EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/807651/2015
Procedure Management and Committees Support Division

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

Vitekta

Elvitegravir

Procedure no.: EMA/H/C/002577/P46/013

Note

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

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1. Introduction

The present paediatric data is submitted by the MAH in accordance with article 46 of Regulation EC No 1901/2006.

The applicant has submitted an abbreviated clinical study report (CSR) of the final data from Study GS-US-183-0130 in accordance with Article 46 of the Regulation (EC) No 1901/2006. An interim Week 192 CSR for Study GS-US-183-0130 was submitted with the initial Vitekta Marketing Authorization Application.

About the product

Vitekta® tablets contain elvitegravir (EVG; 85 or 150 mg). Vitekta was approved for commercial marketing in the United States on 24 September 2014 and in the European Union (EU) on 13 November 2013.

In the EU, Vitekta is indicated to be coadministered with a ritonavir (RTV) boosted protease inhibitor and with other antiretroviral (ARV) agents, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are infected with HIV-1 without known mutations associated with resistance to EVG. Vitekta is also part of an approved single tablet regimen (Stribild®: EVG/cobicistat [COBI]/emtricitabine/tenofovir disoproxil fumarate) for the treatment of HIV-1 infected adults.

Study GS US 183 0130 was conducted to provide continued access to EVG+RTV for adult and paediatric subjects who completed a prior EVG+RTV study without experiencing any treatment limiting toxicity. In addition, long-term safety of EVG+RTV in combination with other antiretroviral agents in subjects who have completed a prior EVG+RTV treatment study were also observed.

This submission presents an abbreviated clinical study report (CSR) of the final data from Study GS-US-183-0130 in accordance with Article 46 of the Regulation (EC) No 1901/2006. An interim Week 192 CSR for Study GS-US-183-0130 was submitted with the initial Vitekta Marketing Authorization Application

Approved indication(s) and posology

Indication

Vitekta is indicated for the treatment of the following infections in adults:

Vitekta coadministered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir (see sections 4.2 and 5.1).

Posology

Adults

The recommended dose of Vitekta is one 85 mg tablet or one 150 mg tablet taken orally once daily with food.

Paediatric population

The safety and efficacy of elvitegravir in children aged 0 to less than 18 years have not yet been established. No data are available.

1. Scientific discussion

1.1. Clinical aspects

Study GS-US-183-0130 was a Phase 2, rollover, open label, multicenter, multiple dose, single arm extension study.

The primary objective was to observe the long-term safety of EVG+RTV in combination with other antiretroviral agents in subjects who have completed a prior EVG+RTV treatment study. Eligible subjects were HIV-1 infected adult and paediatric subjects who had completed a prior EVG+RTV treatment study without experiencing any treatment-limiting toxicity. Subjects were enrolled in this extension study regardless of their baseline HIV 1 RNA level (ie, subjects with baseline HIV 1 RNA levels of either < 50 or ≥ 50 copies/mL were enrolled). Nonvirologically suppressed subjects entering this study had, for the most part, failed prior antiretroviral regimens and had limited treatment options available. Genotyping was not performed at baseline, so subjects who met eligibility requirements were enrolled at the discretion of the investigator.

In this study, subjects who were receiving an RTV boosted protease inhibitor (PI) as part of their antiretroviral regimen took the RTV dose and followed the dosing schedule indicated in the prescribing information for the PI. No additional RTV was required. Subjects whose antiretroviral regimen did not include RTV took RTV 100 mg once daily with their EVG dose. Subjects who were taking lopinavir/r (LPV/r) or atazanavir/r (ATV/r) as part of their antiretroviral regimen received EVG 85 mg tablet once daily due to an established drug drug interaction with these agents; all other subjects received 1 or 2 EVG 150 mg tablets once daily.

While participating in this study, subjects were monitored for safety using periodic assessments of adverse events (AEs), concomitant medications, and clinical laboratory tests. Study visits occurred once every 8 weeks for the first 48 weeks of the study, then once every 12 weeks. Following implementation of protocol amendment 3, subjects who were not treated with EVG in their prior EVG+RTV study were to have an additional study visit at 4 weeks for safety monitoring.

The study was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the protocol.

A total of 192 subjects were enrolled in the study and received EVG. Of the 192 enrolled subjects, 186 were adults and 6 were paediatric subjects. Subject attrition was high, as only 73 subjects (38.0%) completed the study and 119 subjects (62.0%) prematurely discontinued from the study. The most common reasons subjects prematurely discontinued from the study were withdrew consent (29 subjects; 15.1%), lack of efficacy (28 subjects; 14.6%), and investigator's discretion (22 subjects; 11.5%).

The majority of subjects were male (90.1%) and white (72.4%), with a mean age of 46 years in adults (ranging from 18 to 65 years) and 16 years in paediatric subjects (ranging from 15 to 17 years). Categorically, baseline HIV 1 RNA level was < 50 copies/mL in 85 subjects (44.5%), 50 to < 400 copies/mL in 40 subjects (20.9%), and ≥ 400 copies/mL in 66 subjects (34.6%). At

baseline, the mean CD4 cell count was 282 cells/mm3; categorically, 119 subjects (62.6%) had a baseline CD4 cell count > 200 cells/mm3.

The efficacy endpoints for this study included the following:

- The percentages of subjects with HIV 1 RNA < 50 copies/mL
- The percentages of subjects with HIV 1 RNA < 400 copies/mL
- The change from baseline in HIV 1 RNA (log10 copies/mL)
- The change from baseline in CD4 cell count (cells/mm3)

The Efficacy Analysis Set included all enrolled subjects who received at least one dose of EVG and who had at least one post-baseline measurement of either HIV 1 RNA or CD4 cell count. This was the primary analysis set for efficacy analyses.

The percentage of subjects with HIV-1 RNA < 50 copies/mL or < 400 copies/mL were summarized using Missing = Excluded (M = E) analysis. For M = E analysis, subjects with missing data were excluded from both the numerator and denominator (ie, only non-missing data were included when calculating percentages).

Change from baseline in HIV-1 RNA (log10 copies/mL) and CD4 cell count (cells/mm3) were summarized descriptively (sample size, mean, standard deviation, 95% CI, median, Q1, Q3, minimum, and maximum) for each study visit.

Resistance testing was performed if subjects had HIV 1 RNA > 400 copies/mL at the time of study discontinuation or upon virologic rebound and the investigator requested to reconfigure the subject's antiretroviral regimen without including EVG/r.

Efficacy Results

Data were summarized for adult subjects by baseline HIV 1 RNA levels (ie, the baseline HIV 1 RNA < 50 copies/mL group and the baseline HIV 1 RNA ≥ 50 copies/mL group).

For the 83 subjects in the baseline HIV 1 RNA < 50 copies/mL (M = E analysis) subject group, the number and percentage of subjects with plasma HIV 1 RNA levels < 50 copies/mL at Weeks 48, 96, 144, and 192 were 72 of 80 (90.0%), 63 of 73 (86.3%), 59 of 68 (86.8%), and 56 of 63 (88.9%), respectively, and at Weeks 240, 288, 336, 384, and 408 (end of study) were 50 of 59 (84.7%), 51 of 55 (92.7%), 45 of 51 (88.2%), 42 of 46 (91.3%), and 9 of 9 (100%), respectively. The number and percentage of subjects with plasma HIV 1 RNA levels < 400 copies/mL were slightly higher, with similar trends.

For the 102 subjects in the baseline HIV 1 RNA ≥ 50 copies/mL (M = E analysis) subject group, the number and percentage of subjects with plasma HIV 1 RNA levels < 50 copies/mL at Weeks 48, 96, 144, and 192 were 26 of 73 (35.6%), 29 of 64 (45.3%), 30 of 52 (57.7%), and 31 of 45 (68.9%), respectively, and at Weeks 240, 288, 336, 384, and 408 (end of study) were 25 of 36 (69.4%), 26 of 31 (83.9%), 26 of 31 (83.9%), 24 of 27 (88.9%), and 5 of 6 (83.3%), respectively. The number and percentage of subjects with plasma HIV 1 RNA levels < 400 copies/mL were slightly higher, with similar trends.

For the baseline HIV 1 RNA < 50 copies/mL group, as expected from these virologically suppressed subjects, no clinically relevant changes in mean HIV 1 RNA (log10 copies/mL) levels were observed. Mean increases in CD4 cell counts were observed at each assessment point (mean change from baseline range: 31 to 264 cells/mm3).

For the baseline HIV 1 RNA ≥ 50 copies/mL group, mean decreases from baseline in HIV 1 RNA (log10 copies/mL) levels were observed over 408 weeks (mean change from baseline range: −0.18 to−1.59 log10 copies/mL). Mean increases in CD4 cell counts were observed at each assessment

point (mean change from baseline range: 9 to 216 cells/mm3 through 396 weeks (mean change was 511 cells/mm3 at 408 weeks).

Caution is warranted in interpreting these efficacy results due to small sample size and high attrition rate.

A total of 62 adult subjects qualified for resistance analysis, of whom 48 entered the study with pre existing integrase resistance mutations (developed during their original EVG treatment period in Study GS US 183 0105) and 14 had no evidence of integrase resistance at study entry. Among the 48 subjects with pre existing integrase resistance mutations, 39 developed additional integrase resistance mutations during Study GS US 183 0130, 3 had no additional mutations, and 6 had no data available due to assay failures. Among the 14 subjects with no pre existing integrase resistance mutations, 7 developed integrase resistance mutations during Study GS US 183 0130. Among the 85 subjects (all adult subjects) who entered the study fully suppressed with HIV 1 RNA < 50 copies/mL, 9 qualified for resistance analysis. Among these 9 subjects, 4 developed integrase resistance mutations during Study GS US 183 0130.

Overall in Study GS US 183 0130, the majority of resistance development was characterized as an evolution of RT, protease, and integrase resistance that had existed prior to study entry in subjects who were not fully suppressed on their regimen. With regard to integrase resistance, mutation patterns evolved and resulted in a general increase in the level of phenotypic resistance to EVG. Of the 9 subjects who entered the study with fully suppressed HIV 1 RNA, 4 developed integrase resistance.

Paediatric Subjects

For the 6 paediatric subjects, the number and percentage of subjects with plasma HIV 1 RNA levels < 50 copies/mL at Weeks 48, 96, 144, 192, and 240 (no pediatric subjects remained in the study after this visit) were 2 of 6 (33.3%), 1 of 5 (20.0%), 1 of 3 (33.3%), 0 of 2 (0%), and 0 of 1 (0%), respectively. The number and percentage of subjects with plasma HIV 1 RNA levels < 400 copies/mL were slightly higher, with similar trends.

Mean HIV 1 RNA (log10 copies/mL) levels were maintained over 240 weeks (mean change from baseline range: −0.53 to 1.49 log10 copies/mL). Mean decreases in CD4 cell counts were observed at almost every assessment point (mean change from baseline range: −286 to 11 cells/mm3).

Caution is warranted in interpreting these efficacy results due to small sample size and high attrition rate.

All 6 paediatric subjects qualified for resistance analysis, of whom 4 had no evidence of integrase resistance at study entry and 2 had no baseline data. No pediatric subjects developed integrase resistance mutations during Study GS US 183 0130.

Safety Results

The Safety Analysis Set included all enrolled subjects who received at least one dose of EVG. All data collected up to 30 days after subjects permanently discontinued their study drug were included in the safety summaries. This was the primary analysis set for safety analyses.

Most subjects (174 of 186; 93.5%) experienced an AE while receiving EVG (85, 150, or 300 mg) in this study. The most frequently reported AEs (by preferred term) were upper respiratory tract infection (32.3%), sinusitis (26.3%), and diarrhea (25.3%). Most AEs were mild to moderate, not serious, not related to study drug, and few led to study drug discontinuation. Only 6 subjects had a Grade 3 AE that was also considered by the investigator to be related to study drug (necrotizing retinitis, acute pancreatitis, hepatitis B, peripheral neuropathy [2 subjects], and acute kidney injury); no Grade 4 study drug related AEs were reported.

A total of 83 adult subjects (44.6%) had SAEs. Only 3 subjects had an SAE that was considered by the investigator to be related to study drug: necrotizing retinitis, acute pancreatitis, and acute kidney injury. Thirteen subjects died during this study. None of the AEs leading to death were considered by the investigator to be related to study drug. Most SAEs and deaths were due to either complications of the subjects' underlying advanced HIV 1 infection or pre-existing comorbidities.

One adult subject became pregnant during the study. The subject had a spontaneous abortion, which was reported as an SAE and was considered by the investigator to be not related to study drug, concomitant antiretroviral medications, or study procedures.

Few subjects (14 subjects) discontinued study drug due to an AE. All AEs that led to study drug discontinuation were considered by the investigator to be not related to study drug, with the exception of nausea in 1 subject.

A total of 65 subjects (35.1%) had a maximum Grade 3 laboratory abnormality, and 25 subjects (13.5%) had a maximum Grade 4 abnormality. Grade 3 or 4 laboratory abnormalities were most frequently reported for creatine kinase (18 subjects), GGT (18 subjects), serum amylase (15 subjects), urine glucose (15 subjects), and fasting triglycerides (12 subjects). Most of the Grade 3 or 4 laboratory abnormalities were not clinically relevant (eg, creatine kinase elevation or amylase elevation without reported relevant AEs) or were due to underlying comorbidities (eg, glycosuria in subjects with diabetes, GGT elevation in subjects with chronic hepatitis C).

There were no clinically relevant changes from baseline in mean values for systolic blood pressure, diastolic blood pressure, temperature, heart rate, respiration rate, or body weight.

Paediatric Subjects

All 6 pediatric subjects (100%) had an AE while receiving EVG (85 or 150 mg) in this study. The most frequently reported AEs (by preferred term) were cough (4 subjects), and ear pain, nasal congestion, oropharyngeal pain, and pyrexia (3 subjects each). Most AEs were mild to moderate, not serious, and not related to study drug. No Grade 3 or 4 study drug related AEs or AEs leading to study drug discontinuation were reported.

A total of 3 pediatric subjects had SAEs, none of which was considered by the investigator to be related to study drug. Most SAEs were due to either complications of the subjects' underlying advanced HIV 1 infection or pre-existing comorbidities.

One paediatric subject (enrolled at age 16) became pregnant during the study at the age of 18. The subject had an elective abortion, which was only discovered after she completed a social work questionnaire; this is the only documentation of the subject's pregnancy and abortion. A corresponding AE of unintended pregnancy was reported. The subject did not discontinue the study due to these events.

No Grade 3 or 4 laboratory abnormalities were reported for > 1 paediatric subject.

There were no clinically relevant changes from baseline in mean values for systolic blood pressure, diastolic blood pressure, temperature, heart rate, respiration rate, or body weight.

BENEFITS AND RISKS CONCLUSIONS

In this overview, data are presented from Study GS-US-183-0130, which showed that long term exposure to EVG was generally well tolerated when administered in combination with other antiretroviral agents to HIV 1 infected, antiretroviral treatment experienced subjects. No new safety concerns for EVG in the subject populations studied were identified.

Caution is warranted in interpreting these results due to small sample size and high attrition rate.

No updates to the Vitekta prescribing information are warranted in relation to the data presented in this submission. These data also do not change the positive benefit risk balance of Vitekta when used in accordance with the current SmPC.

1.2 Discussion on clinical aspects

The applicant has submitted the result of the long-term follow up of adult and paediatric patients with HIV taking Vitekta. There are no major safety or efficacy issues arising out of it, however the number of 6 paediatric subjects is too small to make any meaningful conclusions.

On the basis of this study, there is no change in the benefit-risk profile of Vitekta for the existing indications. No changes are proposed to the Prescribing information.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The benefit/risk balance remains unchanged and positive in the approved indications at present.

The data provided in this submission do not raise any safety or efficacy concerns for elvitegravir in the paediatric population, although the number of subjects is too small.

Based on these results the applicant proposes no amendments to the SmPC.

No further action is considered necessary.