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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

Isentress

raltegravir

Procedure no: EMEA/H/C/000860/P46/057

Note

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

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Administrative information

Invented name of the medicinal product:	Isentress
INN (or common name) of the active substance(s):	raltegravir
MAH:	Merck Sharp & Dohme Ltd.
Currently approved Indication(s)	HIV-1 infection
Pharmaco-therapeutic group (ATC Code):	J05AG04
Pharmaceutical form(s) and strength(s):	400mg film-coated tablet, 100mg and 25mg chewable tablets, 100mg granules for oral suspension

I. INTRODUCTION

In accordance with Article 46 of Regulation (EC) N° 1901/2006, Merck Sharp & Dohme, is submitting the results of the end of study at 5 years of the IMPAACT P1066 protocol. (P022). This study evaluated the pharmacokinetics (PK), safety, and efficacy of raltegravir (also known as ISENTRESS®, and as MK-518) in paediatric participants 4 weeks to <19 years of age treated with raltegravir given as 400-mg tablets, as chewable tablets (weight-based dosing), or as granules for oral suspension (GFS) (weight-based dosing), in combination with an optimized background therapy (OBT) regimen. Two clinical study reports (CSRs) have been previously prepared and were included in the following Extension Applications: EMEA/H/C/000860/X/0024/G (CSR P022) and EMEA/H/C/000860/X/0044/G (CSR P022V01). This regulatory filing will be the final reporting of results associated with P022 (CSR P022V02).

The MAH states that the data submitted do not influence the benefit-risk balance for raltegravir and therefore do not require taking further regulatory action on the marketing authorization at this stage.

II. SCIENTIFIC DISCUSSION

1. Introduction

Raltegravir is a HIV integrase strand transfer inhibitor approved in both treatment- experienced and treatment-naïve adult patients. Raltegravir received initial marketing authorization in 2007 in adult treatment-experienced and in July 2009 in treatment-naïve adult patients at a dose of 400 mg BID. Based on complete 24 week and partial 48 week data from a Phase I/II study in HIV-1 infected children and adolescents, IMPAACT P1066 (Merck Protocol 022), raltegravir received marketing authorization in the European Union (February 2013) for the treatment of paediatric patients 2 to 18 years of age. Subsequently, the granules for suspension (GFS paediatric formulation was approved for use in infants at least 4 weeks of age for weight based (~6 mg/kg) twice daily oral dosing. The GFS formulation was approved in the US on 20-Dec-2013 (NDA 205- 786), and in the EU on 22-Aug-2014 (EMEA/H/C/000860/X/0044/G).

2. Scientific discussion

IMPAACT P1066 STUDY DESIGN SUMMARY

The overall IMPAACT P1066 trial was a Phase I/II, multi-center, open-label, non-comparative study to evaluate the safety, tolerability, pharmacokinetics, and antiretroviral activity of raltegravir in HIV-1 infected infants, children, and adolescents (4 weeks to 18 years). The study enrolled 152 HIV-1-infected pediatric patients ages ≥4 weeks to <19 years of age. All subjects enrolled into the study were stratified at screening into one of five age groups, in six cohorts:

Cohort	Age and formulation*
Cohort I	≥12 to <19 years of age assigned to receive 400-mg tablets
Cohort IIA	≥6 to <12 years of age assigned to receive 400-mg tablets
Cohort IIB	≥6 to <12 years of age assigned to receive chewable tablets
Cohort III	≥2 to <6 years of age assigned to receive chewable tablets
Cohort IV	≥6 months to <2 years of age assigned to receive GFS
Cohort V	≥4 weeks to <6 months of age assigned to receive GFS
Supplemental Cohort V	≥4 weeks to <6 months of age assigned to receive GFS with more intensive PK including C_{12hr}
* **400-mg Tablet Final Recommended Dose (FRD)**: 400 mg BID for pts 12–18 yrs, and 6 to <12 yrs weighing ≥25 kg. **Chewable Tablet FRD**: Weight based dosing to approximate 6 mg/kg BID, to max of 300 mg BID for pts 2 to < 12 yrs. **GFS FRD:** Weight based dosing to approximate 6 mg/kg BID for pts 4 wks to < 2 yrs.	
BID = twice daily; FRD = Final Recommended Dose; GFS = granules for oral suspension; PK = pharmacokinetics; pts = participants	

This Article 46 submission includes data presented in CSR P022V02 from all participants exposed to raltegravir (at any dose, Stage I or Stage II); this group is denoted as the All Treated Population and is most inclusive and appropriate for this final reporting. In prior submissions, data were presented for the Final Dose Population (a sub-population) and separately for the All Treated Population. The Final Dose Population included participants accrued into Stage I and treated only at the dose ultimately selected for their cohorts, as well as those accrued into Stage II in which participants received only the final selected dose for the respective cohort. Results from the Final Dose Population were considered primary for evaluation of the primary and secondary study objectives at Week 24 and Week 48.

Study Population Characteristics

Overall, a total of 153 previously treated (except Cohort V), HIV-1 positive participants were enrolled in P022: 126 participants into Cohorts I (N=71), IIA (N=16), IIB (N=18), and III (N=21), and 27 participants into Cohorts IV (N=15) and V (including Supplemental Cohort V) (N=12). It is noteworthy that 46.7% of the participants (Cohort 1), were adolescents. One participant in Cohort IV was enrolled but did not receive study drug; therefore 152 infants, children and adolescents were enrolled and treated in this study as detailed in the previous CSRs.

By week 240, 87 (57.2%) of the 152 treated participants remained in the study: 44 (50.6%) of the 87 participants who received the 400-mg tablet in Cohorts I and IIA, 29 (74.4%) of the 39 participants who received the chewable tablet in Cohorts IIB and III, and 14 (51.9%) of the 26 participants who received GFS in Cohorts IV and V. More discontinuations were observed for the 400-mg tablet group (Cohort I and IIA) due to noncompliance than in any other formulation group (21.8% of participants). The chewable tablet group and GFS group discontinuations due to noncompliance were lower as follows: 2.6% and 3.7%, respectively.

Of the 152 treated participants, 82 (53.9%) were male, 97 (63.8%) were Black or African American, and 55 (36.2%) were of Hispanic or Latino ethnicity. The median age by formulation (400-mg tablet/chewable tablet/GFS) was 14 years, 5 years and 28 weeks, respectively.

Mean baseline log10 plasma HIV-1 RNA values by formulation (400-mg tablet/chewable tablet/GFS) were 4.3, 4.3 and 5.7 log10 copies/mL, respectively. The numbers of participants who had baseline HIV-1 RNA above 100,000 copies/mL by formulation (400- mg tablet/chewable tablet/GFS) were 8 (9.2%), 5 (12.8%), and 18 (69.2%), respectively. Baseline viral load was 1 to 2 log higher for Cohorts IV and V compared with the older children and adolescents in Cohorts I through III, in whom baseline HIV-1 RNA values exceeded 100,000 copies/mL in only 10.3%. The higher baseline viral load observed in the youngest children in this study is consistent with the natural history of HIV-1 infection in paediatrics.

Mean baseline CD4 cell count values by formulation (400-mg tablet/chewable tablet/GFS) were approximately 454, 856, and 1515 cells/mm3, respectively. Mean baseline CD4 percentages by formulation (400-mg tablet/chewable tablet/GFS) were 20.9%, 27.4%, and 20.7%, respectively.

Viral subtype was clade B for 104 (68.4%) of the 152 treated participants, non-clade B for 42 (27.6%) participants, and not available for 6 (3.9%) participants.

Most participants were previously treated with multiple antiretroviral (ARV) therapies (ARTs), particularly the oldest age group (Cohort I and IIA) using the 400-mg tablet formulation. In these 2 cohorts, 81.6% of participants were treated with ≥3 classes of ARV prior to study entry; overall, the mean number of prior ARVs used was 8.7 and the mean duration of prior ARV therapy was 11.4 years. The mean durations of prior ARV therapy and mean number of prior ARV agents used by formulation (400-mg tablet/chewable tablet/GFS) were 11.4 years/8.7 agents, 4.6 years/5.1 agents, and 13.7 weeks/1.7 agents, respectively. The most frequently reported (≥35%) concomitant ARVs use in the 152 treated participants included: lamivudine (56.6%), lopinavir/ritonavir (48.7%), ritonavir (43.4%), abacavir (38.2%), and tenofovir (36.2%). According to classification of paediatric HIV-1 by the Centers for Disease Control (CDC), 43 (28.3%) of the 152 treated participants were classified as clinical category A, 41 (27%) as B, 44 (28.9%) as C, and 24 (15.8%) as N.

Efficacy

Raltegravir, administered either as 400-mg tablets, chewable tablets, or GFS, in combination with an OBT, continued to demonstrate a durable antiretroviral effect and immunological benefit through Week 240 in HIV-1 infected infants, children, and adolescents who initiated therapy at ≥4 weeks to 18 years of age. Review of the available raltegravir resistance data indicates only 1 additional participant in Cohort V failed virologically with a raltegravir resistance mutation at AA155 since the previous CSR.

At Week 24, >67% of participants across cohorts achieved HIV-1 RNA values of <400 copies/mL. For Cohorts I and IIA receiving 400-mg tablets, 69.0% achieved HIV-1 RNA <400 copies/mL at Week 24 with 42.4% maintaining HIV-1 RNA <400 copies/mL at Week 240 (Observed Failure [OF]). For Cohorts IIB and III receiving chewable tablets, 66.7% achieved HIV-1 RNA <400 copies/mL at Week 24 with 75.0% maintaining HIV-1 RNA <400 copies/mL at Week 240 (OF). For Cohorts IV and V receiving GFS, 64.0% achieved HIV-1 RNA <400 copies/mL at Week 24 with 80.0% maintaining HIV-1 RNA <400 copies/mL at Week 240 (OF). Virologic suppression over time was similar for participants receiving the chewable tablet and GFS formulations. In comparison, the 400-mg tablet formulation appeared to have lower proportions of participants achieving suppression past the Week 24 time point. This is not unexpected due to the high proportion of adolescent participants receiving this formulation (Cohort I, 71 or 46.7% of all treated participants). Adolescent participants had the most extensive prior treatment (12 year mean duration of prior ARV use with a mean of 9 prior ARV agents), and poorer compliance (15.5% <80% compliant) compared with the younger cohorts, in particular Cohorts III, IV and V who most likely had greater, if not complete, adult supervision of dosing. Overall, sustained responses (HIV-1 RNA <400 copies/mL) in approximately 58% of remaining participants were observed up to Week 240 (OF).

An overall trend of increase in CD4 cell count for each formulation was observed up to Week 48. Participants who received the 400-mg tablet and chewable tablet had sustained increases in CD4 cell count, although decreased over time, for the remainder of the study. Participants receiving GFS experienced overall decreases in absolute CD4 cell count after Week 48. This is not unexpected in these youngest participants due to the expected decline in total percentage of lymphocytes during normal growth and development. For this reason, CD4 percentage over time is a more useful parameter for very young children. For Cohorts I and IIA receiving 400-mg tablets, the mean increase in CD4 cell count was 128.0 cells/mm3 at Week 24 and 31.0 cells/mm3 at Week 240 (OF). For Cohorts IIB and III receiving chewable tablets, the mean increase in CD4 cell count was 160.3 cells/mm3 at Week 24 and 6.7 cells/mm3 at Week 240 (OF). For Cohorts IV and V receiving GFS, the mean change in CD4 cell count was 445.7 cells/mm3 at Week 24 and -143.8 cells/mm3 at Week 240 (OF).

From Week 24, each formulation was associated with at least a 3% increase from baseline in CD4 percent. The increase was sustained up to Week 240. Importantly, the youngest participants, who entered the study below 2 years of age and received the GFS formulation, demonstrated an increase of 8.6% in CD4 percentage at Week 240 despite the decline in absolute CD4 cell count during this period. For Cohorts I and IIA receiving 400- mg tablets, the mean increase in CD4 percent was 4.3% at Week 24 and 3.6% at Week 240 (OF). For Cohorts IIB and III receiving chewable tablets, the mean increase in CD4 percent was 4.1% at Week 24 and 6.0% at Week 240 (OF). For Cohorts IV and V receiving GFS, mean increase in CD4 percent was 7.5% at Week 24 and 8.6% at Week 240 (OF).

Overall, 72 (47.4%) participants experienced virologic failure by Week 240 as follows:
- Cohorts I and IIA (400-mg tablets), 44 (50.6%) participants.
- Cohorts IIB and III (chewable tablets), 17 (43.6%) participants.
- Cohorts IV and V (GFS), 11 (42.3%) participants.

For participants who experienced virologic failures and had genotypic data obtained (N=62),23 (37.1%) across all cohorts displayed signature raltegravir genotypic mutations as follows: 7 (11.3%) at AA148, 9 (14.5%) at AA155, 2 (3.2%) at AA143 and 5 (8.1%) at both AA148 and AA155.

Since the P022V01 CSR, which included a cumulative review of raltegravir resistance across all cohorts, 1 additional participant (Cohort V) failed treatment virologically with a raltegravir resistance mutation at AA155. Although some secondary raltegravir mutations known to confer raltegravir resistance were detected (ie, L74I, T97A) in participants without primary mutations, these mutations are not known to confer clinically significant resistance to raltegravir by themselves.

Safety

Raltegravir administered as 400-mg tablets, chewable tablets, or as GFS, at the recommended dose, continues to be generally safe and well tolerated at Week 240 as long-term therapy in combination with an OBT regimen in paediatric participants. No new safety concerns were identified based upon the review of Week 240 complete study data.

Clinical AEs of any grade (Grades 1–4) were reported by 146 (96.1%) of All Treated participants by Week 240 as follows:
• Cohorts I and IIA (400-mg tablets), 81 (93.1%) participants.
• Cohorts IIB and III (chewable tablets), 39 (100.0%) participants.
• Cohorts IV and V (GFS), 26 (100.0%) participants.

As of Week 240, 41 (27.0%) participants had experienced clinical SAEs, many of which may have been related to underlying diseases. The rate of clinical SAEs was generally comparable across each formulation and age group. Three drug-related clinical SAEs were experienced by 2 (1.3%) participants. One Cohort II participant experienced clinical SAEs of drug-related rash (on Day 17), and drug-related drug-induced liver injury (on Day 141), but neither resulted in treatment interruption or discontinuation. There was one SAE of a Grade 3, drug-related allergic drug rash (Day 7) for a participant in Cohort V, which led to discontinuation of raltegravir. In addition to the above drug-related clinical SAEs, drug related non-serous Grade 3 or greater AEs were reported for 2 participants. One participant in Cohort I experienced 3 drug-related Grade 3 or greater clinical AEs of psychomotor hyperactivity, abnormal behavior and insomnia (on Day 41) which did not limit treatment, and 1 participant in Cohort V experienced drug-related Grade 3 or greater immune reconstitution syndrome (on Day 29) which resolved before Week 24 without treatment interruption.

There were no additional drug-related Grade 3 or greater clinical AEs or drug-related clinical SAEs or discontinuations due to clinical AEs reported since the last CSR.

By Week 240 for all formulations, laboratory AEs of any grade (Grades 1 through 4) were reported by 145 (95.4%) of All Treated participants as follows:
• Cohorts I and IIA (400-mg tablets), 82 (94.3%) participants.
• Cohorts IIB and III (chewable tablets), 38 (97.4%) participants.
• Cohorts IV and V (GFS), 25 (96.2%) participants.

Overall, 4 (2.6%) participants had laboratory SAEs, none of which were considered drug related. Four participants (2.6%) experienced drug-related Grade 3 or greater laboratory events of ALT and AST increased (1 participant), LDL increased (1 participant), and neutrophil count decreased (2 participants). No new drug-related Grade 3 or greater laboratory AEs were reported since the last CSR. No drug-related laboratory SAEs, and no discontinuations or deaths were reported due to laboratory AEs throughout the study.

Discussion on clinical aspects

Raltegravir, an HIV integrase strand transfer inhibitor, continues to provide convincing evidence of its benefits in HIV-1 infected paediatric participants. The final, 240- week efficacy and safety results from P022, which evaluated raltegravir's use in paediatric participants 4 weeks to <19 years of age, are consistent with data presented in the previous CSRs and regulatory submissions EMEA/H/C/000860/X/0024/G (CSR P022) and EMEA/H/C/000860/X/0044/G (CSR P022V01), as well as those reported for HIV-infected adults. These results thereby continue to support the conclusion that there is a favorable benefit/risk ratio with administration of raltegravir at the appropriate recommended dose in HIV-1 infected paediatric patients in these age groups.

On the basis of the results of this paediatric study, there is no change in the benefit-risk profile of Isentress for the existing indications. Therefore, no SmPC changes are needed based on the results of this study at present.

III. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION

Overall conclusion

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