24 by Weight-Band**

	<b>Cohort I N=23</b>	<b>Cohort IIA N=23</b>	<b>Cohorts I and IIA N=46</b>
<b>Weight Band</b>			
≥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.

- **Safety**

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 or higher adverse events reported in more than one subject and possibly related to DTG. No serious adverse events were considered to be related to DTG. 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. However, rash was reported more frequently in pediatric subjects than adults-- 37% vs. ~8% in the Phase 3 trials in ART-naïve adults. Though higher percentages of rash-related AEs were reported in children, the small sample size is likely contributing to the seemingly higher percentage of events. In addition, only one pediatric subject developed treatment-related rash (Grade ≥ 2); this event rate is similar to the proportion of ≥Grade 2 and treatment-related rashes reported during the adult clinical trials. In summary, no new or unexpected toxicities were observed warranting changes to the USPI.

In conclusion, DTG was generally safe and tolerated in children. The overall antiviral activity was comparable to the efficacy outcome observed in treatment-experienced adult subjects. While the exposure of DTG in weight-band 30 to less than 40kg was acceptable, the exposures in weight-band 20 to less than 30 kg were significantly lower as compared to the target exposures (i.e., DTG exposures in adults) and limited PK data is available for the 15 to less than 20kg weight-band. (b) (4)

## **Section 2 – USPI, Section 14**

Based on the results of the analysis conducted by Dr Needles, the following was proposed for Section 14 of the USPI:

At Week 24, the proportion of subjects with HIV-1 RNA less than 50 copies per mL in Cohort 1 and Cohort 2A was 65% (15/23) and 61% (14/23), respectively.

At Week 48, the proportion of subjects from Cohort 1 with HIV-1 RNA less than 50 copies per mL was 61% (**14/23**). Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 71% (17/24) of subjects weighing at least 40 kg and 55% (6/11) of subjects in the 30 to less than 40 kg weight-band. At Week 48, 63% (19/23) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed.

The Sponsor however proposed alternate wording for labeling, as summarized below:

At Week 24, the proportion of subjects with HIV-1 RNA less than 50 copies per mL in Cohort 1 and Cohort 2A was 70% (16/23) and 61% (14/23), respectively. At Week 48, the proportion of subjects from Cohort 1 with HIV-1 RNA less than 50 copies per mL was 61% (14/23). Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 75% (18/24) of subjects weighing at least 40 kg and 55% (6/11) of subjects in the 30 to less than 40 kg weight-band. At Week 48, 63% (**12/19**) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed.

This discrepancy was a typographical error and I agree with the Sponsor's calculation: 63% (19/23).

Additional discrepancies are also noted for Cohort 1. Noted are the differences in efficacy outcome for Cohort 1: overall Week 24 results; Week 24 results for subjects weighing at least 40kg; and Week 48 results for cohort 1 subjects weighing at least 40kg.

The Sponsor speculated that the difference may be due to the Snapshot analysis window used. The FDA's Guidance for Industry HIV-1 Infection: Developing Antiretroviral Drugs for Treatment has a window of 127-210 days for the Week 24 visit (Table A). It is possible that a specific subject (Subject 400321) may be driving the difference. This subject had HIV-1 RNA of 470 copies/mL on Day 169, 2307 copies/mL on Day 195 and 44 copies/mL on Day 204. Additionally, only 19 subjects in Cohort 1 weighed at least 40 kg, with 12 subjects being suppressed at Week 48. The Sponsor thus proposed an update to the virologic outcomes results.

After additional review of the data, the review team agrees with the Sponsor's analysis and has accepted their revised proposal to section 14 of the USPI.

### **Section 3- Clinical Site Inspections**

- **Background**

Trial P1093 is an ongoing, Phase 1/2, open-label, single-arm, multicenter, international trial evaluating the pharmacokinetic, antiviral activity and safety of DTG in children 4 weeks to less than 18 years of age. While GSK/ViiV is the Sponsor for the application, the trial was conducted by Division of AIDS (DAIDS) through the IMPAACT network. A total of 46 subjects ages 6 to less than 18 years of age have been enrolled from 17 sites

from 3 countries – 14 sites in the United States, 2 sites in Thailand, and 1 site in South Africa. Table 3 summarizes the distribution of subjects by country.

**Table 3 Subjects enrolled in Trial P1093**

<b>Country</b>	<b>Number of Sites Enrolling</b>	<b>Number of Subjects Enrolled</b>
United States	14	36
Thailand	2	6
South Africa	1	4

The interim study report summarizing Week 48 results for Cohort 1 and Week 24 results for Cohort IIA was submitted to the FDA on December 9, 2015. (b) (4)

[REDACTED] . On May 31, 2016, unsolicited new information was communicated to the Division through DAIDS summarizing several protocol violations identified during inspection (details summarized below).

It should also be noted that the FDA does not rely on inspections conducted by other regulatory agencies to make regulatory decisions. As such, although the inspection report was taken into consideration and reviewed, the final regulatory decision by the FDA is independent of other agencies.

DAVP does not routinely request clinical site inspections for pediatric trials evaluating antiretroviral drugs unless a specific concern or issue is identified. However, clinical pharmacology analytical sites are generally inspected because HIV pediatric trials rely on the pharmacokinetic data as the primary endpoint to support pediatric dosing recommendation. In this case, the analytical site (b) (4) had been recently inspected; thus the recommendation from the Division of New Drug Bioequivalence Evaluation (DNDBE), Office of Study Integrity and Surveillance was that no new/additional inspection is necessary.

**• Summary of Inspection Report**

GSK/ViiV submitted this efficacy supplement for dolutegravir to the FDA (b) (4)

[REDACTED] The inspection of the SA site generated concerns about inclusion criteria violations. Specifically, 11/12 subjects enrolled at this site lacked a viral load result from within the 8-12 week window prior to screening (inclusion criteria 4.14). Of note, although 12 subjects are identified through the inspection report as being enrolled, not all subjects are from Cohorts I or IIA. In fact, 4 subjects are from Cohorts I and IIA and only one subject is affected by the reported violations, as summarized below.

As described, P1093 is an ongoing trial evaluating dolutegravir in pediatric patients 4 weeks to less than 18 years of age. The current submission pertains to children 6 to less than 18 years of age, which includes Cohorts I and IIA. Forty-six subjects have been enrolled for Cohort I and IIA and are included in this submission. Of the 46, 4 were enrolled from South Africa. Of the 4, only 1 subject is in the 30 to less than 40kg weight band while the other 3 subjects weighed <30 kg. (b) (4)

The one subject (Subject ID 801806) whose weight was in the 30 to less than 40kg weight-band contributed to the safety and efficacy data. No PK data was submitted for this subject. Of note, this subject was considered a virologic failure (HIV RNA 199 copies/mL) but remains on study.

In summary, the data from this one subject do not change the overall conclusion of the study results. In fact, if excluded, the virologic outcome would appear higher than what is currently reported for subjects weighing 30 to less than 40kg - 55% (6/11) vs. 60% (6/10). Therefore, as the overall conclusion of the trial results are unaffected, the Division plans to take regulatory action on the PDUFA goal date and approve the dosing recommendation for the 30 to <40kg weight-band. However, in the interest of completeness, DAVP plans to communicate with the Sponsor (b) (4) to obtain the full inspection report and learn about the final conclusions of the inspection. Furthermore, (b) (4)

#### Section 4- Regulatory Action

- **Approval Action –Supplement 08**  
DAVP will take action on the PDUFA goal date June 9, 2016 to approve dolutegravir for the treatment of HIV infection in pediatric patients who are INSTI-naïve and weigh 30 to less than 40kg.

#### Section 5 – PREA PMRs

- For INSTI-naïve pediatric patients:

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The Division therefore plans to release the current PREA PMR (2078-1) for children 4 weeks to less than 12 years of age (b) (4).

We are waiving the pediatric study requirement for 0 to less than 4 weeks of age in INSTI-naïve and INSTI-experienced patients because with improvement in perinatal transmission prevention strategies there are insufficient numbers of neonatal subjects to be enrolled. Further, even when neonates are identified for enrollment, by the time enrollment is accomplished, dosing is initiated, and drug concentrations have reached steady state, the subjects are likely to be older than 4 weeks of age.

Summarized below are the PREA PMRs for INSTI-naïve pediatrics patients. PREA PMR 2078-1 was issued at the time of the original approval. (b) (4)

2078 -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 4 weeks to less than 12 years of age. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, 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.

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(b) (4)

Summarized below are the PREA PMRs for INSTI-experienced pediatrics patients.  
PREA PMR 2078-2 was issued at the time of the original approval. (b) (4)

2078-2 Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected subjects, ages 2 years to less than 18 years, who are integrase strand transfer inhibitor (INSTI) experienced with certain INSTI associated resistance substitutions or clinically suspected INSTI resistance. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, 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.





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06/08/2016