EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/CHMP/16343/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Isentress

International non-proprietary name: raltegravir

Procedure No. EMEA/H/C/000860/X/0024/G

Note

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

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Product information

Name of the medicinal product:	Isentress
Applicant:	Merck Sharp & Dohme Ltd. Hertford Road Hoddesdon, Herts EN11 9BU United Kingdom
Active substance:	raltegravir
International Nonproprietary Name/Common Name:	raltegravir
Pharmaco-therapeutic group (ATC Code):	Other antivirals (J05AX08)
Therapeutic indication(s):	ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, and children from the age of 2 years.
Pharmaceutical form:	Chewable tablet
Strengths:	25 and 100 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	60 tablets

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List of abbreviations

ADC	AIDS-defining conditions
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AUC_{0-12hr}	Area under the curve from 0 to 12 hours postdose
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
ART	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC	Area under the concentration-time curve
BID	Twice daily
BLOQ	Below the assay limit of quantitation
BMI	Body mass index
BUN	Blood urea nitrogen
C_{12hr}	Concentration at 12 hours postdose
C_{all}	Geometric mean concentration of all samples for a single patient
C_{max}	Maximum plasma concentration
CI	Confidence interval
CRO	Clinical research organization
CSR	Clinical study report
CV	Coefficient of variation
DAIDS	Division of AIDs
DMC	Data and Safety Monitoring Committee
EFV	Efavirenz
FCT	Film-coated tablet
FSG	Fasting serum glucose
GCP	Good clinical practice
GM	Geometric mean
GMR	Geometric mean ratio
GSS	Genotypic sensitivity score
HAART	Highly active anti-retroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Heart rate
IC_{95}	Inhibitory concentration - 95%
ICH	International conference on harmonization
IEC	Independent Ethics Committee
IMPAACT	The International Maternal, Pediatric, Adolescent AIDS Clinical Trials
IRB	Institutional Review Board
LFT	Liver function test
LLOQ	Lower limit of quantification
LPLV	Last patient last visit

LS means	Least-squares means
MED	Minimal effective dose
MRL	Merck Research Laboratories
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSE	Mean square error
NIAID	The National Institute of Allergy and Infectious Diseases
NC=F	Non-completer=failure
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitor
OBT	Optimized Background Therapy
OCSO	Office of Clinical Oversight
OF	Observed failure
OHRP	Office for human research protection
OLPVF	Open-label post-virologic failure
OTC	Over the counter
PI	Protease inhibitor
PID	Patient identification number
PSS	Phenotypic sensitivity score
RBC	Red blood (cell) count
RCC	Regulatory Compliance Center
RNA	Ribonucleic acid
ROC	Receiver operation characteristic
SADR	Suspected adverse drug reaction
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SIP	Study implementation plan
SOP	Standard operating procedure
T_{max}	Time to C_{max}
TDF	Tenofovir disoproxil fumarate
TDM	Therapeutic Drug Monitoring
TMC-114	Darunavir
TPV	Tipranavir
ULN	Upper limit of normal
VF	Virological failure
WAES	Worldwide adverse experience system
WBC	White blood (cell) count
WPS	Worldwide Product Safety

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 4 July 2011 an extension for a Marketing Authorisation to the European Medicines Agency (EMA) for Isentress 25 mg and 100 mg Chewable tablets, through the centralised procedure falling within Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2c and d).

The applicant applied for a new pharmaceutical form: chewable tablets associated with the following strength: 25 mg and 100 mg.

In addition, the applicant applied for the following indication: "*in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, and children from the age of 2 years.*"

Furthermore pursuant to Commission Regulation (EC) No 1234/2008, art.7-2(b), this extension of MA application was grouped with a type II variation to update the section 4.1 of the SmPC for the existing 400mg film-coated tablet with the new paediatric indication (adolescents and children from the age of 6 years) and introduce consequential changes to all sections of the SmPC for the existing 400mg film-coated tablet (except Sections 1 and 3), Annexes II, IIIa and IIIb.

The application submitted is composed of administrative information, complete quality data and clinical data based on applicant's own tests and studies and/or bibliographic literature.

Merck Sharp & Dohme Ltd. is already the Marketing Authorisation Holder for the Isentress 400 mg Film-coated tablet.

The legal basis for this application refers to:

Article 19 of Regulation (EC) No 1234/2008 - Extensions of marketing authorizations

The application submitted a grouping as per Article 7 of Regulation (EC) No 1234/2008 including an extension of MA (25 mg and 100 mg Chewable tablets) and a type II variation (new indication in paediatric patients).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/95/2009) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/95/2009) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP for the present application.

Licensing status

Isentress has been given a Marketing Authorisation in the European Union since 20 December 2007.

1.2. Manufacturers

Manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
NL-2031 BN Haarlem
The Netherlands

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **Pierre Demolis**

- The application was received by the EMA on 4 July 2011.
- The procedure started on 17 August 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 30 November 2011 (Annex 2).
- During the meeting on December 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 December 2012 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 April 2012 (Annex 4).
- During the CHMP meeting on 19 April 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 June 2012.
- The applicant submitted on 13 July 2012 a request to extend the clock stop and delay the oral explanation to September 2012.
- During the CHMP meeting on 19 July 2012, the CHMP agreed on the applicant's proposal to extend the clock stop and delay the oral explanation to September 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 September 2012 (Annex 6).
- During the CHMP meeting on 17 September 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

- During the CHMP meeting on 20 September 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 7).
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 October 2012 (Annex 8).
- During the meeting on 18 October 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Isentress on 18 October 2012.
- During the meeting on 13 December 2012, the CHMP issued a revised positive opinion for granting a Marketing Authorisation to Isentress.

2. Scientific discussion

2.1. Introduction

Isentress (raltegravir) is an integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1). Raltegravir inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is required for viral replication. Inhibition of integrase prevents integration of the HIV genome into the host cell genome. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection.

Isentress is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients. This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients and one double-blind, active-controlled trial in treatment-naïve patients.

2.2. Quality aspects

2.2.1. Introduction

Isentress 25 mg chewable tablets are presented as pale yellow round debossed tablets containing 27.16 mg of raltegravir potassium, equivalent to 25 mg raltegravir. Isentress 100 mg chewable tablets are presented as pale orange oval shaped scored and debossed tablets containing 108.6 mg of raltegravir potassium, equivalent to 100 mg raltegravir. The scored 100 mg tablets can be broken in half along the score line to provide a 50 mg dose.

The list of excipients can be found in section 6.1 of the SmPC. The tablets are presented in HDPE bottles with a polypropylene child-resistant screw cap and silica gel desiccant. Each bottle contains 60 tablets.

2.2.2. Active Substance

Raltegravir potassium, the active substance in Isentress 25 mg and 100 mg chewable tablets is identical to the active substance in the authorized Isentress 400 mg film-coated tablets (EU/1/07/436/001-002). Raltegravir is classified as a BCS class II compound, it has a high permeability and low solubility at physiological pH. For information on the active substance reference is made to Module 3.2.S of the marketing authorisation of the 400 mg strength and subsequent quality variations. The active substance specifications are the same as for the 400 mg tablet, with the

exception of the particle size for which a narrower acceptance limit was set in order to match the particle size of the excipient mannitol.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim was to develop a paediatric formulation for Isentress, suitable for use in children down to two years old, who would not be able to swallow the 400 mg marketed adult tablet. The development focused on finding an effective, palatable dosage form with acceptable size. Clinical needs required the development of two strengths; 25 mg and 100 mg.

In view of the above Quality Target Product Profile (QTPP), the applicant identified the following medicinal product's critical quality attributes (CQA): identity, assay, appearance, elegance, impurities, dissolution, dose uniformity, and deliver suitable stability.

The applicant studied several dosage forms, including orally disintegrating tablets (ODT), chewable tablets and oral granules for suspension. In view of the target population and the bitter taste of the active substance raltegravir, taste masking was identified as an important attribute during the development.

The first step in the development was to develop coated raltegravir granules to achieve taste masking. These taste-masked granules were used as a common starting material for all three formulations. Then, an adequate flavouring system was developed, and the most appropriate dosage form was selected.

Different taste masking systems for paediatric use were evaluated and a granule coating based on Surelease (an ethylcellulose dispersion) and Opadry (a coating suspension) was selected for the final formulation. Ethylcellulose provides taste masking via delayed release due to its insolubility, and when used in the right combination with Opadry, it delays drug release in the oral cavity but still allows immediate release of the drug once in the stomach.

After the development of the taste-masked granules, the applicant focussed on the flavour development and selection of the dosage form. Chewable tablets seemed to be most appropriate based on dissolution data and biocomparability to the initial ODT formulation and the effectiveness of the flavor system based on patient responses to a questionnaire. The chewable tablet formulation required substantial flavor development, because chewing causes some breakage of the taste masking coating, increasing mouth exposure to raltegravir. The flavour development focussed on overcoming the overall basicity of the formulation and included immediate and delayed onset flavouring agents to provide an acceptable flavor. A combination of orange flavor, bitter masking flavor, and banana flavor was chosen for chewable tablets for their particular attributes. The selected flavouring system also includes saccharin and sucralose (two fast onset sweeteners) to provide acceptable sweetness, Magnasweet (a delayed onset sweetener based on monoammonium glycyrrhizinate) to minimize the aftertaste, and mannitol to improve the feel and cooling sensation in the mouth. Questionnaires distributed during clinical trials indicated that the taste acceptability requirements were met. The rationale for the selection of the excipients is adequately explained and justified taking into account the safety profile of these excipients in children. The excipients comply with the Ph.Eur or USP, and the flavouring agents comply with Regulation (EC) No 1334/2008 relating to flavourings for use in foods. No novel excipients are used in the manufacture of Isentress chewable tablets. The full list of excipients can be found in section 6.1 of the SmPC

The applicant applied a quality by design (QbD) approach during the development of the manufacturing process of the chewable tablets. Design of experiments were performed at development scale to increase process understanding of the granulation and coating step and to define univariate proven acceptable ranges (PAR). A thorough risk analysis was performed for the entire manufacturing process to identify the critical process parameters. The results of the risk analysis were used to define the control strategy to ensure that all CQA and the associated QTPP requirements are achieved and that the manufacturing process is robust and reproducible.

The primary packaging proposed is a HDPE bottle with a polypropylene child-resistant screw cap and silica gel desiccant. Desiccant is included to mitigate risk to product quality from exposure to elevated humidity conditions. The material complies with the relevant European Directives and pharmacopoeial monographs and is adequate to support the stability and use of the medicinal product.

Adventitious agents

Isentress chewable tablets do not contain materials of animal or human origin. Assurance has been provided that the magnesium stearate and sodium stearyl fumarate are of vegetable origin only.

Manufacture of the product

The manufacturing process of the chewable tablets consists of a 4-step process and includes delumping and granulation of the drug substance, coating of the drug granules (taste masking), blending and compression. Comprehensive details have been provided on the development and optimisation of the manufacturing process. The process is considered to be a standard manufacturing process.

Critical manufacturing steps have been identified and adequate in-process controls are in place. The test methods and acceptance criteria are considered adequate. Batch analysis data on four 25 mg and four 100 mg batches (pilot scale or larger) show that the chewable tablets can be manufactured reproducible according to the agreed finished product specifications which is suitable for control of this oral dosage form. Formal validation of the manufacturing process in the production facility will take place prior to release of the product to the market. An acceptable validation summary protocol has been provided. This is satisfactory.

Product specification

The Isentress 25 mg and 100 mg chewable tablets release specifications include tests for appearance, identity (HPLC, FTIR), assay (HPLC), degradation products (HPLC), dissolution, content uniformity, microbiological limits, identity of ferric oxide and tablet breakability (100 mg tablet only). The finished product specifications are standard for immediate release tablets. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products are acceptable from the safety point of view. Batch analysis results comply with the predefined specifications and confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability studies on the chewable tablets have been carried out under long term (30°C/75%RH) and accelerated (40°C/75%RH) conditions, on three batches (at least pilot scale), according to the ICH requirements. Up to 52 weeks long term and 26 weeks accelerated stability data have been provided

The batches used for the primary stability studies were prepared in the final market composition and the packaging was representative of the packaging planned for use for the commercial product. Up to 52 weeks additional stability data was provided for bridging batches (at long term and accelerated conditions), manufactured at the commercial site. The parameters tested and analytical methods used in the stability studies are identical to those used for the release specifications, with the exception of identity, content uniformity, microbiological limits and identity of ferric oxide which are tested at release only, and hardness which is tested at the end of shelf-life. The analytical methods used were stability indicating. No significant changes were observed at any storage condition.

In-use stability studies were performed to evaluate the risk of tablet discoloration during the in-use period (i.e. after the induction seal has been breached). Based on the results no in use shelf-life is considered necessary. The applicant confirmed that the in-use stability study will be repeated at the end of the expiry period for the chewable tablets. This is acceptable on the basis of the in-use stability results obtained so far.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrated that the raltegravir chewable tablets can be considered to be stable when exposed to light. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Isentress 25 mg and 100 mg chewable tablets are paediatric strengths. The chewable tablets are manufactured using the same active substance as the authorised 400 mg tablets. Different excipients are used however, to make the tablets chewable and palatable. All excipients were found acceptable for use in the paediatric population.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were no unresolved quality issues.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Since RAL is already approved by oral route, as film-coated tablets, no additional non-clinical studies have been performed to support this application. The MAH has previously submitted juvenile toxicity studies in the rat and no additional toxicities were observed in juvenile animals. The CHMP considers this approach acceptable.

2.3.2. Ecotoxicity / environmental risk assessment

A summary of the Environmental Risk Assessment is presented in Table 1.

Table 1. Table 2 ERA Summary

Substance (INN / Invented Name): raltegravir Isentress			
PBT screening		Result	Conclusion
Bioaccumulation potential log D_{ow} DT_{50}		0.45 at pH 7.4 $DT_{50,sediment}$ = 182 days (Choptank anaerobic system)	Potential PBT: no $DT_{50sediment}$ >180 therefore classified as persistent
Phase I			
Calculation	Value	Unit	Conclusion
$PEC_{surfacewater}$	8.0	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	Protocol	Results	Remarks
Adsorption-Desorption	OECD 121	log K_{oc} = 1.64	<4 threshold
Inherent Biodegradability	OECD 302B	DT_{50} = 224 hours	Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water\ aerobic}$ = 6.4-6.5 days $DT_{50, water\ anaerobic}$ = 5.2-6.8 days $DT_{50, sediment}$ = 90-182 days $DT_{50, whole\ system}$ = not	Relative % of parent and metabolites in the non-extractable component(s) bound to sediment not discernible > 10% of radioactivity present in the sediment at termination of study (Day 100)

Substance (INN/Invented Name): raltegravir Isentress					
		determined			
Phase IIa Effect studies					
Study type	Protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition test on	OECD 201	NOEC	1600	µg/L	Pseudokirchnieriella subcapitata 96-hr exposure
Daphnia sp. Reproduction Test	OECD 211	NOEC	9500	µg/L	21-day study
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	9300	µg/L	Pimephales promelas 33-day study
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	10^6	µg/L	3-hour exposure
Phase IIb Studies					
Study type	Protocol	Endpoint	value	Unit	Remarks
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	Chironomus riparius 28-day study

Outcome of phase II studies			
	PNEC	PEC	PEC/PNEC, and conclusion
Surface water	160 µg/L based on: NOEC determined in the most sensitive aquatic species = 1600 µg/L (algae study) AF = 10	8 µg/L	0.05 (< 1) Raltegravir does not pose a risk to the aquatic environment
Ground water	950 µg/L based on: NOEC determined in the 21-day daphnia study = 9500 µg/L AF = 10	2 µg/L ($0.25 \times PEC_{sw}$)	0.002 (<1) Raltegravir does not pose a risk to ground water organisms
Micro-organisms	10^5 µg/L based on: NOEC determined in the ASRIT = 10^6 µg/L AF = 10	8 µg/L (PEC_{sw})	8.10^{-5} (<0.1) Raltegravir does not pose a risk to micro-organisms

The information regarding the ERA suggests that RAL and/or its metabolites will not constitute a risk to the environment.

2.3.3. Conclusion on the non-clinical aspects

No new non-clinical studies have been performed in support of this application and no further studies are considered necessary by the CHMP. The available pharmacokinetic and toxicology data are considered sufficient by the CHMP to support the use of RAL in paediatric patients from 2 to 18 years of age.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol	Dose(s) of Raltegravir Studied	Final Dose Selected	Number Receiving Raltegravir	Population	Key Purpose
Protocol 068	A: 400 mg raltegravir FMI poloxamer tablet B: 400 mg (4 x 100 mg) raltegravir CT C: 400 mg raltegravir oral granules in a liquid suspension D: 400 mg (4 x 100 mg) raltegravir CT after high fat meal	N/A	12	Healthy adult volunteers	PK and Safety
IMPAACT (P1066) Study 022	Adult Tablet: Dose Ranging: Weight based to approximately 6 mg/kg BID; 200 - 600 mg BID. Chewable Tablet: Dose Ranging: Weight based to approximately 8 mg/kg BID; 75 – 300 mg BID.	Adult Tablet: 400 mg BID for patients 12-18 years and 6-11 years and ≥ 25 kg. Chewable Tablet: Weight based to approximately 6 mg/kg BID (max 300 mg BID) for patients 2-11 years.	87 39	Treatment-experienced pediatric patients	Demonstration of PK and short term safety for dose finding; safety and efficacy with long term dosing

Protocol	Dose(s) of Raltegravir Studied	Final Dose Selected	Number Receiving Raltegravir	Population	Key Purpose
Study 071	RAL: 800 mg q.d. RAL: 400 mg b.i.d. and 800 mg q.d. All patients took one tablet of TRUVADA™ daily	N/A	775	Treatment naïve adults	Evaluate the long-term safety, tolerability, and efficacy of oncedaily (q.d) RAL 800 mg PO compared with twice daily (b.i.d.) RAL 400 mg PO when each was given in combination with TRUVADA™ for up to 96 weeks, which was extended to 120 weeks.

2.4.2. Pharmacokinetics

Analytical Methods

The analytical method for the determination of RAL in human plasma used HPLC-MS/MS. The two validated procedures that were used had linear calibration ranges of 1 - 3000 ng/mL and 10 - 10,000 ng/mL. Separate bio analytical reports have been provided.

Study 068

Study 068 was an open label cross over study to compare the adult tablet as marketed with the candidate chewable tablet. It also evaluated the effect of food on absorption after dosing with the chewable tablet. Subjects each received 4 single dose (400 mg) treatments in a randomised order and with at least 4 days of washout between each treatment period. PK samples were obtained over 72h after each dosing.

- Treatments A and B were administered in the fasting state.
- Treatment D was administered after a high fat breakfast of 827 kcal and 57% fat content.

The data from treatment C wasn't following into the scope of the present application since a different formulation was used.

The comparison between the chewable tablet (treatment B) and adult tablet (FMI poloxamer formulation; treatment A) when administered in the fasting state gave a GMR for AUC0-∞ at 1.78 and 90% CI 1.47, 2.15. The Geometric Mean Ratio (GMR) for C_{max} was 3.22, with 90% CI 2.37, 4.38. Thus, $AUC_{0-\infty}$ and C_{max} observed with the chewable tablet were higher than obtained with the marketed adult tablet and the two formulations were not bioequivalent. Peak concentrations also occurred earlier such that median T_{max} was only 0.5 h for the chewable tablet vs. 4 h for the adult tablet. The C_{12h} concentrations and half-lives were comparable between formulations.
The administration of the chewable tablet with a high-fat meal (treatment D) slowed the rate of absorption with no statistically meaningful change in the extent of absorption but C_{12h} was improved.

Study 022 (P1066; IMPAACT)

Study 022 (P1066; IMPAACT) is an on-going Phase I/II, multi-center, open-label, non-comparative study of approximately 140 HIV-1 infected children and adolescents 4 weeks through 18 years of age

to evaluate the safety, tolerability, PK parameters and efficacy of raltegravir in combination with an optimized background regimen.

The data discussed as part of the present application are related to raltegravir administered orally as the adult tablet or as a chewable tablet (2 through 18 years of age). A third formulation, oral granules for suspension in water, was available to permit study of patients 4 weeks through 2 years of age. These data are not part of the present submission.

Formulations

- Adult tablets (100, 200 and 400 mg erodible tablet formulation; note that only the 400 mg tablet is approved),
- Chewable tablets (25, 50 and 100 mg unscored); the 50 mg has been dropped.

Note: The 50 mg dose was dropped during the study since this strength was not required to titrate the patients. However, the data related to the 50 mg dose were submitted by the applicant in the clinical study report for study P022 which was part of the initial submission.

The 100 mg chewable tablet used in study 068 was of the same formulation and composition as that used in study 022.

Note that the commercial tablet is scored and the applicant performed multimedia (pH 1.2, 4.5, and 6.8) comparative dissolution profiles using the same dissolution testing conditions to bridge between the tablets used in the trial and the commercial ones.

Data from a study on tablets split by hand that quantitate the equivalence of the resulting halves and the amount of powder mass lost during the splitting operation were provided. Comparative dissolution data were obtained for 100 mg scored tablet halves vs. the intact tablet. Hence, the 100 mg chewable tablet can be divided into equal 50 mg doses; however, as indicated in the SmPC, it is not recommended to break the tablets since it is possible to build the dosage with whole 25mg and 100mg chewable tablets.

Since the tablets and the chewable tablets are not bioequivalent, the following statement has been included on the outer carton and on the bottle label the statement "*Do not switch between the chewable tablets and the 400 mg tablet, without first talking with your doctor*."

Objectives

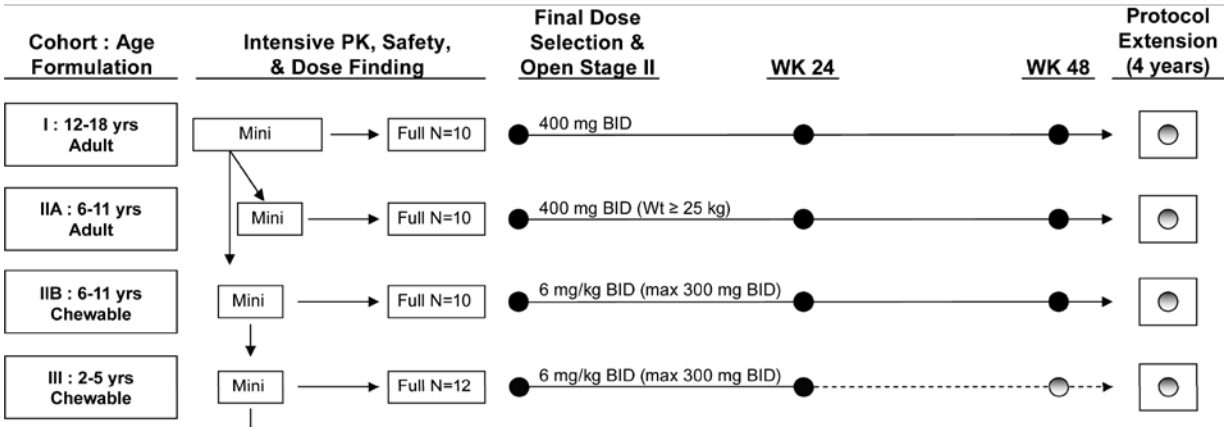
The study design is further described in the section 2.5. The clinical pharmacology objectives were:

- To evaluate the steady state plasma concentration profiles and PK parameters of raltegravir in children and adolescents.
- To evaluate the steady state plasma concentration profiles and PK parameters of raltegravir administered as a poloxamer tablet, a chewable tablet or oral granules for suspension.
- To collect sparse concentration-time data to create a population PK model to describe paediatric exposure to raltegravir and to assess drug-drug interactions.

The aim was to determine a formulation-specific paediatric dose that would provide approximately the same plasma exposure to that achieved in adults using 400 mg BID delivered with the marketed tablet. On this basis the target minimum exposure for each cohort was a GM $AUC_{0\text{-}12h}$ between 14 and 25 µM·hr with a concurrent GM C_{12h} exceeding 33 nM (i.e. the IC95). Additionally, for safety considerations, the maximum AUC0-12h was to be < 45 µM·hr, which represents half the $AUC_{0\text{-}24h}$ that was observed when 1600 mg was administered in Phase I studies.

Methods

Figure 1. Study design P1066 (DLP 14/02/2012)



Note: The week 48 data for Cohort III was submitted with the responses to the D120 LoQ (DLP 15/07/2012)

Stage I examined PK, short-term tolerability and safety in a limited number of patients to permit dose selection for further study in Stage II. Stage I commenced with dosing Cohort I and progressed sequentially to the younger cohorts, in each case obtaining preliminary data from a mini-cohort. The background ARV was optimised after sampling for PK evaluation.

Stage II involved raltegravir dosing for 48 weeks with an optimised background ARV regimen. Sparse PK sampling was performed during the chronic dosing stage.

Upon completion of 48 weeks study treatment raltegravir was made available to patients via a protocol extension inclusive of 5 years from initial exposure.

Cohorts I (≥□12 to 18 years - adult tablets) and Cohort IIA (≥□6 to < 12 years - adult tablets) received poloxamer film-coated tablets twice daily (same formulation as the approved 400 mg tablet). Three strengths (100, 200, and 400 mg) were provided for dosing flexibility.

Cohorts IIB (≥□6 to < 12 years - chewable tablets) and III (≥□2 to < 6 years - chewable tablets) received chewable tablets twice daily. Three strengths (25, 50, and 100 mg) were initially provided to allow dosing flexibility in 25 mg intervals but the 50 mg dose strength was later removed.

Intensive PK sampling

It was performed for all patients in Stage I of each cohort and also following an initial dose or dose change of raltegravir. Intensive PK sampling occurred between Days 5 and 12 after the first raltegravir dose and between Days 7 and 14 after dose adjustment. There was witnessed dosing at approximately 12 hours after the previous dose. Samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post dose. The large majority of patients had plasma concentrations at all time points well above the LLOQ.

Of note, patients were fasted only on the day of PK collection during the intensive PK sampling phase; on all other study days, administration of raltegravir was allowed irrespective of food intake.

Population PK sampling

It was performed for all patients in Stages I and II at Weeks 4, 8, 12 and 24. One blood sample was collected between 10 and 14 hours post dose at Weeks 4 and 12; two blood samples separated by 2

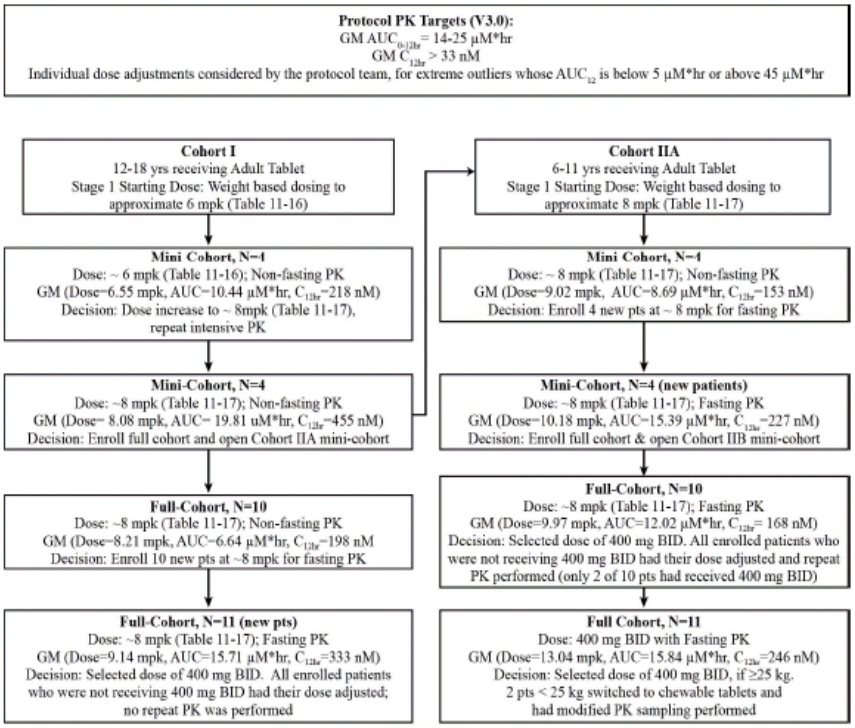
hours were collected between 0.5 and 6 hours post dose at Week 8; and two samples separated by 2 hours were collected between 6 and 12 hours post dose at Week 24.

Dose-finding

Dose-finding with adult tablet formulation (using 100, 200 and 400 mg tablet sizes)

The figure below shows the progression of studied doses and resulting PK parameter values for Cohorts I (≥ 12 to 18 years) and IIA (≥ 6 to < 12 years) using the adult tablet formulation.

Figure 2. Schematic of studied and associated PK parameter values for cohort I and IIA (adult tablets)



The first four patients in Cohort I (≥□12 to < 19 years), Stage 1 received ~6 mg/kg BID (maximum dose 800 mg) using the adult tablet and under non-fasted conditions. The full Cohort I did not meet the AUC PK targets. Since food may have contributed to a lower observed AUC, intensive PK sampling under fasting conditions led to dose adjustment to ~8 mg/kg BID (maximum dose of 600 mg). Subsequently, 11 new patients were enrolled in Cohort I for intensive PK evaluations after dosing in the fasting state. The dose adjustment to 8 mg/kg twice daily meant that the majority of the patients actually received 400 mg twice daily giving a range of 6.7 to 10.5 mg/kg. Data obtained showed that on dosing with ~8mg/kg the GM $AUC_{0\text{-}12hr}$ (15.7 µM·hr) and C_{12h} values (333 nM) for this cohort fell within the pre-defined targets. It was concluded that 400 mg BID would provide mean PK parameter values within the target range.

For Cohort IIA (≥ 6 to < 12 years), dosing was initiated in four patients at 8 mg/kg BID using adult tablet formulations under non-fasted conditions and then 10 new patients were enrolled to receive ~8 mg/kg BID (maximum dose 600 mg) using adult tablet formulations under fasted conditions. The initial dose of approximately 8 mg/kg twice daily gave a GM $AUC_{0\text{-}12hr}$ (12.0 µM·hr) below the minimum target of 14 µM·hr. A fixed dose of 400 mg BID for all patients was then administered and resulted in GM $AUC_{0\text{-}12hr}$ (15.8 µM·hr) and C_{12hr} values (246 nM) that met the pre-defined targets.

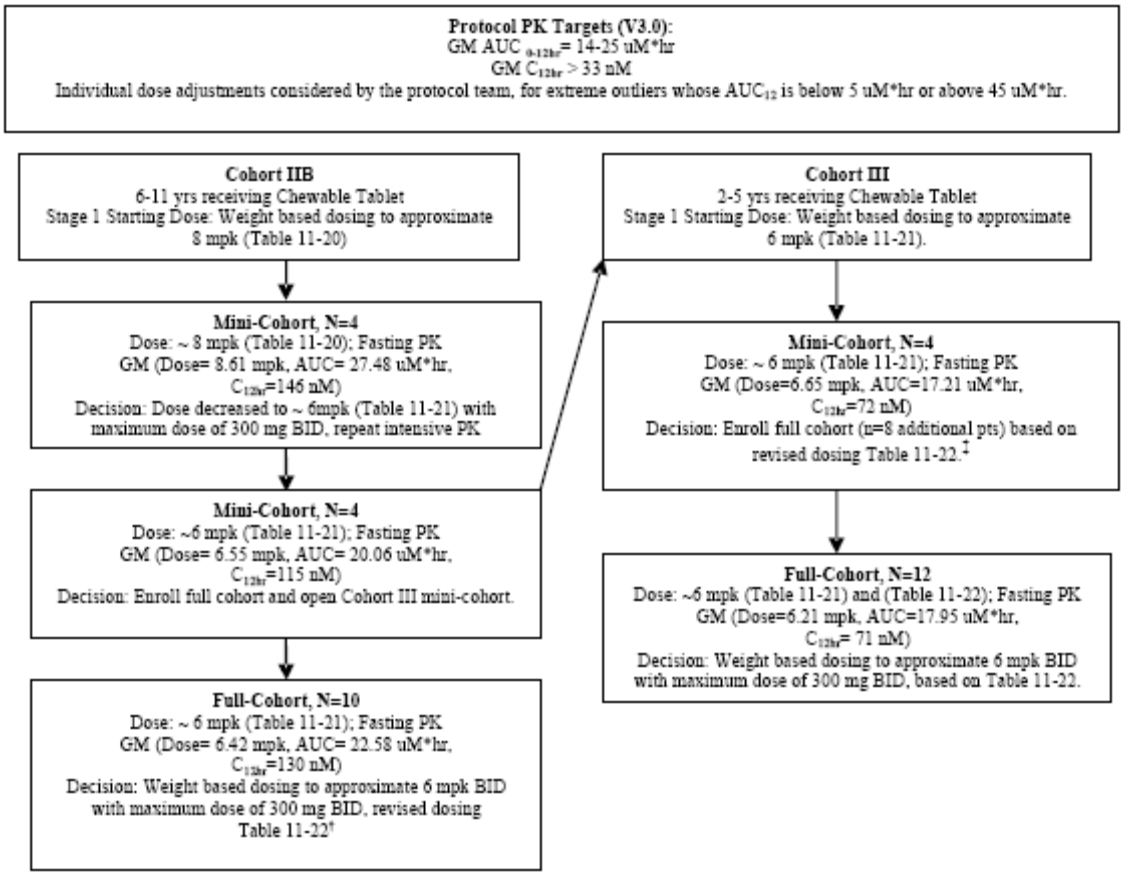
Two subjects with weights below 25 kg had extremely high AUC_{0-12hr} values when administered 400 mg BID while a third subject had AUC_{0-12hr} below the target value. On the contrary, the AUC_{0-12hr} values in children aged 6 with body weight ≥ 25 kg were nearly identical to those observed in adults.

Based on these findings, it is recommended to use a fixed dose of the adult formulation 400 BID when body weight is ≥ 25 kg in children aged 6 to 18 years.

Dose-finding with chewable tablets (using 25, 50 and 100 mg tablet sizes)

The next figure shows the progression of studied doses and resulting PK parameter values for Cohorts IIB (≥ 6 to < 12 years) and III (≥ 2 to < 6 years) when dosed with the chewable tablet.

Figure 3. Schematic of studied and associated PK parameter values for cohort IIB and III (chewable tablets)



Note – The tables mentioned in the figure were included in the marketing authorisation application

The first 4 subjects enrolled in Cohort IIB received approximately 8 mg/kg twice daily, which resulted in a GM AUC_{0-12hr} that was greater than the pre-defined range of 25 µM·hr. Therefore the dose was reduced to approximately 6 mg/kg up to a maximum dose of 300 mg twice daily. Six additional subjects were enrolled at the revised dose and the original subjects had their dose changed. The resulting geometric mean AUC_{0-12hr} and C_{12h}r were within the target ranges. Hence, a dose of approximately 6 mg/kg (maximum 300 mg) twice daily of the chewable tablet was chosen for continued study in the age group 6-11 years.

Twelve patients were enrolled in Stage 1 of Cohort III. Using the recommended 6mg/kg dosing the GM AUC_{0-12hr} and C_{12hr} were within the target ranges.

Weight-based dosing of the chewable tablet for children ages 6 to less than 12 years old with body weight < 25 kg was considered to be supported by examination of clearance as a function of weight. Indeed, clearance values appear relatively constant in children with body weight ≥25 kg, and begin to trend downward with decreasing weights below 25 kg, suggesting that weight-based dosing would be more appropriate for those < 25 kg to maintain similar exposures to those seen in adults.

Since the minimum weight reported in this study was 11.8 kg and there were only seven children in Stage I with weights between 11.8 and 14 kg, the chewable tablets should be used from 12 kg upwards.

Based on these findings, it is recommended to use the weight based regimen of 6mg/kg, to maximum dose 300 mg, twice daily, of the chewable tablets when body weight is ≥ 12 kg in children aged 2 to 12 years.

Analyses

Both intensive and sparse PK data were collected in this study. Since intensive PK data were collected under the most controlled conditions and with observed dosing, intensive PK assessments provide most accurate estimate of PK parameters associated with the administered dose. Hence, the data from the intensive PK data were considered more closely during the application.

Analyses based on sparse sampling data

For all Cohorts, the three non-model based exposure summary measures that were calculated based on the observed sparse concentration data were:

- Call = GM of all samples for a particular patient, regardless of time of collection
- GM C_{12h} = GM of all samples for a particular patient collected between 10-14 h post-dose
- Cmin = minimum value of all samples for a particular patient, regardless of time of collection

Concentrations that were < LLOQ (10 ng/mL) were assigned a value of ½*LLOQ = 5 ng/mL = 11 nM. Values of the non-model based parameters for the Final Dose population from sparse concentration data are shown in the table 2.

Table 2. Geometric Mean (%CV) values for Non-Model based RAL PK parameters calculated from sparse concentration data (cohorts I, IIA, IIB, III, final dose population)

Cohort	N	C_{all} (nM)	N	GM C_{12hr} (nM)	N	C_{min} (nM)
I	58	354 (112)	53	225 (175)	58	72 (163)
IIA	4	1227 (80)	2	558 (93)	4	262 (51)
IIB	13	355 (82)	12	108 (101)	13	50 (77)
III	20	267 (164)	19	130 (161)	20	57 (170)

There was less variability in PK observed when dosing with chewable tablets versus the adult tablet based on all the intensive sampling data obtained in the fasting state. On this basis, no modelling was conducted using the data from Cohorts I and IIA in which the adult tablet was used. A model was developed using the data from Cohorts IIB and III in which the chewable tablet was used to estimate values of $AUC_{0\text{-}12hr}$, Cmax and C_{12hr} based on the sparse concentration data. Values of the model-based parameters for the Final Dose population on the sparse concentration data are shown in the table 3.

Table 3. Geometric Mean (%CV) values for Model based RAL PK parameters calculated from sparse concentration data (cohorts IIB, III, final dose population)

Cohort	N	$AUC_{0\text{-}12hr}$ (μM*hr)	C_{max} (μM)	C_{12hr} (nM)
IIB	13	25.3 (23)	10.8 (31)	244 (89)
III	20	19.7 (75)	8.7 (26)	157 (176)

Analyses based on intensive PK data

Overall exposure (GM $AUC_{0\text{-}12hr}$) and GM Ctrough levels from the intensive PK analyses, both the film-coated and chewable tablets in Cohorts I to III, are presented in table 4.

Table 4. Raltegravir Pharmacokinetic Parameters IMPAACT P1066

Age	**Formulation**	**Dose**	**N†**	**Geometric Mean *(%CV)*** **AUC $_{0\text{-}12hr}$ (μM*hr)**	**Geometric Mean *(%CV)*** **C_{12hr} (nM)**
12 through 18 years	400 mg tablet	400 mg twice daily, regardless of weight‡	11	15.7 (*98 %*)	333 (*78 %*)
6 through 11 years	400 mg tablet	400 mg twice daily, for patients ≥25 kg	11	15.8 (*120 %*)	246 (*221 %*)
6 through 11 years	Chewable tablet	Weight based dosing, see Table 1	10	22.6 (*34 %*)	130 (*88 %*)
2 through 5 years	Chewable tablet	Weight based dosing, see Table 1	12	18.0 (*59 %*)	71 (*55 %*)

†Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
‡Patients in this age group received approximately 8 mg/kg dose at time of intensive PK which met PK and safety targets. Based on review of the individual profiles and receipt of a mean dose of 390 mg, 400 mg twice daily was selected as the recommended dose for this age group.

Chewable tablet doses

There was no obvious trend in Cohorts IIB and III for the PK parameters values to vary by dose or tablet potency received (i.e. 25mg, 100mg).

2.4.3. Pharmacodynamics

Study 071

Study 071 was a phase III multicenter, double-blind, randomized, active comparator-controlled clinical trial to study the safety and efficacy of once daily raltegravir versus twice daily raltegravir, each in combination with Truvada (emtricitabine/tenofovir disoproxil fumarate), in treatment-naïve HIV infected patients. Study 071 showed a statistically significant difference between 400 mg BID and 800 mg QD regimens in the pre-defined primary analysis at Week 48.

Data comparing regimens containing raltegravir 400 mg BID vs. 800 mg QD in this study have suggested a PK/PD relationship with C_{trough}, where low C_{trough} in the 800 mg QD arm was associated with a higher probability of virologic failure. Indeed, a receiver operating characteristic (ROC) analysis identified this threshold C_{trough} of 45 nM. This was consistent with the results of a quartile analysis, showing a lower efficacy response in patients in the lowest quartile of C_{trough} values in the 800 mg QD arm of the study, where the upper bound of the lowest quartile was a C_{trough} value of 43 nM.

The failure to demonstrate non-inferiority for 800 mg QD vs. 400 mg BID and the differences in PK, especially with respect to C_{trough}, were informative to the CHMP with regard to RAL PK/PD relationship and the relative importance of C_{12h} (effectively C_{trough}) versus AUC. Though it is not been possible to identify a robust threshold for C_{trough}, the available data suggest a threshold value ~ 45 nM. Hence, though it was not part of the original PK target definition for study 022, this information has been taken into account in the present assessment.

Study 022

Analyses based on sparse sampling data

The following assumptions were made for the PK/PD analysis: dosing history and sampling times were collected appropriately, plasma concentrations are at steady state for all visits where PK was collected such that longitudinal variation in PK does not need to be considered (except for the time points where there is a change in dose), samples drawn at different visits can thus be pooled together.

Exploratory plots of PK/PD associations were made between the various PK parameters and each of the efficacy parameters. To assess the effect of PK parameter (GM C_{12hr} or GM Call) on the two efficacy endpoints a logistic regression model with PK parameter and baseline HIV RNA level as predictors was used. These two factors were assumed to have no interaction.

Based on all patients in the Final Dose population there were statistically significant associations detected for all combinations of sparse PK parameters and efficacy measures in the analyses of data from all four Cohorts and from Cohorts I and IIA (adult tablet) but not for Cohorts IIB and III (chewable tablet). When those with ≥ 2 BLOQ PK values were removed from the analysis, statistically significant relationships were detected only between GM C_{12h} and HIV RNA <50 copies/mL for all four cohorts. Of note, a statistically significant relationship between GM C_{12h} and HIV RNA <50 at Week 48 of treatment was also observed in treatment-experienced adults in studies 018 and 019 (submitted as part of the initial marketing authorisation application) but consistent relationships between GM C_{12h} and other efficacy endpoints (e.g. HIV RNA < 400, virological failure and presence of resistance mutations) were not observed.

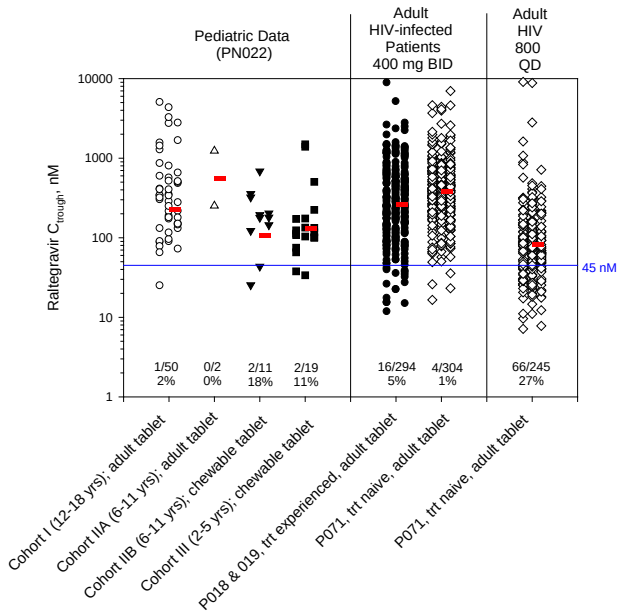
These data should be interpreted with caution due to the relatively small number of patients, the large inter- and intra-subject variability in raltegravir PK and the small number of samples that went into the calculation of GM C_{12h} for each patient (median = 2). In addition, the BLOQ values potentially represent lack of adherence to the treatment regimen. In this regard, the pill count data are difficult to interpret given the large amount of missing data.

The virological response rates were highest in patients with no or only one value BLOQ and these patients mostly had GM Call values above 100 nM. In addition, for all Cohorts pooled in the Final Dose population, 64.2% with no BLOQ values achieved HIV RNA <50 copies/mL at Week 24 compared to 35.7% with 1 BLOQ value and 23.1% with multiple BLOQ values.

The sparse PK data collected in pediatric patients, and using the threshold value of ~ 45 nM, the distribution of individual C_{trough} values obtained using the chewable tablet formulation are shown in Figure 4. These data confirm that the yield C_{trough} >45 nM in the large majority of patients. The

percentage of patients with C_{trough} < 45 nM is ~11% in the youngest age group (2 to less than 6 years of age), which is reasonably consistent with results from the intensive PK analysis, and smaller than that observed with 800 mg QD in adults (27%). The analysis shown treats values BLOQ as missing, which assumes these values are due to non-compliance (which no amount of dose adjustment will address) rather than suboptimal dosing.

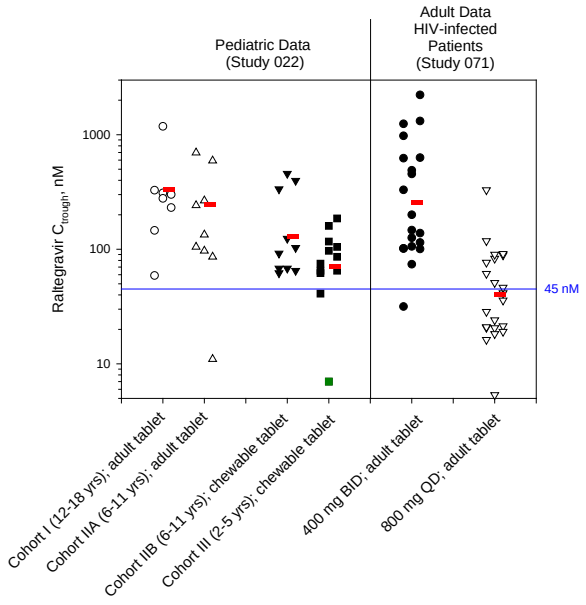
Figure 4. C_{trough} values from Sparse PK in Pediatrics (Study 022) versus in Adults Taking 400 mg BID or 800 mg QD (QDMRK, Study 071)



Analyses based on intensive PK data

The intensive PK data collected in pediatric patients, and using the threshold value of ~ 45 nM, the distribution of individual C_{trough} values obtained using the chewable tablet formulation are shown in Figure 5. For the chewable tablet, none of the ten patients in Cohort IIB (6 to less than 12 years old) had C_{trough} less than 45 nM, and, for Cohort III (2 to less than 6 year olds), there were 1 or 2 patients out of 12 with C_{trough} <45 nM. Note that one of these two values, the very low trough value, is not a measured value – due to administration of a dose in this patient between 8 and 12 hours postdose that invalidated the nominal C_{12hr} sample collected, the value shown was extrapolated using a very conservative method and is very likely an underestimate. The observed distribution of C_{trough} for children receiving the chewable tablet is above that observed for adults receiving 800 mg QD of raltegravir in study 077, where 12 of 22 patients (54%) had C_{trough} values below 45 nM.

Figure 5. C_{trough} values from Intensive PK in Pediatrics (Study 022) versus in Adults Taking 400 mg BID or 800 mg QD (QDMRK, Study 071)



Based on intensive sampling and the final dose cohort the comparisons of GM AUC_{0-12} and C_{trough}, including numbers with C_{trough} <45nM and AUC < 14-25nM.h, were as follows:

Table 5. GM AUC 0-12 and Ctrough, including numbers with Ctrough <45nM

Cohort (n*)	**GM AUC (CV)**	**GM Ctrough (CV)**	**#patients with Ctrough <45nM (n/N)**	**#patients with AUC <14-25 nM.h**
Adult 400mg BID (n=20)	13.4-14.3 (56-60)	257 (167)	1/20	
Adult 800mg QD (n=22)	30.87 (70)	40 (111)	12/22	
Cohort I 400mg BID (n=11)	15.7 (71)	333 (78)	0/11	5/11
Cohort IIa 400mg BID (n=11)	15.8 (128)	246 (221)	1/11	5/11
Cohort IIb 6mg/kg BID (n=10)	22.6 (34)	130 (88)	0/10	1/10
Cohort III 6mg/kg BID (n=12)	18.0 (59)	71 (55)	2/12	5/11

*Number of patients with intensive PK results at the final recommended dose

Both the film-coated and chewable tablets in Cohorts I to III met the pre-specified PK targets. The GM Ctrough decreased with decreasing age, while there was no consistent trend for the GM AUC. The number and proportion with AUC < 14 nM was not higher in the cohorts that received 6 mg/kg using chewable tablets vs. the Cohorts that received adult tablets. With the exception of 800 mg once daily, which is not an approved regimen, the individual numbers with C_{trough} < 45 nM were 0-2 per group.

2.4.4. Discussion on clinical pharmacology

Design and conduct of clinical studies

Study 071 was a phase III multicenter, double-blind, randomized, active comparator-controlled clinical trial to study the safety and efficacy of once daily raltegravir versus twice daily raltegravir, each in combination with Truvada (emtricitabine/tenofovir disoproxil fumarate), in treatment-naïve HIV infected patients. Study 071 showed a statistically significant difference between 400 mg BID and 800 mg QD regimens in the pre-defined primary analysis at Week 48. The failure to demonstrate non-inferiority for 800 mg QD vs. 400 mg BID and the differences in PK, especially with respect to C_{trough}, were informative to the CHMP with regard to RAL PK/PD relationship and the relative importance of C_{12h} (effectively C_{trough}) versus AUC.

Study 022 is an ongoing Phase I/II, multi-center, open-label, non-comparative study in HIV-1 infected children and adolescents ages ≥4 weeks to <19 years of age to evaluate the safety, tolerability, pharmacokinetic parameters and efficacy of raltegravir.

Patients were stratified by age, enrolling adolescents first (Cohort I) and then successively younger children. Patients received either the 400 mg film-coated tablet formulation (Cohorts I and IIA; 6 through 18 years of age) or the chewable tablet formulation (Cohorts IIB and III; 2 through 11 years of age). Raltegravir was administered with an optimized background regimen.

Study 022 design includes two stages. The initial dose-finding stage (Stage I) included intensive pharmacokinetic evaluation. Dose selection for each cohort was based upon achieving similar raltegravir plasma exposure as seen in adults, and adequate trough concentrations based on the *in vitro* IC95 for antiviral activity. Specifically, the goal was to maintain both a GM $AUC_{0\text{-}12hr}$ between 14 and 25 uM*hr and a GM C_{12hr} greater than 33 nM (the *in vitro* IC95), as well as to demonstrate acceptable short term safety. After dose selection, additional patients were enrolled (Stage II) for evaluation of long term safety, tolerability, and efficacy. Sparse PK sampling was performed during the chronic dosing stage. Of the 126 patients enrolled (All Treated population) in Cohorts I to III, 96 patients received only the recommended dose of raltegravir, and are considered the Final Dose population.

Data and additional analyses

Study 022 aimed to identify regimens providing comparable plasma exposure to that achieved in adults when dosed at 400 mg BID using the marketed tablets. In principle, this is an appropriate and sufficient approach for selecting a paediatric dose schema when the PK/PD is expected to be the same in children as in adults. The target GM $AUC_{0\text{-}12h}$ was based on data obtained from HIV-1 infected adults during 400 mg BID monotherapy and on dosing along with tenofovir and lamivudine while the target C_{12h} corresponded to the in-vitro IC95 for antiviral activity. Since two formulations were proposed for use and since the two were shown not to be bioequivalent, separate dose recommendations were identified, with an option to use either formulation in the age group 6-11 years.

The objective of Study 022 dose finding was to match overall exposure (AUC) observed with 400 mg BID regimen in adults (geometric mean (GM) value 14 - 25 µM·hr), and maintain reasonable GM C_{trough}

levels, in this case defined as above the IC95 of 33 nM. Both the film-coated and chewable tablets in Cohorts I to III met the pre-specified PK targets.

CV% was lower with the chewable tablets versus adult poloxamer tablets. Across the study Cohorts it is also clear that CV% is not higher when using chewable tablets in IIB and III as compared to adults and to Cohorts I and IIA, which were dosed with 400 mg BID.

The CHMP considered that the data from study 071 were informative with regard to the PK/PD relationship and the relative importance of C_{12h} (effectively C_{trough}) vs. AUC. Indeed, the failure to demonstrate non-inferiority for 800 mg QD vs. 400 mg BID could be attributable to the low C_{trough} values. It has not been possible to identify a robust threshold but the available data suggest a threshold value ~ 45 nM.

The GM C_{trough} in study 022 decreased with decreasing age, while there was no consistent trend for the GM AUC.

Although the GM C_{trough} in study 022 was lower in cohort IIB compared to cohort IIA, the number and proportion with AUC < 14 nM was not higher in the cohorts that received 6 mg/kg using chewable tablets vs. the Cohorts that received adult tablets. Likewise, the number of patients with C_{trough} < 45 nM were comparable. Hence, the two formulations (chewable tablets and tablets) were considered suitable for the age range 6 to 11 years.

However, due to the very limited sample size in this trial, some uncertainties remained during the application regarding the downward trend in mean C_{trough} levels with decreasing age and the applicability of the target minimum C_{trough} to young children, who may have high viral loads before starting a RAL-containing regimen. Hence, the applicant was invited to an Oral Explanation during the September CHMP meeting.

During this meeting, satisfactory clarification and reassurance were provided by the applicant. Indeed, based on the C_{trough} threshold of ~45 nM, the intensive sampling data and the CV% values support the dosing recommendations, regardless of the fact that GM C_{trough} derived from intensive sampling drifts downwards with decreasing age. The individual numbers with C_{trough} < 45 nM were 0-2 per age group/dose cohort as summarised in Table 5. Focusing on the C_{trough} comparisons, neither the intensive nor the (calculation-corrected) sparse sampling C_{trough} suggest that there would be a higher risk of values below 33 (or even 45) nM when using the chewable tablets from the age of 2 years compared with other age group / dose cohort.

The need for Therapeutic Drug Monitoring (TDM) in children aged 2 to 6 years was discussed during the Oral Explanation; however, the CHMP considered that TDM wasn't required to monitor the exposure in this population.

Given the limited number of patients enrolled in this paediatric study 022, the CHMP requested the applicant to collect additional data in children aged 2 to <6 years of age to provide further data on the adequacy of the recommended posology with particular reference to the threshold value of C_{trough} ~ 45nM.

The applicant will therefore collect additional PK information through a sub study of IMPAACT P1066. In approximately 10 patients receiving chewable tablets, who may have enrolled in study P022 to receive the oral granules formulation, C_{trough} from non-observed dosing (11-13 hrs post dose) would be obtained. These data are expected with the coming application presenting the results of study P022 in the younger age group (i.e. 4 weeks to 2 years of age). This information will be especially relevant for children who may have high viral loads before starting a RAL-containing regimen.

Should the actual data suggest a substantial risk that levels fall below 45 nM then the CHMP will consider the need to modify the prescribing information and/or request further data from this age cohort. The applicant could also explore a different dose regimen (e.g. 4mg/kg TID as suggested by the applicant during the oral explanation).

2.4.5. Conclusions on clinical pharmacology

Data from study P022 support the recommendation to use a fixed dose of the adult formulation 400 BID when body weight is ≥ 25 kg in children aged 6 to 18 years and a weight based regimen of 6mg/kg, to maximum dose 300 mg, twice daily, of the chewable tablets when body weight is ≥ 12 kg in children aged 2 to 12 years. Administration of raltegravir was allowed without regard to food intake during most of study P022 as no significant food effect has been detected with the various raltegravir formulations; hence, the SmPC states that raltegravir can be used with or without food.

Based on the C_{trough} threshold of ~45 nM, the intensive sampling data and the CV% values support the dosing recommendations. Further data are awaited from the applicant to prospectively assess the relationship between C_{trough} values and viral load in younger children.

2.5. Clinical efficacy

2.5.1. Main study

Study 022 (P1066; IMPAACT) is an on-going Phase I/II, multi-center, open-label, non-comparative study of approximately 140 HIV-1 infected children and adolescents 4 weeks through 18 years of age to evaluate the safety, tolerability, PK parameters and efficacy of raltegravir in combination with an optimized background regimen.

Study Participants

HIV-1 infection was defined as positive results from two samples (blood, serum or plasma) collected at different time points and the tests that were to be used were defined in the protocol by age group.

Eligibility for any of Cohorts I, IIA, IIB and III required that the patient had been on an unchanged therapeutic regimen for at least 12 weeks or were treatment experienced but had not been on treatment for ≥ 4 weeks prior to study entry.

Dose adjustments for growth, formulation substitutions and substitutions within class for toxicity management within the prior 12 weeks were permitted.

Subjects must have had ≤ 1 log drop in HIV RNA within 12 weeks prior to the screening visit or screening HIV RNA ≥ 25,000 copies/mL (with the exception of patients who had not received ARV therapy for ≥ 4 weeks prior to entry). HIV RNA was to be ≥ 1,000 copies/mL at the screening visit.

Treatments

See section 2.4.2 for details on raltegravir treatment. The content of the OBT could be changed during the study provided this was confined to substitution within class (rarely across class for documented toxicity), discontinuation of a background ARV or formulation substitutions.

Objectives

- Stage I: to evaluate the short term safety of raltegravir in infants, children and adolescents and to evaluate the steady state plasma concentration profiles and pharmacokinetic parameters of raltegravir in infants, children and adolescents.
- Stage II: to evaluate the safety and tolerability of raltegravir at the selected dose in combination with OBT in children and adolescents in the age groups defined by Cohort.

Outcomes/endpoints

P1066 was not designed or powered to demonstrate efficacy. However, efficacy measurements included HIV RNA, CD4 cell counts and percentages and viral resistance testing. The mode of testing and quantifying HIV RNA was defined in the protocol and was primarily based on testing by local CLIA-certified (or equivalent) laboratories using the AMPLICOR HIV-1 MONITOR Test (Version 1.5), ultrasensitive method. For all patients, blood samples for viral resistance assays were collected at screening and subsequently at Weeks 12, 24, 36 and 48 and at time of failure.

Sample size

There were no hypotheses for this study.

Statistical methods

The All Treated population included all enrolled patients who received any dose of raltegravir.

The Final Dose population included patients who received only the final selected dose, whether enrolled in Stage I or Stage II. This population was considered the evaluable population and was used for the primary assessment of safety and efficacy since the data are most relevant to the intended commercial use.

For each of the defined virological responses (successes), the following two approaches were used to handle missing values for patients who prematurely discontinued assigned treatment:

- Observed Failure (OF): Patients who prematurely discontinued assigned treatment due to lack of efficacy were considered as failures thereafter. Patients who prematurely discontinued assigned treatment, for reasons other than lack of efficacy, were excluded from the analyses.
- Non-Completer = Failure (NC=F): Patients who prematurely discontinued assigned treatment regardless of reasons were considered as failures thereafter. Intermittent missing values were assigned as failures unless immediately flanked by 2 successes.

<u>Definition of virological failure</u>

To distinguish non-response from rebound, the final definition of virological failure was as follows:

1) never achieved ≥ 1 log drop from baseline in plasma HIV RNA or HIV RNA < 400 copies/mL through Week 24

OR

2) virological rebound at Week 24 or later defined as (a) confirmed HIV RNA ≥ 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA < 400 copies/mL or (b) confirmed > 1.0 $\log_{10}$ increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart). Nadir was defined as the lowest HIV RNA by the evaluated time point.

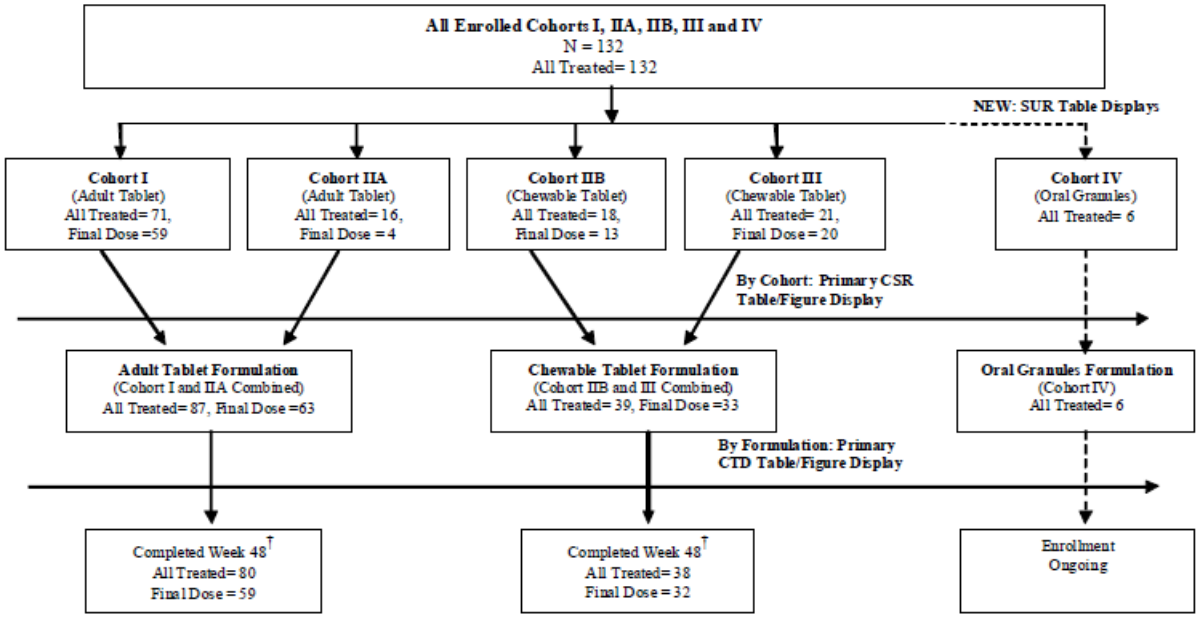
Analysis by Demographic and Prognostic Factors

The protocol specified that logistic/linear regression model would be used to identify variables contributing to virological success and favourable CD4 changes. The analysis of efficacy by PK parameters used the average raltegravir concentration from each patient's random PK measures as a covariate in predicting virological outcome at Week 24. The specific background regimen was not used as a prognostic factor because of the sparse use of various different regimens.

Results

Participant flow

Figure 6. Schematic of Study 022 (15 July 2011)



† Patients were on study treatment to at least Rel Day 295.

Recruitment

Patients were enrolled at 40 of the 56 study sites that were initiated across North and South America and Southern Africa. The majority of patients in Cohorts I, IIA and IIB were enrolled in the US while the majority of patients in Cohort III (≥ 2 through < 6 years of age) were enrolled in South Africa and Brazil.

Baseline data

Table 6. Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066

Parameter	Final Dose Population N=96
Demographics	
Age (years), median [range]	13 [2 – 18]
Male Gender	49 %
Race	
Caucasian	34 %
Black	59 %
Baseline Characteristics	
Plasma HIV-1 RNA (log_{10} copies/ml), mean [range]	4.3 [2.7 - 6)]
CD4 cell count (cells/mm^3), median [range]	481 [0 – 2361]
CD4 percent, median [range]	23.3 % [0 – 44]
HIV-1 RNA >100,000 copies/ml	8 %
CDC HIV category B or C	59 %
Prior ART Use by Class	
NNRTI	78 %
PI	83 %

Numbers analysed

A cumulative total of 126 patients (All Treated population) were enrolled and treated in Cohorts I, IIA, IIB and III, as of the data cutoff of 15-Jul-2011, including 87 patients in the adult tablet formulation group (Cohort I and IIA) and 39 patients in the chewable tablet formulation group (Cohort IIB and III).

Outcomes and estimation

Efficacy

P1066 was not designed or powered to demonstrate efficacy.

Based upon the OF approach > 70% of the patients in each cohort had ≥ 1 log drop in HIV RNA or HIV RNA < 400 copies/mL at Week 24 except for Cohort IIA (with only 4 patients in the Final Dose population and a response rate of 50%).

At Week 24 all Cohort IIB and III patients had complete data. Based on the OF approach in the final dose population, 76.9% (10/13) and 70% (14/20) in respective cohorts had ≥ 1 log drop from baseline in HIV RNA or < 400 copies/mL at Week 24 while 53.8% (7/13) and 50% (10/20) achieved < 50 copies/mL. Mean change from baseline in CD4 cell count was > 140 cells/mm^3 for all 33 children and the mean change in CD4% from baseline was 3.5% (0.8% in Cohort IIB and 5.3% in Cohort III).

$AUC_{0\text{-}12hr}$ and C_{12hr} values by age and weight showed that the final dosing recommendations for each cohort (I, IIA, IIB, and III) resulted in consistent and acceptable (based on the protocol pre-defined values) estimates for $AUC_{0\text{-}12hr}$ and C_{12hr} across the entire ranges of age (2 to 18 years) and weights (12 to 60 kg).

Table 7. Efficacy analysis by cohort; final dose population; week 24; observed failure approach

Parameter	Cohort I (N=59)		Cohort IIA (N=4)		Cohort IIB (N=13)		Cohort III (N=20)		Total (N=96)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of patients with >=1 log10 drop from baseline in HIV RNA or HIV RNA <400 copies/mL	42/58	72.4 (59.1, 83.3)	2/4	50 (6.8, 93.2)	10/13	76.9 (46.2, 95)	14/20	70 (45.7, 88.1)	68/95	71.6 (61.4, 80.4)
Proportion of patients with HIV RNA <50 copies/mL	32/58	55.2 (41.5, 68.3)	2/4	50 (6.8, 93.2)	7/13	53.8 (25.1, 80.8)	10/20	50 (27.2, 72.8)	51/95	53.7 (43.2, 64)
Proportion of patients with HIV RNA <400 copies/mL	40/58	69 (55.5, 80.5)	2/4	50 (6.8, 93.2)	9/13	69.2 (38.6, 90.9)	12/20	60 (36.1, 80.9)	63/95	66.3 (55.9, 75.7)
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Change from baseline in CD4 cell count (cells/mm3)	114.4	(73.7, 155.1)	-35.8	(-348.8, 277.3)	143.4	(-12.9, 299.6)	147.2	(-2.7, 297.1)	119.0	(74.9, 163.1)
Change from baseline in CD4 percent	4.1	(2.8, 5.3)	2.2	(-7.2, 11.5)	0.8	(-3.6, 5.2)	5.3	(2.9, 7.7)	3.8	(2.7, 4.9)

N = Number of patients in each cohort.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of patients.
For continuous endpoints: mean change with (95% CI) was reported. Normal distributions were assumed for continuous endpoints.
Observed Failure Approach for handling missing data:
-For binary endpoints, missing values were considered as failures for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.
-For continuous endpoints (e.g. change from baseline in CD4 cell counts and percent), baseline values were carried forward for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.

The results for the All Treated population were generally comparable to those for the Final Dose population. With more patients included in All Treated population for Cohort IIA (N=16), the viral and CD4 responses in this cohort were more consistent with the other cohorts.

The Week 48 results showed a similar pattern those for Week 24. There was a slight increase in overall proportions with a virological response and a larger increase in CD4 cell count and CD4 percent. Again, the results for the All Treated patients at Week 48 were comparable to those for the Final Dose population.

Table 8. Efficacy analysis by cohort; final dose population; week 48; observed failure approach

Parameter	Cohort I (N=59)		Cohort IIA (N=4)		Cohort IIB (N=13)		Total (N=76)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of patients with >=1 log10 drop from baseline in HIV RNA or HIV RNA <400 copies/mL	42/56	75 (61.6, 85.6)	3/4	75 (19.4, 99.4)	10/11	90.9 (58.7, 99.8)	55/71	77.5 (66, 86.5)
Proportion of patients with HIV RNA <50 copies/mL	32/56	57.1 (43.2, 70.3)	2/4	50 (6.8, 93.2)	6/11	54.5 (23.4, 83.3)	40/71	56.3 (44, 68.1)
Proportion of patients with HIV RNA <400 copies/mL	39/56	69.6 (55.9, 81.2)	2/4	50 (6.8, 93.2)	10/11	90.9 (58.7, 99.8)	51/71	71.8 (59.9, 81.9)
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Change from baseline in CD4 cell count (cells/mm3)	168.2	(117.5, 218.9)	189.5	(-154.2, 533.2)	76.8	(-85.3, 238.9)	155.1	(107.9, 202.2)
Change from baseline in CD4 percent	5.2	(3.9, 6.6)	6.0	(-2.6, 14.6)	1.6	(-2.7, 5.9)	4.7	(3.4, 6)

N = Number of patients in each cohort.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of patients.
For continuous endpoints: mean change with (95% CI) was reported. Normal distributions were assumed for continuous endpoints.
Observed Failure Approach for handling missing data:
-For binary endpoints, missing values were considered as failures for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.
-For continuous endpoints (e.g. change from baseline in CD4 cell counts and percent), baseline values were carried forward for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.

The results obtained when the NC=F approach was used in the Final Dose and All Treated populations were generally comparable to those observed using the primary OF missing data approach.

From Week 4 onwards over 80% of patients in each cohort achieved ≥ 1 log10 drop from baseline in HIV RNA or HIV RNA < 400 copies/mL. Between Weeks 12 and 24 there were small drops in percentages meeting the primary virological response criteria. Patients in Cohorts I, IIB and III achieved similar virological suppression over time with sustained responses up to Weeks 24 and 48. At Week 80, the success rate for Cohort I patients was > 60%. Cohort IIA (N=4) had a response rate comparable to other cohorts through Week 12 but by Week 24 two experienced an increase in HIV RNA although another regained suppression by Week 48. The data were also shown separately for those with < 400 copies/mL over time, with a similar pattern observed.

At Week 8, 59% of all patients achieved HIV RNA < 50 copies/mL. Sustained responses were observed until Week 24 for each cohort and up to Week 48 for Cohorts I, IIA and IIB. At Week 80 45% of Cohort I patients had HIV RNA <50 copies/mL.

In the All Treated population 25 patients across all cohorts failed by Week 24 and 34 patients failed by Week 48. Most failures involved rebound and there were very few non-responders. Most failures that occurred between Weeks 24 and 48 (7/9) were in Cohort I.

Treatment adherence

In cohort IIB, 33.3% of patients were 100% compliant, 11.1% of patients were 99 to 90% compliant and 22.2% of patients were 89 to 80% compliant. In cohort III, 33.3% of patients were 100% compliant, 42.9% of patients were 99 to 90% compliant and 14.3% of patients were 89 to 80% compliant (all treated population; DLP 14/02/11). One patient in Cohort IIB was reported to have discontinued due to intolerance. No patient in Cohort III discontinued the chewable tablet due to palatability issues. However, it should be noted that treatment adherence data were not reliable as these were not available for every patient or every time point during the treatment period.

No clear relationship was detected between adherence and failure but again this result may be unreliable due to the considerable amount of missing data on pill counts.

Resistance

Of the 34 All Treated patients with virological failure 18 (53%) had at least 1 BLOQ PK sample and 10 (29%) had ≥ 2 BLOQ PK samples. However, none of the patients in the Final Dose population that failed and had a virus showing acquired resistance had BLOQ PK samples.

Patients had not been exposed to raltegravir or an experimental integrase inhibitor prior to enrolment. Viruses isolated in screening visit samples from patients who ultimately failed included: one with T97A that was phenotypically sensitive, two with L741, both phenotypically sensitive, one with I203 M that was phenotypically sensitive. All other baseline viruses either showed no known raltegravir RAMs or the results are not available.

Of the 31 All Treated patients who failed and had any genotypic data available, viruses obtained at the time of failure from 10 (32.3%) displayed signature resistance mutations as shown below.

Table 9. Number (%) of virologic failure patients with HIV integrase mutations at amino acids 143, 148 and/or 155 by cohort; all treated population; weeks 0-48

	Cohort I (N=18) n (%)	Cohort IIA (N=6) n (%)	Cohort IIB (N=4) n (%)	Cohort III (N=3) n (%)	Total (All Cohorts) (N=31) n (%)
Number (%) With Mutation at Amino Acid 143, 148 or 155	2 (11.1)	4 (66.7)	2 (50.0)	2 (66.7)	10 (32.3)
With Mutation at Amino Acid 143	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (3.2)
With Mutation Y143C	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
With Mutation Y143H	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
With Mutation Y143R	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (3.2)
With Mutation at Amino Acid 148	1 (5.6)	3 (50.0)	1 (25.0)	2 (66.7)	7 (22.6)
With Mutation Q148H	1 (5.6)	1 (16.7)	1 (25.0)	0 (0)	3 (9.7)
With Mutation Q148K	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
With Mutation Q148R	0 (0)	2 (33.3)	0 (0)	2 (66.7)	4 (12.9)
With Mutation at Amino Acid 155	2 (11.1)	1 (16.7)	1 (25.0)	1 (33.3)	5 (16.1)
With No Mutation at either Amino Acid 143, 148 or 155	16 (88.9)	2 (33.3)	2 (50.0)	1 (33.3)	21 (67.7)
With Other Known RAL Resistance Mutations[†]	2 (11.1)	0 (0)	0 (0)	0 (0)	2 (6.5)
With No Other Known RAL Resistance Mutations	14 (77.8)	2 (33.3)	2 (50.0)	1 (33.3)	19 (61.3)

[†]HIV Integrase resistance mutations were identified by the Monogram Biosciences, Inc. GeneSeq Integrase Genotypic Test.
N = Number of virologic failure patients with integrase mutation test done in each cohort.
n (%) = Number (percent) of patients in each subcategory.
Complete Week 48 data is available for 52.4% (11/21) of Cohort III.

Two of the 21 virological failures whose viruses did not display a primary raltegravir resistance mutation at the time of failure had viruses containing other known raltegravir resistance mutations.

Among the All Treated patients who failed by Week 48, there were 26 patients with both baseline and post-baseline phenotypic resistance data. Viruses from these patients at baseline showed phenotypic susceptibility. Viruses obtained after virological failure showed mean and median fold-changes in IC50 of 33.8 and 1.0 (range 0.6 to 150.2), respectively.

Virological response rates were broadly consistent across race, ethnicity, baseline HIV RNA category, baseline CD4 cell count category, viral subtype and number of classes of ARV drugs previously exposed. The response rate for male patients was 22.6% higher than that for females and response rates for patients with fewer than 2 active drugs in their OBT based on PSS and GSS were higher (by 20.6% and 29.2%, respectively) than those with 2 or more active drugs in OBT. The response rate was slightly higher in those with higher viral load at baseline and for non-clade B virus. However, it should be noted that the number analysed are relatively small.

GSS / PSS

Analyses using the univariate logistic regression model showed that gender and GSS had significant associations with the virological response. The PSS effect was in the same direction as the GSS effect but was not as strong. This model did not control for confounding of associations by other covariates.

Summary of main study

The following tables summarise the results from the main studies supporting the present application. These summaries should be read in conjunction with the discussions as well as the benefit risk assessment.

Table 10. Summary of Efficacy for trial IMPAACT P1066 (Merck P022)

Title: Phase I/II, multi-center, open-label, non-comparative study in HIV-1 infected children and adolescents 2 years through 18 years of age to evaluate the safety, tolerability, PK parameters and efficacy of raltegravir in combination with an optimized background regimen		
Study identifier	Study 022 (IMPAACT P1066)	
Design	Phase I/II, multi-center, open-label, non-comparative study of approximately 140 HIV-1 infected children and adolescents 2 years through 18 years of age to evaluate the safety, tolerability, PK parameters and efficacy of raltegravir in combination with an optimized background regimen.	
	Duration of main phase: Duration of Extension phase:	24 weeks (primary), 48 weeks (secondary) 4 years (total study duration 240 weeks)
Hypothesis	No hypotheses were specified.	
Treatments groups	Film-coated tablets	Raltegravir adult tablet 400 mg b.i.d + optimized background regimen for patients 6-18 years old
	Chewable Tablet	Raltegravir chewable tablet approximately 6mg/kg b.i.d + optimized background regimen for patients 2-11 years old

Endpoints and definitions	Objectives	Stage I: to evaluate the short term safety of raltegravir in infants, children and adolescents and to evaluate the steady state plasma concentration profiles and pharmacokinetic parameters of raltegravir in infants, children and adolescents. Stage II: to evaluate the safety and tolerability of raltegravir at the selected dose in combination with OBT in children and adolescents in the age groups defined by Cohort. Note: P1066 was not designed or powered to demonstrate efficacy.

Results and Analysis

Pharmacokinetics	Age	Formulation	Dose	Number of subjects (Intensive PK)	Geometric Mean (%CV) AUC 0-12hr (µM*hr)	Geometric Mean (%CV) C12hr (nM)
	12 through 18 years	Film-coated tablets	400 mg twice daily, regardless of weight	11	15.7 (98 %)	333 (78 %)
	6 through 11 years	Film-coated tablets	400 mg twice daily, for patients ≥25 kg	11	15.8 (120 %)	246 (221 %)
	6 through 11 years	Chewable tablet	Weight based dosing	10	22.6 (34 %)	130 (88 %)
	2 through 5 years	Chewable tablet	Weight based dosing	12	18.0 (59 %)	71 (55 %)

Safety	The safety data did not give rise to any new or major concerns.		
Efficacy	Time point	24 weeks	48 weeks
	Number of subject	96	96
	Achieved ≥1 log10 HIV RNA drop from baseline or <400 copies/mL	72%	79%

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has broadly complied with the advice given on paediatric development in the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02).

Efficacy data and additional analyses

The changes in CD4 cell counts and percentages over time demonstrated comparable patterns across the cohorts except for Cohort IIA, which had large variability due to the small sample size. The results for the All Treated population were comparable to those for the Final Dose population. Change from

baseline in HIV RNA at Week 24 and virological success at Week 24 were significantly correlated with Week 24 CD4 cell count change.

2.5.3. Conclusions on the clinical efficacy

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02), based on the identification of suitable dose regimens and the expectation that PK/PD relationships are the same in children as in adults, an extrapolation of efficacy data obtained in adults to children may be accepted.

As per the above, Study P022 has been designed accordingly and therefore efficacy wasn't a primary endpoint. The numbers per cohort and in the various sub-groups of interest are too small to draw definite conclusions, but taking into account the overall virological and immunological response rates in study P022 which were satisfactory, the CHMP concludes that the extrapolation was appropriate to the paediatric population covered by the proposed indication.

2.6. Clinical safety

Patient exposure

All patients who received at least one dose of raltegravir in study 022 were included in the evaluation of safety. Patients who switched raltegravir formulations during the study were included with their originally assigned age cohort and formulation for safety reporting.

- The mean number of days (range) for Final Dose patients on any dose of raltegravir was 565 (28 to 1112) days. The mean number of days (range) for All Treated patients on raltegravir at any dose was 626 (28 to 1246) days.
- The mean number of days (range) for Cohort I and IIA (tablet) Final Dose patients on raltegravir tablets at 400 mg BID was 657 (28 to 1112) days. Over 40 patients in Cohort I had received raltegravir for more than 96 weeks by the cut-off date for the CSR.
- The mean number of days on raltegravir for Cohorts IIB and III (chewable tablet) was 351 (179 to 604) days. Total daily doses were weight-based and ranged from 75 to 300 mg twice daily.

Adverse events

Final Dose, Weeks 0–24

Table 11. Summary of clinical AE by cohort; final dose population; weeks 0-24

	Cohort I (N=59)	Cohort IIA (N=4)	Cohort IIB (N=13)	Cohort III (N=20)	Total (N=96)
	n (%)	n (%)	n (%)	n (%)	n (%)
With one or more clinical adverse events	50 (84.7)	3 (75)	10 (76.9)	14 (70)	77 (80.2)
With no clinical adverse event	9 (15.3)	1 (25)	3 (23.1)	6 (30)	19 (19.8)
With one or more serious clinical adverse events	9 (15.3)	0 (0)	2 (15.4)	2 (10)	13 (13.5)
With one or more serious drug related† clinical adverse events	0 (0)	0 (0)	0 (0)	1 (5)	1 (1)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
With one or more Grade 3 or greater clinical adverse events	8 (13.6)	0 (0)	2 (15.4)	3 (15)	13 (13.5)
With one or more Grade 3 or greater drug related† clinical adverse events	1 (1.7)	0 (0)	0 (0)	0 (0)	1 (1)

N = Number of patients in each cohort.
n (%) = Number (percent) of patients in each subcategory.
Events were included if they occurred while on study drug or within 14 days after discontinuation of study drug.
†Drug related adverse events were determined by the investigator to be possibly, probably or definitely related to raltegravir.

The most frequently reported AEs were cough (32.3%), pyrexia (24%) and rhinorrhoea (18.8%). The profile of AEs for All Treated patients was generally similar to that for Final Dose patients.

The most frequently reported AEs of Grade 3 or greater were various pneumonias [7.3% Final Dose patients; including bronchopneumonia (1), lobar pneumonia (1), pneumonia (3), pneumococcal pneumonia (1) and RSV pneumonia (1)], pyrexia (2.1%), gastroenteritis (2.1%) and suicidal behaviour (2.1%). Only three Grade 3 or greater AEs (in one patient) were considered drug-related (events of abnormal behaviour, psychomotor hyperactivity and insomnia).

Final Dose, Weeks 0–48

Clinical AEs (Grades 1–4) were reported by 85.4% of Final Dose patients up to Week 48. The profile of clinical adverse events at Week 48 was generally similar to that at Week 24 for Final Dose patients. The most frequently reported were cough (42.7%), pyrexia (32.3%), and rhinorrhoea (27.1%).

Table 12. Summary of clinical AE by cohort; final dose population; weeks 0-48

	Cohort I (N=59)	Cohort IIA (N=4)	Cohort IIB (N=13)	Cohort III (N=20)	Total (N=96)
	n (%)	n (%)	n (%)	n (%)	n (%)
With one or more clinical adverse events	53 (89.8)	4 (100)	11 (84.6)	14 (70)	82 (85.4)
With no clinical adverse event	6 (10.2)	0 (0)	2 (15.4)	6 (30)	14 (14.6)
With one or more serious clinical adverse events	10 (16.9)	0 (0)	2 (15.4)	2 (10)	14 (14.6)
With one or more serious drug related† clinical adverse events	0 (0)	0 (0)	0 (0)	1 (5)	1 (1)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
With one or more Grade 3 or greater clinical adverse events	10 (16.9)	0 (0)	2 (15.4)	3 (15)	15 (15.6)
With one or more Grade 3 or greater drug related† clinical adverse events	1 (1.7)	0 (0)	0 (0)	0 (0)	1 (1)

Table 13. All clinical AE by cohort (incidence ≥10% in one or more cohorts); final dose population; weeks 0-48

System Organ Class Preferred Term	Cohort I (N=59) n (%)	Cohort IIA (N=4) n (%)	Cohort IIB (N=13) n (%)	Cohort III (N=20) n (%)	Total (N=96) n (%)
Number of patients with one or more adverse events	53 (89.8)	4 (100)	11 (84.6)	14 (70)	82 (85.4)
Blood and lymphatic system disorders	7 (11.9)	0 (0)	1 (7.7)	6 (30)	14 (14.6)
Lymphadenopathy	6 (10.2)	0 (0)	0 (0)	6 (30)	12 (12.5)
Ear and labyrinth disorders	11 (18.6)	0 (0)	1 (7.7)	3 (15)	15 (15.6)
Ear pain	9 (15.3)	0 (0)	1 (7.7)	1 (5)	11 (11.5)
Otorrhoea	2 (3.4)	0 (0)	0 (0)	2 (10)	4 (4.2)
Eye disorders	8 (13.6)	0 (0)	1 (7.7)	0 (0)	9 (9.4)
Gastrointestinal disorders	33 (55.9)	1 (25)	4 (30.8)	7 (35)	45 (46.9)
Abdominal pain	8 (13.6)	1 (25)	1 (7.7)	0 (0)	10 (10.4)
Abdominal pain upper	7 (11.9)	0 (0)	0 (0)	0 (0)	7 (7.3)
Breath odour	1 (1.7)	0 (0)	2 (15.4)	0 (0)	3 (3.1)
Diarrhoea	9 (15.3)	0 (0)	0 (0)	4 (20)	13 (13.5)
Nausea	11 (18.6)	0 (0)	0 (0)	0 (0)	11 (11.5)
Vomiting	14 (23.7)	0 (0)	1 (7.7)	5 (25)	20 (20.8)
General disorders and administration site conditions	22 (37.3)	1 (25)	6 (46.2)	6 (30)	35 (36.5)
Pyrexia	18 (30.5)	1 (25)	6 (46.2)	6 (30)	31 (32.3)
Hepatobiliary disorders	0 (0)	0 (0)	0 (0)	3 (15)	3 (3.1)
Hepatomegaly	0 (0)	0 (0)	0 (0)	3 (15)	3 (3.1)
Infections and infestations	27 (45.8)	0 (0)	10 (76.9)	12 (60)	49 (51)
Fungal skin infection	0 (0)	0 (0)	2 (15.4)	0 (0)	2 (2.1)
Gastroenteritis	2 (3.4)	0 (0)	3 (23.1)	2 (10)	7 (7.3)
Impetigo	0 (0)	0 (0)	0 (0)	3 (15)	3 (3.1)
Oral herpes	0 (0)	0 (0)	2 (15.4)	2 (10)	4 (4.2)
Otitis media	2 (3.4)	0 (0)	1 (7.7)	5 (25)	8 (8.3)
Sinusitis bacterial	0 (0)	0 (0)	2 (15.4)	1 (5)	3 (3.1)
Tonsillitis	0 (0)	0 (0)	0 (0)	2 (10)	2 (2.1)
Metabolism and nutrition disorders	3 (5.1)	0 (0)	1 (7.7)	2 (10)	6 (6.3)
Musculoskeletal and connective tissue disorders	15 (25.4)	0 (0)	1 (7.7)	0 (0)	16 (16.7)

System Organ Class Preferred Term	Cohort I (N=59) n (%)	Cohort IIA (N=4) n (%)	Cohort IIB (N=13) n (%)	Cohort III (N=20) n (%)	Total (N=96) n (%)
Nervous system disorders	21 (35.6)	2 (50)	1 (7.7)	0 (0)	24 (25)
Dizziness	6 (10.2)	0 (0)	0 (0)	0 (0)	6 (6.3)
Headache	10 (16.9)	2 (50)	0 (0)	0 (0)	12 (12.5)
Psychiatric disorders	8 (13.6)	1 (25)	1 (7.7)	0 (0)	10 (10.4)
Anger	0 (0)	1 (25)	0 (0)	0 (0)	1 (1)
Mood swings	0 (0)	1 (25)	0 (0)	0 (0)	1 (1)
Reproductive system and breast disorders	8 (13.6)	0 (0)	0 (0)	1 (5)	9 (9.4)
Respiratory, thoracic and mediastinal disorders	32 (54.2)	2 (50)	7 (53.8)	10 (50)	51 (53.1)
Cough	28 (47.5)	2 (50)	5 (38.5)	6 (30)	41 (42.7)
Nasal congestion	14 (23.7)	1 (25)	3 (23.1)	2 (10)	20 (20.8)
Oropharyngeal pain	13 (22)	0 (0)	3 (23.1)	0 (0)	16 (16.7)
Rhinorrhoea	19 (32.2)	0 (0)	3 (23.1)	4 (20)	26 (27.1)
Wheezing	6 (10.2)	1 (25)	1 (7.7)	2 (10)	10 (10.4)
Skin and subcutaneous tissue disorders	26 (44.1)	1 (25)	2 (15.4)	6 (30)	35 (36.5)
Eczema	1 (1.7)	0 (0)	2 (15.4)	1 (5)	4 (4.2)
Macule	1 (1.7)	0 (0)	0 (0)	2 (10)	3 (3.1)
Rash	2 (3.4)	1 (25)	1 (7.7)	0 (0)	4 (4.2)
Rash generalised	0 (0)	0 (0)	2 (15.4)	0 (0)	2 (2.1)

Grade 3 or greater clinical AEs were reported by 15.6% of patients and 10.4% reported Grade 3 or greater AEs that mapped to the Infections and Infestations SOC. Additional AEs reported between Weeks 24 and 48 included bacterial pneumonia, abdominal pain, iron deficiency anaemia, decreased weight, failure to thrive, bacterial sepsis, convulsion, reversible posterior leucoencephalopathy syndrome, erythema, conjunctival hyperaemia, periorbital cellulitis and influenza-like illness.

AEs of special interest

The applicant's database was explored for a series of pre-defined AEs of special interest based on what is known about raltegravir and also other ARTs. Some highlighted cases include AEs of rash (none of these events was reported as Grade 3 or 4 or serious) and psychiatric disorders (by week 48 of the study, 10.4% of final dose patients reported psychiatric disorders including one reported Grade 3 AEs considered possibly related to raltegravir by the investigator).

Serious adverse event / deaths / other significant events

One patient in the All Treated population had a SAE of pneumonia resulting in death by the data cut-off date. The investigator determined that Grade 5 bilateral pneumonia was not related to study raltegravir

By Week 24, 13 Final Dose patients had reported 16 SAEs including pyrexia, acute renal failure, metrorrhagia, pneumonia (7 events), infection, asthma, suicidal behaviour (2 events), respiratory tract infection and allergic dermatitis. Also, there was one SAE of depression in an All Treated patient. The category with the highest frequency of SAEs was Infections and Infestations (9 patients [9.4%]), all in

Cohort I. The only SAE considered related to study raltegravir by the investigator was the case of allergic dermatitis.

At Week 48 there had been 21 SAEs reported by 14 (14.6%) patients in the Final Dose population. The 5 additional SAEs that occurred between Weeks 24 and 48 included pneumonia, failure to thrive, convulsion, anaemia and periorbital cellulitis. These events were not considered related to study raltegravir by the investigator. There were no additional reports of SAEs by All Treated patients between Weeks 24 and 48. Between Week 48 and the data cut-off date, there were 11 additional SAEs including pain in extremity, pneumonia, oesophagitis, anaemia (3 events for the same patient), cachexia, pyrexia, *Mycobacterium Avium* complex infection, bacterial pneumonia and respiratory distress. These events were not considered related to study raltegravir by the investigators. Three additional All Treated patients reported SAEs after Week 48 and all events were considered not related to study raltegravir by the investigators.

There were three pregnancies reported of which one resulted in intra-uterine fetal death not considered to be treatment-related.

Laboratory findings

Final Dose, Weeks 0–24

Laboratory AEs were reported by 75% of Final Dose patients. Most were Grade 1 and 2. The most frequently reported included decreased neutrophil count (21% [20/96]), which ranged from Grades 1 to 4, decreased non-fasting blood glucose (20% [19/96]), which were primarily Grade 1, and decreased blood sodium (18% [17/96]), which were primarily Grade 1 events. There were two laboratory SAEs of which one was considered drug-related by the investigator. Grade 3 or greater laboratory AEs were reported in 13.5% of which one patient in Cohort III had AEs considered to be drug-related (increased ALT and AST; see below).

Final Dose, Weeks 0-48

Laboratory AEs were reported by 84.4% of Final Dose patients. Most laboratory AEs were Grades 1 and 2 and the most frequently reported were similar to those observed at Week 24. Additional Grade 3 or greater laboratory AEs reported by Final Dose patients between Weeks 24 and 48 included decreased haemoglobin, increased blood glucose, increased blood bilirubin, increased ALT (5 events) and increased AST (8 events). The most frequently reported event was decreased neutrophil count (8.3%).

Three All Treated patients reported Grade 3 or greater laboratory adverse events considered possibly drug-related by the investigator. One patient in Cohort IIB had increased low density lipoprotein by Week 24. One in Cohort I had decreased neutrophil count by Week 24 and one on Cohort IIA had drug-related decreased neutrophil count (2 events, both possibly related) by Week 48.

Alanine aminotransferase (ALT)

There were two Final Dose patients who had a Grade 3 or greater serum ALT increase that represented a worsening from baseline. One considered possibly related to study raltegravir and one considered not related to raltegravir by the investigators.

Aspartate aminotransferase (AST)

One patient in Cohort IIB reported increased AST (highest report: Grade 4) that was considered not related to study raltegravir by the investigator.

Discontinuation due to adverse events

No patients from the Final Dose or All Treated population discontinued due to a clinical or laboratory AE up to the data cut-off date.

2.6.1. Discussion on clinical safety

The safety data do not give rise to any new or major concerns. In particular, the choice of Final Dose was not in any way limited by issues of safety when administered as either the adult tablet or chewable tablet formulation in combination with OBR.

All the adverse reactions reported in the clinical trial have been included in the Summary of Product Characteristics.

In the view of the safety profile of the chewable tablets, the CHMP considers that the PSUR cycle of this medicinal product should remain unchanged.

2.6.2. Conclusions on the clinical safety

The safety data in the claimed paediatric indication do not give rise to any new safety findings in the paediatric population in comparison to the adult population. In addition, no specific safety concerns in the paediatric population were identified in the data submitted with the present application. Therefore, the CHMP concludes that the safety profile of raltegravir in the proposed indication is acceptable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

No update of the pharmacovigilance system was submitted with the present application.

Risk Management Plan

The applicant submitted a risk management plan, which included an update of the existing risk minimisation plan to reflect the extension of the marketing authorisation to children from 2 to 18 years and the new chewable tablets. The risk management plan was reviewed and agreed by the CHMP.

Given the limited number of patients enrolled in the paediatric 022, the CHMP requested the applicant to collect additional data in children aged 2 to <6 years to provide further data on the adequacy of the recommended posology with particular reference to the threshold value of C_{trough} ~ 45nM.

Since the start of the procedure, the applicant has submitted an updated version of the RMP (v9, 17 August 2012) with the procedure (EMEA/H/C/860/II/37) which included the changes related to the present application.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

No full user consultation with target patient groups on the package leaflet for the 25mg chewable tablets has been performed on the basis of a bridging report making reference to the 100mg chewable tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Raltegravir has been shown to be effective in adults. However, the *in-vitro* and *in-vivo* data have clearly underlined the importance of administering it as part of a total ART regimen that preferably includes at least two other agents predicted to be active.

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02), based on the identification of suitable dose regimens and the expectation that PK/PD relationships are the same in children as in adults, an extrapolation of efficacy data obtained in adults to children may be accepted.

Data from study 022 lead to recommendation to use a fixed dose of the adult formulation 400 BID when body weight is ≥ 25 kg in children aged 6 to 18 years and a weight based regimen of 6mg/kg, to maximum dose 300 mg, twice daily, of the chewable tablets when body weight is ≥ 12 kg in children aged 2 to 12 years. These dose recommendations were considered adequate by the CHMP.

Based on the C_{trough} threshold of ~45 nM, the CHMP was of the opinion that the intensive sampling data and the CV% values from study P022 support these dosing recommendations. Indeed, based on the C_{trough} threshold of ~45 nM, the intensive sampling data and the CV% values support the dosing recommendations, regardless of the fact that GM C_{trough} derived from intensive sampling drifts downwards with decreasing age. The individual numbers with C_{trough} < 45 nM were 0-2 per age group/dose cohort. Focusing on the C_{trough} comparisons, neither the intensive nor the (calculation-corrected) sparse sampling C_{trough} suggest that there would be a risk of values below 33 (or even 45) nM when using the chewable tablets in children aged 2 to <6 years of age compared with other age group / dose Cohort.

Study P022 has been designed in line with the recommendations of the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02). Therefore efficacy wasn't a primary endpoint; however, the overall virological and immunological response rates in study P022 were satisfactory.

Uncertainty in the knowledge about the beneficial effects

Despite the supportive PK/PD data and the overall good virological and immunological response rates, this design of study P022 presents some limitations (i.e. open label trial, small number of patients enrolled, etc…).

The Committee was of the opinion that these limitations are inherent to the settings of this PK study and the provision of limited data in paediatric cohorts is considered acceptable for an antiretroviral agent that has been shown to be efficacious in adults as it is the case for raltegravir.

However, given the limited number of patients enrolled in this paediatric study, the CHMP requested that the applicant collects additional information in children aged 2 to <6 years of age to provide further data on the adequacy of the recommended posology with particular reference to the threshold value of C_{trough} ~ 45nM.

Risks

Unfavourable effects

The safety data in the claimed paediatric indication do not give rise to any new safety findings in the paediatric population in comparison to the adult population. In addition, no specific safety concerns in the paediatric population were identified in the data submitted with the present application. Therefore, the CHMP concludes that the safety profile of raltegravir in the proposed indication is acceptable.

Uncertainty in the knowledge about the unfavourable effects

Despite the overall safety profile similar to adults and the absence of new findings specific to the paediatric population, the sample size was expectedly too small to draw definite conclusions.

Benefit-risk balance

As stated in the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02), provided that reliable pharmacokinetic data support robust dose recommendations, an extrapolation of efficacy data obtained in adults to children may be accepted.

Data from study 022 supports the use of a fixed dose of the adult formulation 400 BID when body weight is ≥ 25 kg in children aged 6 to 18 years and a weight based regimen of 6mg/kg, to maximum dose 300 mg, twice daily, of the chewable tablets when body weight is ≥ 12 kg in children aged 2 to 12 years.

Based on the C_{trough} threshold of ~45 nM, the intensive sampling data and the CV% values from study P022 support these dosing recommendations.

Therefore, the CHMP concludes that extrapolation from adult to the paediatric population covered by the proposed indication is acceptable.

This is supported by the overall satisfactory virological and immunological response rates in Study P022.

In addition, the safety data in the claimed paediatric indication do not give rise to any new safety findings in the paediatric population in comparison to the adult population. No specific safety concerns in the paediatric population were identified in the data submitted with the present application.

As a consequence, the CHMP concluded that the benefit /risk balance is favourable for use of raltegravir with a fixed dose of the adult formulation 400 BID when body weight is ≥ 25 kg in children aged 6 to 18 years and a weight based regimen of 6mg/kg, to maximum dose 300 mg, twice daily, of the chewable tablets when body weight is ≥ 12 kg in children aged 2 to 12 years.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority that the risk/benefit balance of the extension of Marketing Authorisation for Isentress chewable tablets 25 mg and 100 mg in the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral

therapy (ART)-experienced paediatric patients from the age of 2 years is favourable and therefore recommends the granting of the marketing authorisation subject to the current conditions below.

In addition, the CHMP considers by consensus the following variation acceptable and recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variations requested		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update the section 4.1 of the SmPC for the existing 400mg film-coated tablet with the new paediatric indication (adolescents and children from the age of 6 years) and introduce consequential changes to all sections of the SmPC for the existing 400mg film-coated tablet (except Sections 1 and 3), Annexes II, IIIA and IIIB.

Changes to the product information were introduced in line with the QRD template.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/95/2009) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Divergent positions to the majority recommendation on the extension of MA are appended to this report.

5. Appendix

Divergent Positions

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the variation of the marketing authorisation of Isentress.

The reasons for divergent opinion were as follows:

Balancing the benefit of raltegravir as a treatment alternative in very small children, and the risks related to uncertainties about adequate drug exposure, we do not consider that the chewable tablet regimen for patients aged 2-6 years is approvable. The data on C_{12h} and AUC from detailed and sparse sampling suggest that the recommended posology could result in inadequate exposures to raltegravir compared to adults.

Failure with a raltegravir-based regimen is very often accompanied by high level raltegravir resistance, as well as resistance to cytidine analogues. The consequences of virological failure due to suboptimal dosing in small children, in terms of remaining treatment options, would be of considerable relevance.

From ages 6 years and upwards the adult formulation can be used.

London, 13 December 2012

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Pierre Demolis Kristina Dunder

…… ……

Harald Enzmann Jan Mueller Berghaus