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Committee for Medicinal Products for Human Use (CHMP)

Viread

(tenofovir disoproxil fumarate)

Procedure No. EMEA/H/C/000419/P46/243

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. INTRODUCTION

In accordance with Article 46 of Regulation (EC) No 1901/2006, Gilead is submitting the 144 week interim report for Study GS-US-104-0321, '*A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents*'.

The 48 week interim report for Study GS-US-104-0321 was submitted in accordance with Article 46 on 09 September 2009 (eCTD sequence 0013). The report was then submitted in support of a variation application to extend the indication of Viread for the treatment of HIV-1 in treatment-experienced adolescents 12 to < 18 years of age (EMEA/H/C/419/II/0098; eCTD sequence 0029). **Following major objections raised by the CHMP during the variation assessment, Gilead chose to no longer pursue the indication extension.**

The MAH stated that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, **the data submitted do not influence the benefit-risk balance for Viread** 245 mg film-coated tablets and therefore no further regulatory action is required on the marketing authorisation for Viread 245 mg film-coated tablets.

2. SCIENTIFIC DISCUSSION

Pediatric development is ongoing in HIV-1 infected pediatric subjects. Three Gilead-sponsored clinical studies of tenofovir DF in HIV-1 infected pediatric subjects have been completed (GS-02-983, GS-01-926, and GS-01-927) and 2 studies are ongoing (Study GS-US-104-0321 and Study GS-US-104-0352). All studies were (or are being) conducted in accordance with the principles of Good Clinical Practice and with the version of the Declaration of Helsinki that applied at the time of study conduct. Approval of ethics committees or institutional review boards was sought and informed consent/assent was obtained from all subjects/guardians as appropriate.

Data from the completed studies in addition to the interim 48-week data from Study GS-US-104-0321 and the interim 48-week and 96-week data from Study GS-US-104-0352 have been previously submitted.

Study GS-US-104-0352 is long-term, Phase 3 study being conducted in HIV-1 infected subjects 2 to < 12 years of age. This is an open-label, comparator-controlled study in subjects on a stable antiretroviral regimen including stavudine or zidovudine at study entry. Both the commercially available tenofovir DF tablet and an oral powder formulation of tenofovir DF suitable for use in younger children are being investigated. Study GS-US-104-0352 will provide long-term efficacy and safety data for tenofovir DF in HIV-1 infected subjects 2 to < 12 years of age.

This submission presents interim 144-week efficacy and safety data for HIV-1 infected subjects 12 to < 18 years of age treated with the commercially available tenofovir DF tablet in an ongoing, long-term, Phase 3 study, GS-US-104-0321. This was a study in treatment-experienced adolescents who were failing to achieve virologic suppression on their existing antiretroviral regimen. The first 48 weeks of GS-US-104-0321 consisted of a randomized, double-blind, placebo-controlled treatment period (ie, the randomized phase). The study had a randomized design to provide a controlled assessment of efficacy and safety of the tenofovir DF 300-mg tablet plus a genotype-guided optimized background regimen (OBR) versus placebo plus OBR.

Following the randomized phase, eligible subjects were given the option to roll over into 3 consecutive 96-week study extensions (collectively referred to as the extension phase) to receive open-label

tenofovir DF in addition to a background regimen for a total duration of up to 336 weeks. The study is ongoing in the open-label extension phase.

This submission presents **data from 81 subjects** treated with tenofovir DF in Study GS-US-104-0321 (the All TDF group), including 45 subjects who were randomized to tenofovir DF plus a genotype-guided OBR at study entry (the tenofovir DF subgroup) and 36 subjects who were randomized to placebo and switched to tenofovir DF plus a background regimen (the placebo/TDF subgroup).

Of the 81 subjects in the All TDF group, **21 subjects are ongoing at the data cut-off for the 144-week analysis.** Interim data reported in this submission demonstrated the following for tenofovir DF in HIV-1 infected subjects 12 to < 18 years of age:

• **Interpretation of long-term efficacy in this study population of antiretroviral treatment-experienced, HIV-1 infected subjects 12 to < 18 years of age is compromised by a high attrition rate, resulting primarily from extensive baseline HIV-1 drug resistance and a high degree of nonadherence/noncompliance**. However, some subjects were able to achieve and maintain virologic and immunologic responses to treatment with tenofovir DF in combination with a background regimen (the tenofovir DF subgroup and the placebo/TDF subgroup with HIV-1 ribonucleic acid (RNA) < 1000 copies/mL at the time of switch to tenofovir DF). Virologic response was poor for subjects who did not respond to a genotype-guided OBR during the randomized phase and who switched to tenofovir DF during the extension phase (the placebo/TDF subgroup with HIV-1 RNA ≥ 1000 copies/mL at the time of switch to tenofovir DF).

• The resistance development in antiretroviral treatment-experienced adolescents with extensive resistance in their HIV-1 at baseline was comparable to that observed in heavily treatment-experienced adults. The K65R mutation developed in 1 subject in the All TDF group.

• The safety profile of tenofovir DF in pediatric subjects aged 12 to < 18 years with HIV-1 infection was generally consistent with the known safety profile in adults. In these adolescent subjects, **modest decreases from baseline in spine and total body bone mineral density (BMD) Z-scores were seen over the first 48 to 96 weeks of treatment with tenofovir DF (versus 24 to 48 weeks in adults), with little or no further progression through Week 144.** No new safety concerns were identified from the long-term data.

3. Rapporteur's Overall Conclusion and recommendation

As a reminder, the MAH submitted the 48 weeks results of the ongoing study GS-US-104-0321 in June 2010 to support the extension of the indication for Viread in treatment-experienced adolescents infected with HIV. Following review of the data the CHMP concluded the following: "The study initiated in 2006 is characterized by an outdated design and was conducted exclusively in Brazil and Panama. No EU adolescents were included in the pivotal study and few data from EU children are available to support the application. The study population consists of highly treatment experienced adolescents.

The study failed to meet its primary efficacy endpoint. No significant differences were found in virologic response between patients treated with TDF or placebo (+OBR). The 300mg TDF yielded to similar exposure in adolescents as compared to adult patients. The poor efficacy reported in the TDF arm could reflect the pejorative baseline characteristics (in terms of OBR susceptibility and TDF resistance) in adolescent included in the TDF arm. However, concerns remain to judge the benefit of a drug in adolescents on a basis of a "negative" study on virologic endpoints.

As regards the safety, the bone toxicity of this drug makes it "a priori" a non optimal candidate for the paediatric population. The trend for a lower increase of total BMD in the tenofovir group compared to the placebo group as well as the occurrence of osteopenia after a medium term duration raises concerns on bone toxicity. Furthermore, no long term data are available in this population.

Overall, the study submitted raised concerns on the safety and efficacy of Viread in adolescents and cannot be regarded as an adequate basis for the extension of indication of Viread in this target population and the CHMP raised major objections".

Following the major objections raised by the CHMP the MAH had not pursued the request to extend the therapeutic indication to include treatment-experienced adolescents 12 to < 18 years of age and with body weight ≥ 35 kg. The results of this study were reflected in the SmPC.

In section 4.4, the following warning has been added:

"*Paediatric population:* Viread may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1)".

In section 5.1: "*Paediatric population:* In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm^3 and the mean baseline plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/ml. The primary efficacy endpoint was time-weighted average change from baseline through week 24 ($DAVG_{24}$) in plasma HIV-1 RNA. No additional benefit over OBR was observed with the addition of tenofovir disoproxil fumarate compared to placebo ($DAVG_{24}$ -1.58 $\log_{10}$ copies/ml *versus* -1.55 $\log_{10}$ copies/ml respectively, p = 0.55). K65R developed in 1 subject in the tenofovir disoproxil fumarate group. In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. The efficacy and safety data derived from this study do not support the use of Viread in adolescents".

The 144-week data submitted in the setting of article 46 did not bring new data that may change the CHMP conclusion as regards the use of VIREAD in HIV-infected adolescents. The long-term efficacy data are very limited and hardly interpretable and the safety data up to 144 weeks did not provide reassurance as regards the bone toxicity of the drug. No change of the SPC is warranted based on the poorly informative data gained through 144 weeks of the study.

Recommendation

☒ Fulfilled – No further action required.