10 February 2015
EMA/85104/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Isentress

Intenational non-proprietary name: raltegravir

EMEA/H/C/000860/P46/056

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Invented name of the medicinal product:	Isentress
INN (or common name) of the active substance(s):	raltegravir
MAH:	Merck Sharp & Dohme Corp.,
Currently approved Indication(s)	HIV-1 infection
Pharmaco-therapeutic group (ATC Code):	J05AG04
Pharmaceutical form(s) and strength(s):	Tablet, chewable tablet

1. Introduction

In accordance with Article 46 of Regulation (EC) N° 1901/2006, Merck Sharp & Dohme, is submitting the results of the trough concentration substudy, a part of the IMPAACT P1066 protocol. This substudy was implemented as a result of a concern raised during review of IMPAACT P1066 study results by the CHMP that raltegravir C_{trough} values may be lower in some children in the Cohort III age range (2 to < 6 years of age) than in the other age groups. This study was undertaken via protocol amendment of P1066 study, to provide additional data to ensure adequate trough concentrations (≥45 nM) are achieved in the paediatric age group.

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.

2. Scientific discussion

2.1. 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.

2.2. 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 Group and Formulation
Cohort I	≥12 to <19 years of age assigned to receive poloxamer film coated tablets
Cohort IIA	≥6 to <12 years of age and ≥ 25 kg assigned to receive poloxamer film coated 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 (defined as 180 days) to <2 years of age assigned to receive oral granules for suspension
Cohort V	≥4 weeks (defined as 30 days) to <6 months of age assigned to receive oral granules for suspension

* This table reflects the final dosing age groups. The weight restriction in Cohort IIA was added after pharmacokinetic data were evaluated.

TROUGH CONCENTRATION SUBSTUDY RATIONALE

Ctrough (C12hr) has been identified as an important PK parameter for predicting outcome of raltegravir treatment. In QDMRK (Protocol 071), troughs <45 nM were more frequently seen in the 800

mg QD regimen and were associated with lower virologic responses than 400 mg BID. In IMPAACT P1066, Ctrough for Cohort III tended to be lower than other cohorts, with a small number (2) of patients having results < 45 nM.

TROUGH CONCENTRATION SUBSTUDY OBJECTIVES

At the time of the initial approval of raltegravir in children and adolescents 2 to 17 years of age, the CHMP requested that a trough concentration substudy be performed for P1066 in an effort to further confirm the adequacy of the chewable tablet formulation in an additional subset of patients. The substudy was implemented as a result of a concern raised during review of IMPAACT P1066 study results by the CHMP. The concern from the CHMP was that raltegravir Ctrough values may be lower in some children in the Cohort III age range (2 to < 6 years of age) than in the other age groups.

The trough concentration substudy was conducted via letter of amendment to the IMPAACT P1066 protocol. The targeted enrollment for this substudy was 10 patients. The objective was to further evaluate trough concentrations (Ctrough) in patients currently 2 to < 6 years of age (irrespective of age at study enrollment) receiving raltegravir chewable tablets at the currently approved dose of 6 mg/kg BID, and thereby provide additional data to ensure adequate trough concentrations (≥45 nM) are achieved.

ELIGIBILITY

All IMPAACT P1066 enrolled patients who were 2 to <6 years of age when the substudy was implemented, and receiving the raltegravir chewable tablet at the approved dose of ~ 6 mg/kg BID were eligible. Note that participation in the substudy was voluntary. The substudy was presented to the study participants as an opportunity to add important study information/data to the study but there was no requirement for the site to participate or the participant to consent for this component of the study. Patients enrolled into Cohort IV and V who had reached their 2nd birthday were eligible provided that they passed the 48 week time point (to avoid potential confounding with primary/secondary study end points) and the individual was been on the chewable formulation for >2 weeks to ensure that they reached steady state.

TROUGH CONCENTRATION SUBSTUDY DESIGN

Subjects enrolled in this substudy had 2 plasma samples obtained to assess trough (C12hr) concentrations; the first was drawn following an unobserved dose and the second following an observed dose. Sites confirmed before scheduling the PK visit that the patient was receiving the currently approved 6 mg/kg BID dose. If a weight-based dose adjustment was necessary, it was done at least 2 weeks before the PK visit. All enrolled patients had two blood sample collections, 2 mL per sample. On a single study visit day, the patient had two PK samples collected approximately 12 hours apart: the first as an unobserved pre-dose sample (C12hr unobserved) sample and the second as an observed collection 12 hours after dosing (C12hr observed). The unobserved C12hr plasma PK sample was collected between 11 and 13 hours after the prior (unobserved) raltegravir dose, and just before an observed dose. The time of the previous (unobserved) raltegravir dose was recorded by the study site on the case report form (CRF). The first PK sample collection was scheduled such that the witnessed dose of raltegravir on the day of the study visit was as close as possible to 12 hours (between 11-13 hours) after the previous unobserved dose. The patient then received a site staff administered (i.e., witnessed [observed]) raltegravir dose of 6 mg/kg, and returned to the clinic later that day for the second C12hr plasma sample collection, between 11 and 13 hours after the witnessed (observed) dose. The second PK sample collection was collected as close as possible to 12 hours after the witnessed raltegravir dose. In the event of doses vomited <30 minutes after dosing; PK sample

collection was cancelled and rescheduled. There were no dietary restrictions on the day of the study visit.

Both PK samples from this visit were sent within one week for raltegravir concentration determination. All PK samples were registered in the Laboratory Data Management System (LDMS) database and sent immediately after collection to the Antiviral Pharmacology Laboratory. The study database was kept up to date by close tracking of samples. PK sample assays and summary statistics were performed on a rolling basis and results were discussed with the protocol team.

SAMPLE INFORMATION

Whole blood (2 mL) for raltegravir determination in plasma was collected at trough following an unobserved and an observed dose; all samples were collected in K-EDTA purple-top tubes. Samples were received from various clinical sites affiliated with the IMPAACT clinical trials group. Blood samples were drawn and plasma prepared at the clinical sites. CRFs detailing information such as height, weight, raltegravir dose amount, cohort number, the timing of subject doses and blood draws were prepared at the clinical sites. No identifying information was present on CRFs. Clinical sites used the Laboratory Data Management System (LDMS) to generate the Specimen ID, Global Specimen ID, and shipping manifests. Tubes were labeled with the specimen ID, global ID, protocol number, draw dates and time. Shipping manifests were prepared to reflect the data for shipped samples. Samples were then packaged in dry ice and shipped according to the safe handling of biological specimens. All samples were received frozen on dry ice and in good condition.

The first trough samples were received in July 2013 and arrived periodically according to enrollment of subjects. The final set of samples arrived in June 2014 and, at that time, the trough concentration substudy was closed.

METHODS FOR PHARMACOKINETIC ANALYSES

Due to the sparse nature of the trough concentrations collected in the substudy, they are presented in summary statistical and graphical format. All concentration-time results have been internally quality controlled by the Antiviral Pharmacology Laboratory and externally quality controlled by the IMPAACT Data Management Center (DMC).

RESULTS

A total of 11 subjects were enrolled into the trough concentration substudy. One subject (8502049A) had the unobserved trough collected at 6.3 hours post dose and the second observed sample was not collected. This participant was excluded from the tables/analyses included below. Table 1 below lists the concentration results for the remaining 10 participants.

Table 1. Raltegravir Trough Concentration Results in the IMPAACT P1066 Trough Concentration Substudy

Participant	PID	Original Cohort	Week	Time Post Dose (h)	RAL Conc (ng/mL)	RAL Conc (nM)
1	0362885G	III	176	13.0	45.3	102.0
	0362885G	III	176	11.3	62.8	141.4
2	801524G	III	161	12.0	105.5	237.6
	801524G	III	161	12.0	157.0	353.6
3	801536A	IV	90	11.5	123.9	279.1
	801536A	IV	90	13.0	177.9	400.7
4	382192K	IV	96	11.1	21.0	47.3
	382192K	IV	96	12.0	14.1	31.8
5	801526B	IV	131	11.3	298.6	672.5
	801526B	IV	131	12.6	182.9	411.9
6	801537K	IV	83	11.7	706.1	1590.3
	801537K	IV	83	12.5	203.7	458.8
7	801535D	V	113	11.1	119.8	269.8
	801535D	V	113	11.5	149.1	335.8
8	8504252I	IV	104	11.5	215.9	486.3
	8504252I	IV	104	12.2	124.9	281.3
9	801399E	III	169	11.8	304.2	685.1
	801399E	III	169	11.1	79.3	178.6
10	801525E	IV	168	9.8	144.6	325.7
	801525E	IV	168	12.3	82.1	184.9
Mean			129.1	11.7	165.9	373.7
SD			35.5	0.8	149.9	337.5
%CV			27.5	6.5	90.3	90.3
Median			122.0	11.7	134.8	303.5
Min			83.0	9.8	14.1	31.8
Max			176.0	13.0	706.1	1590.3
Geometric Mean			124.4	11.7	119.2	268.4

Figures 1A and 1B depict these concentration results on linear (1A) and logarithmic (1B) scales in nM units. Figures 2A and 2B show the data in ng/mL units. The dashed line represents 45 nM (20 ng/mL)

Figure 1A. Raltegravir Trough Concentration Results in the IMPAACT P1066 Trough Concentration Substudy (linear, nM)

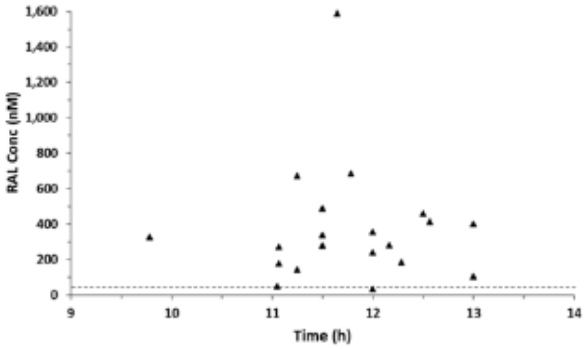


Figure 1B. Raltegravir Trough Concentration Results in the IMPAACT P1066 Trough Concentration Substudy (log, nM)

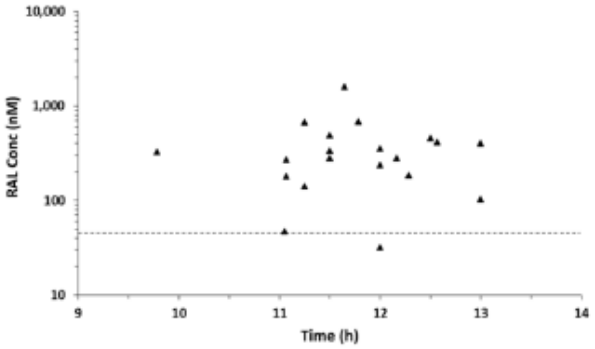


Figure 2A. Raltegravir Trough Concentration Results in the IMPAACT P1066 Trough Concentration Substudy (linear, ng/mL)

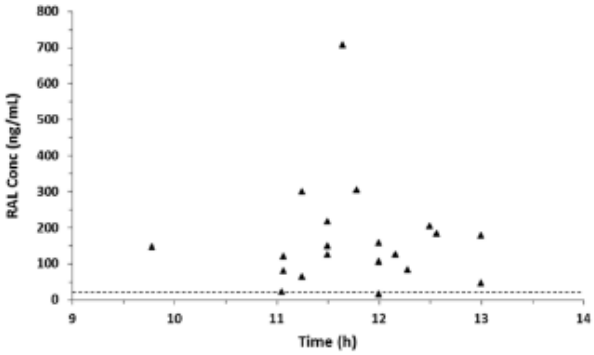
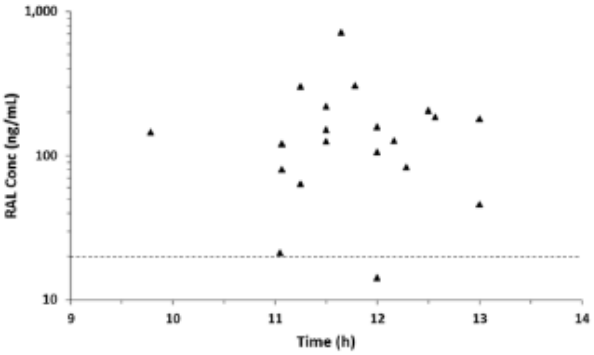


Figure 2B. Raltegravir Trough Concentration Results in the IMPAACT P1066 Trough Concentration Substudy (log, ng/mL)



The median trough concentrations were 303.5 nM (134.8 ng/mL) and the geometric mean was 268.4 nM (119.2 ng/mL) at a mean time of 11.7 hours post dose. Variability in trough concentrations was high at approximately 90%, but consistent with prior raltegravir data. Importantly, only 1 (out of 20, 5%) trough concentration fell below the 45 nM threshold for all samples collected. This occurred following the observed dose trough collection.

Trough concentration data were also examined as observed and unobserved concentration results. Tables 2 (unobserved) and 3 (observed) describe these results.

Table 2. Raltegravir Trough Concentration Results Following Unobserved Dosing in the IMPAACT P1066 Trough Concentration Substudy

Participant	PID	Cohort*	Week	Time Post Dose (h)	RAL Conc (ng/mL)	RAL Conc (nM)
1	0362885G	III	176	13.0	45.3	102.0
2	801524G	III	161	12.0	105.5	237.6
3	801536A	IV	90	11.5	123.9	279.1
4	382192K	IV	96	11.1	21.0	47.3
5	801526B	IV	131	11.3	298.6	672.5
6	801537K	IV	83	11.7	706.1	1590.3
7	801535D	V	113	11.1	119.8	269.8
8	8504252I	IV	104	11.5	215.9	486.3
9	801399E	III	169	11.8	304.2	685.1
10	801525E	IV	168	9.8	144.6	325.7
Mean			129.1	11.5	208.5	469.6
SD			36.5	0.8	199.0	448.2
%CV			28.2	7.1	95.5	95.5
Median			122.0	11.5	134.3	302.4
Min			83.0	9.8	21.0	47.3
Max			176.0	13.0	706.1	1590.3
Geometric Mean			124.4	11.4	140.4	316.3

*Cohort to which the patient was originally enrolled into the study.

Table 3. Raltegravir Trough Concentration Results Following Observed Dosing in the IMPAACT P1066 Trough Concentration Substudy

Participant	PID	Cohort*	Week	Time Post Dose (h)	RAL Conc (ng/mL)	RAL Conc (nM)
1	0362885G	III	176	11.3	62.8	141.4
2	801524G	III	161	12.0	157.0	353.6
3	801536A	IV	90	13.0	177.9	400.7
4	382192K	IV	96	12.0	14.1	31.8
5	801526B	IV	131	12.6	182.9	411.9
6	801537K	IV	83	12.5	203.7	458.8
7	801535D	V	113	11.5	149.1	335.8
8	8504252I	IV	104	12.2	124.9	281.3
9	801399E	III	169	11.1	79.3	178.6
10	801525E	IV	168	12.3	82.1	184.9
Mean			129.1	12.0	123.4	277.9
SD			36.5	0.6	61.5	138.5
%CV			28.2	5.1	49.8	49.8
Median			122.0	12.1	137.0	308.6
Min			83.0	11.1	14.1	31.8
Max			176.0	13.0	203.7	458.8
Geometric Mean			124.4	12.0	101.1	227.7

*Cohort to which the patient was originally enrolled into the study.

The median trough concentrations for the unobserved and observed groups were similar at 302 and 309 nM, respectively. The variability, however, was considerably lower for trough concentrations collected following the observed dose (50%). This decrease in variability following observed dosing is not unexpected and is reflected in Figures 3A (linear scale) and 3B (log scale) below. Where solid triangles are unobserved dosing trough results and green circles are observed dosing trough results. Dashed lines represent 45 nM.

Figure 3A. Raltegravir Trough Concentration Results by Dosing Group in the IMPAACT P1066 Trough Concentration Substudy (linear, nM)

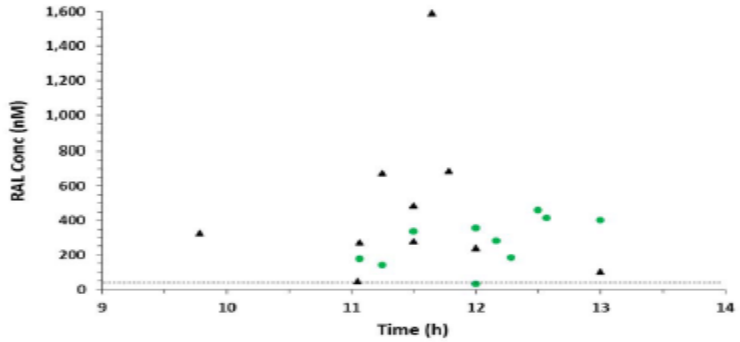
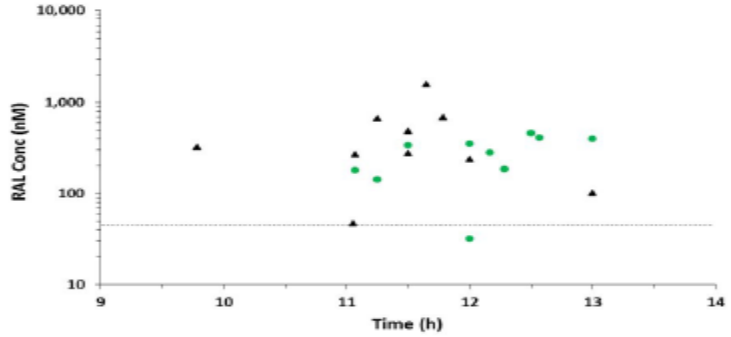


Figure 3B. Raltegravir Trough Concentration Results by Dosing Group in the IMPAACT P1066 Trough Concentration Substudy (log, nM)



The trough concentration data overall are similar to or higher than results observed in previous IMPAACT P1066 cohorts and from adult RAL studies. In IMPAACT P1066, the geometric mean C12hr (# of subjects with C12hr values <45 nM based on intensive PK) in Cohorts IV and V (ages 4 weeks to less than 2 years of age receiving oral granules for suspension) were 108 (0) and 117 nM (1), respectively. In Cohorts IIB and III (ages 2 to less than 12 years), where all subjects received the chewable tablets, the geometric mean C12hr (# of subjects with C12hr values <45 nM based on intensive PK) was 130 (0) and 71 (2) nM, respectively. In Cohorts I and IIA (ages 12 to less than 19 years), where all subjects received the adult poloxamer film-coated tablet formulation (400 mg BID); the geometric mean C12hr (# of subjects with C12hr values <45 nM based on intensive PK) for these groups were 333 (0) and 246 (1) nM, respectively.

CONCLUSIONS

This report summarizes the results of the Trough Concentration Substudy of IMPAACT P1066. A total of eleven subjects were enrolled into the substudy, and 10 subjects were considered evaluable for PK, with two trough concentrations collected from each, one following an unobserved dose and one following an observed dose. Among the 10 evaluable patients, the median trough concentrations were 303.5 nM (134.8 ng/mL) and the geometric mean was 268.4 nM (119.2 ng/mL). Only one result (5%)

fell below the 45 nM trough concentration threshold in comparison to 2 subjects in the original Cohort III group based on intensive PK. Overall results are consistent with prior pediatric pharmacokinetic results from IMPAACT P10662, and provide supportive evidence for the dosing regimen of 6 mg/kg BID of the chewable tablet formulation in children 2 to <6 years of age.

2.3. Discussion on clinical aspects

The applicant has submitted the results of the trough concentration substudy, which was undertaken as part of the IMPAACT P1066 protocol. This substudy enrolled 11 patients 2 to < 6 years of age, with eligible samples available from 10 patients. Except one patient, all achieved adequate trough concentrations (≥45 nM). There is a lot of variability in raltegravir concentrations between subjects and even within subjects for the observed and the unobserved doses. The sample size is also small and therefore it is difficult to make any firm conclusions. However it is also noted that one or two patients, within the other age cohorts also had lower concentrations.

Therefore overall, it appears that the dosing regimen of 6 mg/kg BID of the chewable tablet formulation in children 2 to <6 years of age is appropriate.

The MAH should continue to monitor the impact on the safety and efficacy of raltegravir in the paediatric population, and also perform if possible, at least sparse PK sampling in any ongoing/future studies in the paediatric age group to confirm these findings.

On the basis of the results of this paediatric substudy, 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.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

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