23 April 2015
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Procedure Management and Committees Support 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/P46/055

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):	Tablet, chewable tablet

I. INTRODUCTION

In accordance with Article 46 of Regulation (EC) N° 1901/2006, Merck Sharp & Dohme, is submitting the final report for a paediatric clinical study (Protocol PN248), a Phase II, open-label trial to evaluate the safety and tolerability of Isentress in HIV-infected children 2 to <18 years, receiving either the raltegravir 400 mg film-coated tablet or the chewable tablet formulations.

The MAH states that in accordance with Article 16(2) of Regulation (EC) N° 726/2004, the data submitted do not influence the benefit-risk balance for Isentress and therefore do not require taking further regulatory action on the marketing authorization for Isentress 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. An extension application (EMEA/H/C/000860/X/44/G) submitted in June 2013 for granules for oral suspension in children from 4 weeks to < 2years of age is currently under EMA review.

2. Study P 248

A Phase II, multicenter, open-label, non-comparative study of raltegravir (MK-0518) in two oral formulations in combination with other antiretroviral agents to evaluate the safety, tolerability and antiretroviral activity in HIV-1 infected Russian children and adolescents.

Data collected from this single country clinical study in a local patient population was intended to supplement the safety, efficacy, and pharmacokinetic (PK) data already generated in IMPAACT P1066 in the 2 to 18 year age range.

This trial was conducted in ten (10) centres, of which nine (9) allocated subjects to study treatment.

Ethical conduct

The MAH states that “clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.”

2.1 Description of the study

Both treatment-experienced and treatment-naïve patients were eligible to participate in this study. Thirty-two (32) HIV-infected paediatric patients, ages 2 years to <18 years of age (at the time of signing the informed consent) participated in this study. Treatment-experienced patients included patients who were failing or who were intolerant to other licensed ARTs.

Patients weighing > 7kg, with a screening HIV RNA >1,000 copies/mL, were eligible. Patients with ALT, AST or AP > 5x ULN or HCV or HBV co-infection were excluded. The study treatment duration for a given patient was 24 weeks.

Co- administration of phenobarbital, phenytoin and rifampicin was prohibited. Use of systemic immunosuppressive therapy or immune modulators within one month prior to treatment in this study was also prohibited

Based on the U.S. Prescribing Information (USPI) at the time Protocol 248 was started, the following dosing recommendation by age group were studied:

- patients 12 to 18 years: 400 mg twice daily (BID) of the film-coated tablet;
- patients 6 to < 12 years: either 400 mg BID of the film-coated tablet (if ≥25 kg) or a weight-based dose of the chewable tablet formulation (maximum of 300 mg) BID;
- patients 2 to < 6 years: a weight based dose of the chewable tablet formulation (maximum of 300 mg) BID.

Table 9-4
Recommended Dose for Raltegravir (MK-0518) Chewable Tablets in Pediatric Patients 2 to Less Than 12 Years of Age

Body Weight (Kg)	Dose	Number of Chewable Tablets
7 to less than 10	50 mg twice daily	0.5 x 100 mg* twice daily
10 to less than 14	75 mg twice daily	3 x 25 mg twice daily
14 to less than 20	100 mg twice daily	1 x 100 mg twice daily
20 to less than 28	150 mg twice daily	1.5 x 100 mg* twice daily
28 to less than 40	200 mg twice daily	2 x 100 mg twice daily
At least 40	300 mg twice daily	3 x 100 mg twice daily
The weight-based dosing recommendation for the chewable tablet was based on approximately 6 mg/kg/dose twice daily. * The 100 mg chewable tablet can be divided into equal halves.		

Source: Protocol [16.1.1]

The chewable tablets are available in dose strengths of 100 mg (scored) and 25 mg.
The study physician determined which raltegravir formulation to administer.

CHMP's comment

For comparison, the EU prescribing information is as follows:

Chewable tablets
Children 2 to < 12 Years of Age

Body Weight (kg)	Dose
12 to < 14	75mg bd
14 to < 20	100mg bd
20 to < 28	150mg bd
28- <40	200mg bd
≥ 40	300mg bd

400mg film coated tablet

Children and adolescents
The recommended dosage is 400 mg twice daily for adolescents 12 years of age and older, and children 6 through 11 years of age, weighing at least 25 kg.

- ## Objectives

Primary Objective: To evaluate the safety and tolerability of raltegravir in two oral formulations (film-coated tablets, chewable tablets) in combination with other antiretroviral agents in pediatric patients, as assessed by review of accumulated safety data.

Secondary Objective: Evaluate the antiretroviral activity of raltegravir in two oral formulations in combination with other antiretroviral agents in pediatric patients, as measured by the following parameters at Week 24:

- Proportion of patients achieving ≥1 log10 drop from baseline in HIV RNA or HIV RNA <200 copies/mL
- Proportion of patients achieving HIV RNA <40 copies/mL
- Proportion of patients achieving HIV RNA <200 copies/mL
- Change from baseline in CD4 cell counts (cells/mm3)
- Change from baseline in CD4 percent

- ## Statistical Methods

All efficacy and safety analyses provided descriptive statistics only; no formal comparisons were made between the groups receiving the different formulations.

Primary analysis: The All-Patients-as-Treated (APaT) population was employed for safety analyses. The APaT population consisted of all enrolled patients who received at least one dose of study treatment.

Secondary analysis: The efficacy analyses were based on the Full Analysis Set (FAS) population. The FAS population included all patients who took at least one dose of study medication, and had baseline (required for change from baseline endpoints only) and at least one postbaseline evaluation.

The proportion of patients with virologic responses (achieving ≥1 log10 drop from baseline in HIV RNA or HIV RNA <200 copies/mL; achieving HIV RNA <40 copies/mL; achieving HIV RNA <200 copies/mL) was summarized for the whole population as well as by formulation group at each time point, with primary interest at Week 24. Point estimate and the associated 95% CI calculated using exact binomial method were provided.
The Observed Failure (OF) approach was used as the primary approach to handle missing HIV RNA values. Under this approach, monotone missing values after premature discontinuations were imputed as failures if the discontinuation was due to lack of efficacy.
Other missing values were excluded from the analysis. In addition to the OF approach, sensitivity analysis was performed using the Non-Completer = Failure (NC=F) approach.

- **Pharmacokinetic Parameter Analysis**

PK parameters were not evaluated in this study.
Trial status 18-DEC-2012 first subject first visit to 16-DEC-2013 last subject last visit Database lock 16-JAN-2014.

2.2 Results

2.2.1 Subjects and treatment information

Disposition of Patients
(All Patients Allocated)

	Raltegravir Film-coated tablet		Raltegravir Chewable tablet		Total	
	n	(%)	n	(%)	n	(%)
Total Allocated	4		28		32	
Never Treated	0		0		0	
Treated	4		28		32	
Completed	4	(100.0)	25	(89.3)	29	(90.6)
Discontinued	0	(0.0)	3	(10.7)	3	(9.4)
Lost to Follow-up	0	(0.0)	2	(7.1)	2	(6.3)
Protocol Violation	0	(0.0)	1	(3.6)	1	(3.1)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.

- **Baseline characteristics**

Patient Characteristics and Baseline Disease Characteristics
(All Patients as Treated)

	Raltegravir Film-coated tablet (n=4)	Raltegravir Chewable tablet (n=28)	Total (n=32)
Gender n (%)			
Male	3 (75.0)	12 (42.9)	15 (46.9)
Female	1 (25.0)	16 (57.1)	17 (53.1)
Age(years)			
≥2 to <6	0 (0.0)	11 (39.3)	11 (34.4)
≥6 to <12	2 (50.0)	17 (60.7)	19 (59.4)
≥12 to <18	2 (50.0)	0 (0.0)	2 (6.3)
Mean (SD)	11.8 (3.77)	6.4 (2.64)	7.1 (3.27)
Median (min, max)	10.5 (9, 17)	7.0 (2, 11)	7.0 (2, 17)
Race n (%)			
White	4 (100.0)	27 (96.4)	31 (96.9)
Asian	0 (0.0)	1 (3.6)	1 (3.1)
Ethnicity n (%)			
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	4 (100.0)	28 (100.0)	32 (100.0)
Not Reported	0 (0.0)	0 (0.0)	0 (0.0)
Primary Diagnosis n (%)			
HIV-1	4 (100.0)	28 (100.0)	32 (100.0)
Height (cm)			
N	4	28	32
Mean (SD)	145.8 (14.89)	114.4 (15.95)	118.3 (18.81)
Median (min, max)	146.5 (128, 162)	119.5 (86, 144)	120.5 (86, 162)
HIV RNA (copies/mL)			
N	4	28	32
Mean (SD)	110863.5 (69558.35)	247631.8 (627690.72)	230535.8 (587994.59)
Median (min, max)	136272.0 (11546, 159364)	39862.5 (1033, 3001812)	42827.0 (1033, 3001812)

Patient Characteristics and Baseline Disease Characteristics (continued)
(All Patients as Treated)

	Raltegravir Film-coated tablet (n=4)	Raltegravir Chewable tablet (n=28)	Total (n=32)
HIV RNA (log_{10} copies/mL)			
N	4	28	32
Mean (SD)	4.9 (0.55)	4.7 (0.75)	4.7 (0.72)
Median (min, max)	5.1 (4, 5)	4.6 (3, 6)	4.6 (3, 6)
HIV RNA (copies/mL)			
0 to <2000	0 (0.0)	1 (3.6)	1 (3.1)
2000 to <10000	0 (0.0)	2 (7.1)	2 (6.3)
10000 to <100000	1 (25.0)	19 (67.9)	20 (62.5)
100000 above	3 (75.0)	6 (21.4)	9 (28.1)
CD4 Cell Count (cells/mm^3)			
N	4	28	32
Mean (SD)	433.3 (260.55)	608.5 (365.74)	586.6 (355.73)
Median (min, max)	403.0 (183, 744)	517.5 (22, 1295)	517.5 (22, 1295)
CD4 Percent			
N	4	28	32
Mean (SD)	20.0 (5.77)	22.0 (10.23)	21.8 (9.74)
Median (min, max)	20.0 (15, 25)	22.0 (2, 35)	22.0 (2, 35)
Viral Subtype			
A	0 (0.0)	5 (17.9)	5 (15.6)
A1	3 (75.0)	13 (46.4)	16 (50.0)
AG	1 (25.0)	1 (3.6)	2 (6.3)
Complex	0 (0.0)	8 (28.6)	8 (25.0)
NR	0 (0.0)	1 (3.6)	1 (3.1)
ART Treatment Experience			
Naïve	3 (75.0)	23 (82.1)	26 (81.3)
Experienced	1 (25.0)	5 (17.9)	6 (18.8)

N = Number of patients in each group.
n (%) = Number (percent) of patients in each sub-category.
NR=Not reportable

The medical history profiles of patients were consistent with those expected for children with HIV infection. Most secondary diagnoses were infections and infestations and blood and lymphatic system disorders. The most common (≥10% in all patients) condition reported overall was anemia.

- **Antiretroviral therapy**

Raltegravir could have been taken without regard to food. At baseline, the investigator selected the other ARTs to be used in combination with raltegravir based on current treatment guidelines, the patient's prior treatment history, the results of the HIV-1 genotypic antiretroviral resistance testing at screening, and prior antiretroviral resistance testing, if available.

The treatment regimen consisted of ARTs approved and licensed for use in adult patients, even if not currently approved for use in paediatric patients. Any changes in background ART while on study were discussed with the Sponsor or designee. Unless the change was specifically permitted, patients whose background ART was changed after initiation of study therapy were considered treatment failures. The following changes to background therapy were permitted during the study:

• Substitution within class or rarely, across class for documented toxicity
• Discontinuation of a background ART
• Formula substitutions

Table 10-5
Patients with Specific Prior Medications (Incidence >0% in One or Both Formulation Groups)
Anti-Retroviral Therapies
(All Patients as Treated)

	Raltegravir Film-coated tablet		Raltegravir Chewable tablet		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	4		28		32	
With one or more Anti-Retroviral Therapies	1	(25.0)	5	(17.9)	6	(18.8)
With no Anti-Retroviral Therapies	3	(75.0)	23	(82.1)	26	(81.3)
Antiinfectives For Systemic Use						
Antivirals For Systemic Use	**1**	**(25.0)**	**5**	**(17.9)**	**6**	**(18.8)**
Abacavir	1	(25.0)	1	(3.6)	2	(6.3)
Didanosine	1	(25.0)	1	(3.6)	2	(6.3)
Fosamprenavir Calcium	1	(25.0)	0	(0.0)	1	(3.1)
Lamivudine	1	(25.0)	3	(10.7)	4	(12.5)
Lamivudine (+) Zidovudine	0	(0.0)	1	(3.6)	1	(3.1)
Lopinavir (+) Ritonavir	1	(25.0)	5	(17.9)	6	(18.8)
Ritonavir	1	(25.0)	0	(0.0)	1	(3.1)
Zidovudine	1	(25.0)	2	(7.1)	3	(9.4)

Every patient is counted a single time for each applicable specific prior medication. A patient with multiple prior medications within a medication category is counted a single time for that category.
A medication class or specific medication appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Source: Section 16.4

Table 10-6
Patients with Specific Concomitant Medications (Incidence >0% in One or Both Formulation Groups)
Anti-Retroviral Therapies
(All Patients as Treated)

	Raltegravir Film-coated tablet		Raltegravir Chewable tablet		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	4		28		32	
With one or more Anti-Retroviral Therapies	4	(100.0)	28	(100.0)	32	(100.0)
With no Anti-Retroviral Therapies	0	(0.0)	0	(0.0)	0	(0.0)
Antiinfectives For Systemic Use						
Antivirals For Systemic Use	**4**	**(100.0)**	**28**	**(100.0)**	**32**	**(100.0)**
Abacavir	0	(0.0)	5	(17.9)	5	(15.6)
Abacavir Sulfate	1	(25.0)	3	(10.7)	4	(12.5)
Azidothymidine Phosphonate	1	(25.0)	7	(25.0)	8	(25.0)
Efavirenz	0	(0.0)	2	(7.1)	2	(6.3)
Fosamprenavir Calcium	0	(0.0)	1	(3.6)	1	(3.1)
Lamivudine	2	(50.0)	19	(67.9)	21	(65.6)
Lamivudine (+) Zidovudine	1	(25.0)	4	(14.3)	5	(15.6)
Lopinavir	0	(0.0)	1	(3.6)	1	(3.1)
Lopinavir (+) Ritonavir	1	(25.0)	0	(0.0)	1	(3.1)
Raltegravir[1]	4	(100.0)	25	(89.3)	29	(90.6)
Ritonavir	0	(0.0)	1	(3.6)	1	(3.1)
Stavudine	1	(25.0)	3	(10.7)	4	(12.5)
Zidovudine	0	(0.0)	7	(25.0)	7	(21.9)

Every patient is counted a single time for each applicable specific concomitant medication. A patient with multiple concomitant medications within a medication category is counted a single time for that category.
A medication class or specific medication appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
[1]Raltegravir was provided after completion of the study to all patients whose continued use of raltegravir was considered medically necessary. Patients who were taking the chewable tablet during the study were likewise given the chewable tablet formulation post-study free of charge via Merck Program 083. Patients who were taking the film-coated tablet during the study were likewise given the film-coated tablet formulation post-study via a government funded program.

2.2.2 Pharmacocinetic results

Not applicable

2.2.3 Safety results (Primary analysis)

The mean duration (range) of treatment for the raltegravir film-coated tablet at any dose was 170.5 days (167 to 174 days). Patients in this formulation group were mostly exposed to 800 mg daily of the film-coated tablet. The mean duration (range) for the raltegravir chewable tablet at any dose was 171.8 days (28 to 224 days). Patients in this formulation group were mostly exposed to 300 mg daily

(14 patients) and 150 mg daily (12 patients), with the 300 mg dose daily having the greatest mean duration (166.2 days).

Clinical and laboratory adverse events at 24 Weeks for the APaT population

Clinical adverse events were reported by 12 (37.5%) patients overall. Drug-related clinical adverse events were reported by 4 (12.5%) patients overall. Laboratory adverse events were reported by 1 (3.1%) patient overall. Drug-related laboratory adverse events were reported by 1 (3.1%) patient overall. There were no serious adverse events, deaths, discontinuations due to an adverse event, or adverse events of special interest reported in this study.

Summary of Clinical Adverse Events
(All Patients as Treated)

	Raltegravir Film-coated tablet		Raltegravir Chewable tablet		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	4		28		32	
With one or more adverse events	0	(0.0)	12	(42.9)	12	(37.5)
With no adverse events	4	(100.0)	16	(57.1)	20	(62.5)
with drug-related[†] adverse events	0	(0.0)	4	(14.3)	4	(12.5)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related[†] adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[§] due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

Population is based on all allocated patients receiving at least one dose of study treatment.
[†]Determined by the investigator to be related to the study therapy or other suspect therapy.
[§]Study medication withdrawn.

Summary of Laboratory Adverse Events
(All Patients as Treated)

	Raltegravir Film-coated tablet		Raltegravir Chewable tablet		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	4		28		32	
With one or more adverse events	0	(0.0)	1	(3.6)	1	(3.1)
With no adverse events	4	(100.0)	27	(96.4)	31	(96.9)
with drug-related[†] adverse events	0	(0.0)	1	(3.6)	1	(3.1)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related[†] adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[§] due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

Population is based on all allocated patients receiving at least one dose of study treatment.
[†]Determined by the investigator to be related to the study therapy or other suspect therapy.
[§]Study medication withdrawn.

Clinical adverse events related to raltegravir alone were reported in 3 (9.4%) of the 32 treated patients overall. The drug-related clinical adverse events related to raltegravir alone were the following: diarrhea, vomiting, and somnambulism.

All 3 clinical adverse events were experienced by patients in the raltegravir chewable tablet group. Patient 1 xperienced vomiting on Day 77 (450 mg total daily dose). The event was assessed by the investigator as mild in intensity. It persisted for 1 minute then resolved. Patient 2 experienced somnambulism on Day 29 (400 mg total daily dose). The event was assessed by the investigator as mild in intensity. It persisted for 63 days then resolved. Patient 3 experienced diarrhea on Day 3 (300 mg total daily dose). The event was assessed by the investigator as mild in intensity. It persisted for 2 days then resolved.

Clinical adverse events related to raltegravir in combination with background ART were reported in 1 (3.1%) of the 32 treated patients overall.
The drug-related clinical adverse events related to raltegravir in combination with background ART were the following: abdominal pain and nausea. The patient who experienced the 2 clinical adverse events was in the raltegravir chewable tablet group. Patient 4 experienced abdominal pain and nausea on Day 1 (300 mg total daily dose). The events were assessed by the investigator as mild in intensity. They persisted for 6 days then resolved.

There were no patients in either formulation group who experienced laboratory adverse events that were related to raltegravir alone. Laboratory adverse events related to raltegravir in combination with background ART were reported in 1 (3.1%) of the 32 treated patients overall.
The patient who experienced the laboratory adverse event was in the raltegravir chewable tablet group. Patient 4 experienced a decrease in platelet count on Day 85 (150 mg total daily dose). The event was assessed by the investigator as mild in intensity. It persisted for 84 days then resolved.

2.2.4 Efficacy results (Secondary analysis)

At Week 24, 86.2% of patients overall achieved ≥1 log10 drop from baseline in HIV RNA or HIV RNA <200 copies/mL. At Week 24, the proportion of patients overall with HIV RNA at <40 copies/mL and <200 copies/mL were 44.8% and 72.4%, respectively. The mean change from baseline in CD4 cell count and percent were 266.7 cells/mm3 and 5.7%, respectively.
Efficacy analyses were all based on the Observed Failure approach.

Plasma HIV RNA and CD4 count were performed at each clinic visit. Plasma HIV RNA determination was performed at each visit, by a central laboratory specified by the Sponsor or designee, using the Abbott RealTime HIV-1 assay, which has a linear range of 40 to 10,000,000 copies/mL.
Blood samples for genotypic viral resistance testing were collected at the Screening visit and at Week 24 or the 14-Day post-therapy follow-up (if not already obtained at the Week 24 visit) or at an Early discontinuation visit (if applicable) and were tested in patients identified as confirmed virologic failures.

Table 11-1
Proportion of Patients With Virologic Response at Week 24
Observed Failure Approach†
(Full Analysis Set)

Endpoint	Raltegravir Film-coated tablet		Raltegravir Chewable tablet		Total	
	n/N	%(95% CI)‡	n/N	%(95% CI)‡	n/N	%(95% CI)‡
Proportion of patients achieving ≥ 1 $\log_{10}$ drop from baseline in plasma HIV RNA or HIV RNA < 200 copies/mL	3/ 4	75.0 (19.4, 99.4)	22/ 25	88.0 (68.8, 97.5)	25/ 29	86.2 (68.3, 96.1)
Proportion of patients achieving HIV RNA < 40 copies/mL	2/ 4	50.0 (6.8, 93.2)	11/ 25	44.0 (24.4, 65.1)	13/ 29	44.8 (26.4, 64.3)
Proportion of patients achieving HIV RNA < 200 copies/mL	2/ 4	50.0 (6.8, 93.2)	19/ 25	76.0 (54.9, 90.6)	21/ 29	72.4 (52.8, 87.3)
Proportion of patients achieving ≥ 1 $\log_{10}$ drop from baseline in plasma HIV RNA or HIV RNA < 400 copies/mL	3/ 4	75.0 (19.4, 99.4)	22/ 25	88.0 (68.8, 97.5)	25/ 29	86.2 (68.3, 96.1)
Proportion of patients achieving HIV RNA < 50 copies/mL	2/ 4	50.0 (6.8, 93.2)	13/ 25	52.0 (31.3, 72.2)	15/ 29	51.7 (32.5, 70.6)
Proportion of patients achieving HIV RNA < 400 copies/mL	2/ 4	50.0 (6.8, 93.2)	19/ 25	76.0 (54.9, 90.6)	21/ 29	72.4 (52.8, 87.3)

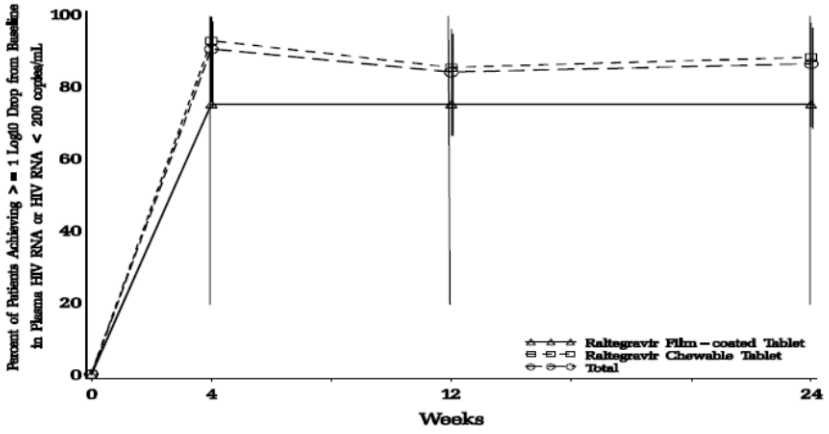
†Approach to handling missing values: Observed Failure (OF) Approach
‡ 95% CI calculated using exact binomial method
N = Number of patients in each group
n = Number of patients in each subcategory

The overall mean increase in CD4 cell count from baseline to Week 24 was 266.7 cells/mm3 (95% CI: 119.2, 414.3) (See Table 11-4). The mean increase from baseline to Week 24 in CD4 percent was 5.7% (95% CI: 3.8, 7.7) (See Table 11-5).

Efficacy response over time

Figure 11-1
Proportion of Patients Achieving ≥1 $\log_{10}$ Drop From Baseline in Plasma HIV RNA or HIV RNA < 200 copies/mL
Observed Failure Approach
(Full Analysis Set)

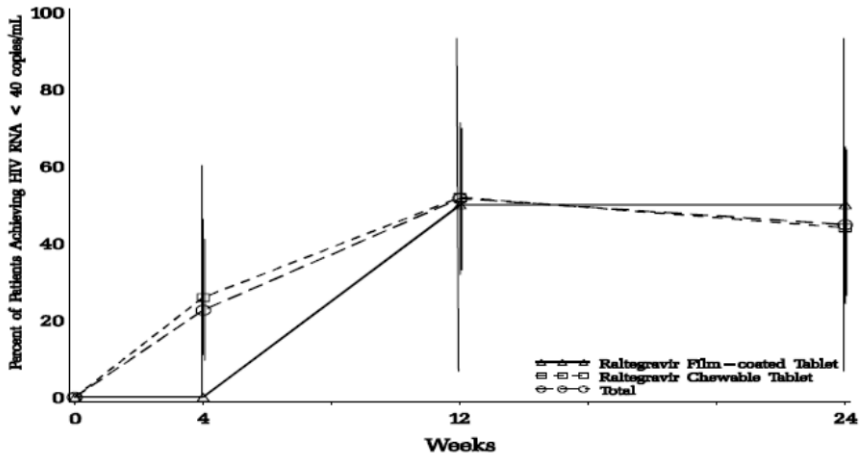
Table 14.2.4.3
Proportion of Patients Achieving >=1 Log10 Drop from Baseline in HIV RNA or HIV RNA<200 copies/mL
Observed Failure Approach
(Full Analysis Set)



	Number of Contributing Patients			
Film-coated Tablet	4	3	3	3
Chewable Tablet	28	25	23	22
Total	32	28	26	25

Figure 11-2
Proportion of Patients Achieving HIV RNA < 40 copies/mL
Observed Failure Approach
(Full Analysis Set)

Table 14.2.4.4
Proportion of Patients Achieving HIV RNA < 40 copies/mL
Observed Failure Approach
(Full Analysis Set)



	Number of Contributing Patients			
Film-coated Tablet	4	0	2	2
Chewable Tablet	28	7	14	11
Total	32	7	16	13

Table 11-3
Change from Baseline in Log_{10} Plasma HIV RNA Over Time
Observed Failure Approach†
(Full Analysis Set)

Endpoint	Visit	Raltegravir Film-coated tablet			Raltegravir Chewable tablet			Total		
		N	Baseline Mean	Mean Change from Baseline (95% CI)‡	N	Baseline Mean	Mean Change from Baseline (95% CI)‡	N	Baseline Mean	Mean Change from Baseline (95% CI)‡
Change from Baseline in Log_{10} Plasma HIV RNA (Log_{10} copies/mL)	Week 4	4	4.9	-2.4 (-4.1, -0.6)	27	4.7	-2.5 (-2.8, -2.2)	31	4.7	-2.5 (-2.8, -2.2)
	Week 12	4	4.9	-2.7 (-5.0, -0.4)	27	4.7	-2.5 (-3.0, -2.0)	31	4.7	-2.5 (-3.0, -2.1)
	Week 24	4	4.9	-2.5 (-4.6, -0.5)	25	4.7	-2.5 (-3.0, -2.1)	29	4.7	-2.5 (-3.0, -2.1)

† Approach to handling missing values: Observed Failure (OF) Approach
‡ 95% CI calculated using t-distribution.
N= number of patients in each group.

Viral resistance

Definition of virologic failure for the efficacy analyses:
1) Non-responder: patients who never achieved ≥1 log10 drop from baseline in plasma HIV RNA or HIV RNA <200 copies/mL through Week 24
OR
2) Virologic rebound at Week 24, defined as:
a) Confirmed HIV RNA ≥200 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <200 copies/mL or
b) Confirmed >1.0 log10 increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

Of the 4 viral failure patients, 3 had post-baseline genotypic data available. (Testing on the 4th patient's sample could not be performed). Overall in the 3 patients with post-baseline genotype data, viruses from 1 patient displayed a signature resistance mutation (at AA 155), along with L74I. The other 2 patients had no signature mutations at AA 143, 148, or 155 (1 patient had another known RAL resistance mutation [L74I, which by itself does not confer resistance to raltegravir, and 1 patient had no other known RAL resistance mutations).

MAH's discussion and conclusion

The general patterns of safety, tolerability, and efficacy were comparable to the results found in the IMPAACT P1066 study, a Phase 1/2 multicenter, open-label, noncomparative study of HIV-infected children and adolescents ≥2 to <19 years of age to evaluate the pharmacokinetics, safety, tolerability, and efficacy of raltegravir (film-coated tablet and chewable tablet formulations) in this HIV-infected age population. In the IMPAACT P1066 study, there were also no deaths or discontinuations due to an adverse event. Of the 96 final dose patients, 87.5% experienced clinical adverse events (including 14 serious adverse events and 1 serious drug-related adverse event) and 88.5% experienced laboratory adverse events (including 1 serious adverse event and no serious drug-related adverse events). The higher frequency of clinical and laboratory adverse events (including serious adverse events) may be due to the greater number of treatment experienced patients with more advanced HIV disease in the IMPAACT P1066 study. As mentioned, there was only 1 serious drug-related adverse event overall.

The efficacy data (likewise based on the OF approach) at Week 24 in the IMPAACT P1066 study was also very similar to that of the P248 study. At Week 24, overall patient data demonstrated 71.6% achieved ≥1 log10 drop from baseline in HIV RNA or HIV RNA <400 copies/mL. At Week 24, the proportion of patients overall with HIV RNA at <50 copies/mL and <400 copies/mL were 53.7% and

66.3%, respectively. Immunologic benefit was also demonstrated at Week 24 for all patients: the mean change from baseline in CD4 cell counts and CD4 percent were 119 cells/mm3 and 3.8%, respectively. The P248 study had more stringent efficacy endpoints and had higher overall percentages of patients achieving those endpoints as compared with the IMPAACT P1066 study. Again, this may be due to sample size and demographic differences.

Data from P248 based on the OF approach demonstrated that raltegravir in combination with other ARTs has acceptable efficacy at Week 24 in the Russian paediatric population, as measured by key efficacy parameters. There were 3 additional supportive endpoints recorded in this study at Week 24 (≥1 log10 drop or <400 copies/mL; <50 copies/mL; <400 copies/mL), and the results for these were generally consistent with the corresponding primary endpoints.

Immunologic benefit was also demonstrated at Week 24 for all patients, based on the OF approach: the mean change from baseline in CD4 cell counts and CD4 percent were 266.7 cells/mm3 and 5.7%, respectively. The results of analyses for patients overall using the NC=F approach were generally comparable to the results using the OF approach.

In Russian HIV-infected children and adolescents ≥2 to <18 years of age, raltegravir administered as either the adult film-coated tablet formulation or the pediatric chewable tablet formulation, in combination with an optimized background antiretroviral regimen, through 24 weeks,
• was generally safe and well tolerated as chronic therapy at the recommended dose,
• had a favorable antiretroviral effect as measured by the proportions of patients who achieved pre-specified virologic responses,
• and demonstrated immunological benefit as measured by changes from baseline in CD4 cell count and CD4 percent.

The MAH states that efficacy and safety data collected from Protocol 248, which evaluated raltegravir use in pediatric patients 2 to <18 years of age in Russia, are consistent with data collected in the pediatric study IMPAACT P1066, thereby continuing to support the conclusion that there is a favourable benefit/risk ratio with administration of raltegravir at the appropriate recommended dose in HIV infected paediatric patients in this age group.

CHMP's comment

In this study, children were dosed according to the US prescribing information. EU prescribing information differs from the US posology insofar as Isentress is not approved in the EU for children weighing less than 12kg and children weighing 12- <14kg receive a dose of 75mg bd. Difference in dosing and possibly exposure would hence be expected for children weighing 10- 12kg. The report does not allow verifying if any children from this weight bracket were included in the study.

The majority of patients (>80%) were treatment naive. Most presented with a VL <100,000c/ml and a CD 4 count > 500 cells/mm^3. Twenty- eight of the 32 subjects received the chewable tablet, only four the film coated tablet.
The information on concomitant ART is limited. The most commonly used NRTIs were lamivudine, zidovudine, and abacavir. Only two patients received an NNRTI (efavirenz), and 3 (?4) received a PI. Study duration was 24 weeks.

No PK data were collected. No firm conclusions can be drawn from the efficacy results of this small study, which were reportedly in line with previous paediatric results. The evaluation of safety did not produce any unexpected results. Overall 12.5% of patients experienced drug related AEs. The study was not designed to compare formulations.

III. CHMP'S OVERALL CONCLUSION AND RECOMMENDATION

The MAH submitted the final report for P248, a Phase II, multicenter, open-label, non-comparative study of raltegravir (MK-0518) in two oral formulations in combination with other antiretroviral agents to evaluate the safety, tolerability and antiretroviral activity in HIV-1 infected Russian children and adolescents.

A chewable tablet and weight- based dose is already approved for children weighing 12kg or more in the EU. An application for granules for oral suspension in children from 4 weeks to < 2years of age is currently under EMA review. The doses used in this trial are largely in line with the EU prescribing information.

The additional information obtained from this study is limited. The MAH does not consider that the study results require changes to the product information to be made. The CHMP agrees.

➢ Recommendation

☒ **Fulfilled – No further action required.**