9 November 2017
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Human Medicines Evaluation Division

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

Emtriva

emtricitabine

Procedure no: EMEA/H/C/000533/P46/051

Note

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

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1. Introduction

On 7-8-17, the MAH submitted a completed paediatric study for Emtriva in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study GS-US-162-0112, '*A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine'* is a standalone study.

2.2. Information on the pharmaceutical formulations used in the study

Emtriva 200 mg capsule or 10 mg/mL oral solution.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for GS-US-162-0112, '*A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine'.* Study GS-US-162-0112 was a rollover study to provide subjects completing Study FTC-203 in South Africa with continued access to emtricitabine.

Study FTC-203 was a multi-centre, open-label, non-randomised Phase 2 clinical study to evaluate the safety, antiretroviral activity and pharmacokinetics of emtricitabine in combination with other antiretroviral agents in paediatric HIV-infected patients. The study enrolled 116 HIV-1 infected, antiretroviral therapy (ART)-naive and ART-experienced, male and female paediatric patients between the ages of 3 months and 17 years, inclusive, across 12 study centres located in the USA (8; 22 subjects), South Africa (2; 59 subjects), Mexico (1; 6 subjects) and Panama (1; 29 subjects).

Subjects were treated in Study FTC-203 for an initial period of at least 48 weeks. This was subsequently extended to 96 weeks, and then extended again until the drug was available via market distribution in the subject's country of residence, providing subjects met and continued to have plasma HIV-1 RNA ≤ 400 copies/mL or, if HIV-1 RNA was > 400 copies/mL, it was < 1.0 $\log_{10}$ above the nadir recorded after Week 8 and there was reliable genotypic evidence showing a lack of viral resistance to emtricitabine.

With the last subjects completing the original 48-week study duration in May 2004, the decision was made to close the FTC-203 study after the last subjects completed their Week 96 visit. In those countries where regulatory approval for market distribution of emtricitabine had yet to be sought and/or was pending, alternative means to continue to provide FTC-203 study participants with access to emtricitabine were implemented.
The purpose GS-US-162-0112 study was to allow those FTC-203 study subjects in South Africa to continue to receive emtricitabine (either capsule or oral solution formulation) beyond completion of the FTC-203 study. Eligible subjects electing to participate thus continued to receive emtricitabine,

administered in combination with other antiretroviral medications, so long as virologic criteria were met.

Study GS-US-162-0112 is now complete. A synoptic clinical study report (CSR) detailing the results of the study is included in this Article 46 paediatric study submission to fulfil the obligation to submit any MAH-sponsored studies involving the use of an authorised medicinal product in the paediatric population to the EMA.

2.3.2. Clinical study

GS-US-162-0112, *'A Rollover Protocol to Provide Subjects Completing the FTC-203 Study in South Africa with Continued Access to Emtricitabine'*

Description

This was an uncontrolled open-label study of follow-on treatment. Subjects were managed using local standard of care practices with the subject returning to the clinic approximately every 12 weeks for study visits (4 visits per year). The Investigator could choose to have the subject return to the clinic on a more frequent basis as part of their standard of care, but these visits were outside of the protocol defined visit schedule.

Data collection was limited to the reporting of adverse events (AEs) that (1) met the criteria for a serious adverse event (SAE), (2) resulted in permanent discontinuation of the study drug, emtricitabine, and/or (3) were associated with skin discoloration (hyperpigmentation).

HIV-1 RNA viral load levels were assessed at each clinic visit to ensure continued subject eligibility regarding the virologic criteria; however, these data were not recorded in the case report form (CRF).

Results

This submission presents the results of the analysis performed after the last subject had completed Study GS-US-162-0112.

In Study FTC-203, 59 subjects were enrolled at 2 study centres in South Africa; of these, 50 subjects continued in the rollover Study GS-US-162-0112 and received at least 1 dose of study drug. Nine of the 50 (18.0%) completed the study, 23 (46.0%) rolled over to Study GS-US-292-1515 and 18 (36.0%) prematurely discontinued the study. Reasons for premature discontinuation of the study were as shown in the table below.

A total of 52.0% (26 subjects) were male. The mean age was 8 years (range, 4 to 16 years). The majority was black (98.0%, 49 subjects).

No subject died and none experienced an AE leading to study discontinuation.

There were 3 pregnancies during the study: one pregnancy was terminated and resulted in incomplete abortion; the other 2 pregnancies resulted in healthy infant births.

Table 1: Subject Disposition
All Enrolled Set

	FTC
Subjects Enrolled	50
Subjects in Safety Analysis Set	50
Subjects Completing Study	9 (18.0%)
Subjects Rolled Over to Study GS-US-292-1515	23 (46.0%)
Subjects Discontinuing Study	18 (36.0%)
Reasons for Prematurely Discontinuing Study	
Serious Adverse Event / Non-Serious Adverse Event	0
Lost to follow-up	1 (2.0%)
Study medication non-compliance	1 (2.0%)
Virologic Failure	8 (16.0%)
Protocol Violation(s)	1 (2.0%)
Investigator and/ or patient request for withdrawal from study	5 (10.0%)
Market Approval	0
Death of patient	0
Other	2 (4.0%)

Table 2: Demographics
Safety Analysis Set

	FTC (N=50)
Age (Years)	
N	50
Mean (SD)	8 (2.5)
Median	8
Q1, Q3	7, 10
Min, Max	4, 16
Sex	
Male	26 (52.0%)
Female	24 (48.0%)
Ethnicity Origin	
Black	49 (98.0%)
Other	1 (2.0%)

A total of 38.0% (19 subjects) experienced hyperpigmentation. The hyperpigmentation usually affected the hands (89.5%, 17 subjects) and feet (42.1%, 8 subjects); other areas affected were the oral mucosa (10.5%, 2 subjects) and arms (5.3%, 1 subject). In 8 of the 19 subjects (42.1%), the hyperpigmentation was reported only at baseline, indicating that it resolved while continuing treatment with FTC.

Thirteen of the 50 subjects had SAEs; all SAEs were assessed by the investigator as not related to emtricitabine. Narratives are provided. Review of these narratives by the assessor indicates that most were due to intercurrent illness or trauma. It is agreed that none seem likely to have been related to treatment with emtricitabine. One case of anaemia and neutropenia appears to have been related to introduction of zidovudine into her ART regimen.

2.3.3. Discussion on clinical aspects

In the adult clinical trials, skin discoloration was reported more frequently in patients treated with emtricitabine, as compared to patients enrolled in control groups. The skin discoloration occurred as hyperpigmentation, most commonly on the palms and/or soles, and was always mild or moderate, generally asymptomatic and without association with any pathologic skin condition. If a subject developed hyperpigmentation while participating in this rollover study, the hyperpigmentation was documented as an AE and a Hyperpigmentation Assessment CRF was completed.
The subject may also have had one or more dermatological consultations and possibly other explorations, as deemed necessary by the dermatologist.

The reported rate for hyperpigmentation in this study makes this ADR very common. The SmPC for Emtriva lists hyperpigmentation as a common ADR but there is a footnote to the table in section 4.8 that states that it was very common in paediatric subjects. Therefore, the observed rate in the study is already reflected in the SmPC.

No viral load data were captured but the protocol did include criteria that had to be met to allow continued treatment with Emtriva. It seems that 8 subjects (16%) were discontinued due to virologic failure, which is not such an unusual rate in paediatric trials.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

N/A

MAH responses to Request for supplementary information

N/A