London, 26 June 2014
EMA/486645/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ISENTRESS

International non-proprietary name: raltegravir

Procedure No. EMEA/H/C/000860/X/0044/G

Note

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

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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
$AUC_{0\text{-}12hr}$	Area under the curve from 0 to 12 hours post-dose
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 post-dose
Call	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
HPLC	High Performance Liquid Chromatography
HR	Heart rate
IC95	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
FTIR	Fourier transform infrared spectroscopy
LFT	Liver function test
LLDPE	Linear low-density polyethylene
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
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PI	Protease inhibitor
PID	Patient identification number
PSS	Phenotypic sensitivity score
QbD	Quality by Design
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
Tmax	Time to Cmax
TDF	Tenofovir disoproxil fumarate
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 28 June 2013 an extension for a Marketing Authorisation to the European Medicines Agency (EMA) for ISENTRESS 100 mg Granules for oral suspension, 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: granules for oral suspension associated with the following strength: 100 mg.

In addition, the applicant applied for the following indication:

Furthermore pursuant to Commission Regulation (EC) No 1234/2008, art.7-2(b), *Grouping of a line extension application to introduce a new pharmaceutical form (100 mg granules for oral suspension) and a type II variation to extend the indication to toddlers and infants from 4 weeks to less than 2 years of age. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and separate SmPC is introduced for the new pharmaceutical form. The Package Leaflet and Labelling are updated in accordance. In addition, minor updates are made to SmPC sections 5.1 and 6.1, Labelling and the PL. Furthermore, the product information is brought in line with the latest QRD version 9.3.*

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 25 and 100 Chewable tablet and 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 (100 mg Granules for oral solution) 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/99/2013) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/99/2013) 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.

The development programme/compliance with CHMP guidance/scientific advice

The current guidance on the clinical development of medicines for the treatment of HIV infection (EMEA/CPMP/EWP/633/02 Revision 2) states that:

"Provided that reliable pharmacokinetic data support robust dose recommendations, an extrapolation of efficacy data obtained in adults to children may be accepted. However, at least non-comparative data in children on the safety and efficacy of the proposed dose regimens over appropriate time-spans should be provided. Due to high viral loads in the youngest children, viral response data in these patients are of particular interest.

The provision of adequate data in children is especially important should large inter-individual pharmacokinetic variability be observed in the paediatric population. Also, additional drug-drug interaction studies may be considered necessary, at least as post-marketing commitments, and population pharmacokinetic studies should be considered."

The Applicant has broadly complied with this advice.

In addition, the content of this programme falls within the agreed PIP.

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 were:

Rapporteur: Greg Markey Co-Rapporteur: Pierre Demolis

- The application was received by the EMA on 28 June 2013.
- The procedure started on 21 August 2013.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 31 October 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 November 2013.
- PRAC Risk Management Plan advice and assessment overview was adopted by PRAC on 5 December 2013.
- The Rapporteurs circulated the Joint Assessment Report on 13 December 2013.
- During the meeting on 19 December 2013, 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 19 December 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 February 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 March 2014.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 April 2014.
- During the CHMP meeting on 22-25 April 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 26 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 9 June 2014.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 20 June 2014.
- During the meeting on 26 June 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional 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 in adults, adolescents, and children from the age of 2 years.

The Applicant initially developed 400 mg poloxamer tablets for use in adults. In the line extension application X/24G (Commission Decision issued on 25/02/2013), the Applicant sought approval for 25 mg and 100 mg chewable tablets (CT) for use from the age of 2 years with an option to use either the adult tablet or CT from the age of 6 years and body weight 25 kg. The Applicant seek approval for

granules for oral suspension for use in younger subjects aged from 4 weeks to < 2 years and with body weight from 3-<20 kg. The data to support this application come from the Phase 1 PK study P068 (which also supported use of the CT) and from the final Cohorts enrolled into study P022 (which also supported use of the adult and CT in older children according to age and weight).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as granules for oral suspension containing 100 mg/sachet of raltegravir (as potassium salt) as active substance resulting in a suspension of 20 mg/ml after reconstitution with water.

Other ingredients are: hydroxypropyl cellulose, sucralose, mannitol, monoammonium glycyrrhizinate, sorbitol (E420), fructose, banana flavour, sucrose, crospovidone type A, magnesium stearate, hypromellose 2910/6cP, macrogol/PEG 400, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, microcrystalline cellulose and carmellose sodium.

The product is available in PET/Alu /LLDPE sachets. One carton contains 60 sachets, two reusable 5 ml oral dosing syringes for administration and 2 reusable mixing cups for reconstitution.

2.2.2. Active Substance

The active substance is the same as that used in the currently approved 400 mg tablets and 25 and 100 mg chewable tablets, EU/1/07/436/001-004. For information on the active substance reference is made to Module 3.2.S of the marketing authorisation of the 400 mg tablets and 25 and 100 mg chewable tablets. Suitability of the active substance specification for the pharmaceutical form granules for suspension (e.g. particle size) was demonstrated.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Development of raltegravir pediatric formulations focused on identifying an effective, palatable dosage form, suitable for use in children down to 4 weeks.

Several key components were considered during formulation and process development including dose uniformity, palatability, and development of a dosage form with acceptable physical, mechanical and chemical attributes.

In view of the above Quality Target Product Profile (QTPP), the applicant identified the following critical quality attributes (CQA): identity, assay, appearance, impurities, content uniformity, microbial limits, elegance, moisture, processability, sachet integrity and functionality, taste, weight uniformity, yield.

Initial development sought to develop a tablet for dispersion to form an oral suspension. The tablet for dispersion concept was abandoned after it was determined that excipients providing a uniform suspension did not give tablets with adequate mechanical strength or acceptable suspension properties. To achieve an unpreserved, suspension formulation, a granule for suspension formulation was developed with appropriate palatability and taste masking. A coated granule intermediate was used. The same coated granule intermediate has already been authorised in the chewable tablets. This coated intermediate, once dispersed in water begins to dissolve its coating therefore, flavour and sweeteners are included as part of the taste masking system. Consequently the coated granule

intermediate is then blended with flavour, sweeteners, mannitol, crospovidone, magnesium stearate and a suspending agent, co-processed microcrystalline cellulose and carboxymethylcellulose sodium. This combination provides taste modulation to increase patient compliance and suspension uniformity to allow dose adjustment with an oral syringe. All the excipients of the formulation, apart from the microcrystalline cellulose/carboxymethylcellulose sodium mixture, are already authorised for the chewable tablets.

The flavour system for raltegravir granules for oral suspension was developed to be simplified relative to the chewable tablet due to the younger patient population. Banana flavour was selected with two sweeteners sucralose and magnasweet (a delayed onset sweetener containing fructose, sorbitol and monoammonium glycyrrhizinate). During the clinical studies (PN 068 and PN1066), taste was evaluated using a questionnaire and caregiver assessments of patient dosing and compliance. These assessments supported that taste was overall acceptable (see clinical part). During taste assessment, it was found that taste of the constituted product deteriorated with time after dilution, with a 30 minute dosing window maximum supported by questionnaire results.

Raltegravir granules for oral suspension was formulated as a variant of the raltegravir chewable tablets formulation. As a result, their manufacturing processes are similar sharing a common standard fluid bed granulation, a common bottom-spray coating process and similar extra-granular excipients in the final blend. During the development of the common granulation the suitability for the raltegravir granules for oral suspension process was also assessed. Downstream development from the coated granule intermediate was specific for the granules for oral suspension.

To establish a comprehensive development plan, a risk assessment for raltegravir granules for suspension process was conducted using a Failure, Mode and Effects Analysis method (FMEA). This assessment was conducted prior to the start of development, to identify key risks or knowledge gaps associated with the process. Development studies were subsequently performed on the unit operations that were shown to have knowledge gaps or significant potential risk. The results of the risk analysis were then used to support the development of the proposed control strategy that ensures the drug product can consistently be produced to meet the predetermined critical quality attributes.

The formulation used during clinical studies is the same that the used for marketing.

The primary packaging is PET/Alu/LLDPE sachets. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. A CE mark declaration of conformity is provided for the syringe.

Manufacture of the product and process controls

The same coated active substance granules as already approved for the chewable tablets are used as an intermediate: this is performed by granulating the drug substance with the binder hydroxypropyl cellulose and then coating these drug granules with an aqueous taste masking system: opadry YS-1-19025-A (containing hypromellose 2910/6cP and macrogol/PEG 400) and surelease E-7-19040 (containing ethylcellulose 20 cP (E462), ammonium hydroxide (E527), medium chain triglycerides and oleic acid). As the drug substance is known to be moisture sensitive the granulation of the drug substance is done using bottom spray fluid bed granulation. The coated granules are then blended with mannitol, crospovidone, thickening agents (microcrystalline cellulose and carboxymethylcellulose sodium), sweeteners (sucralose, magnasweet), banana flavour, and lubricant (magnesium stearate), followed by filling.

In-process controls during granulation, coating and drying for the product bed temperature and coating drying end point have been established, and are considered critical in-process controls. Product bed temperature determines granule particle size, an important parameter for maintaining acceptable content uniformity during blending, lubrication, re-blending, and sachet filling, as shown in the process risk assessment. Control of product bed temperature is achieved by modulation of inlet air temperature and spray rate within their established NORs. Coating drying end point is determined via loss-on-drying (LOD) method, and assures moisture content suitable to meet product stability requirements.

No process parameters were considered critical for the milling, blending, lubrication, and re-blending steps. Over the ranges established, the impact to CQAs was considered low by the applicant.

For the sachet filling and sachet sealing processes, routine in-process controls for average net fill weight and leak testing have been established. These in-process controls are considered critical.

Adequate in-process controls are in place. Proven acceptable ranges have been defined. The test methods and acceptance criteria are considered adequate.

A summarised process validation protocol has been provided for commercial batches. The manufacturing process may be considered as a standard process in line with the draft guideline on process validation (CHMP/QWP/70287/2012). The data provided in the development section of the dossier demonstrate that the applicant has a good understanding of the process and the provided data show that the process is well controlled. Based on the provided information it is considered acceptable that no process validation data are provided to date. Instead the validation of the manufacturing process will take place prior to launching of the product unto the market.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identity (HPLC, FTIR), assay (HPLC), degradation products (HPLC), dissolution (HPLC), uniformity of dosage units (Ph. Eur.2.9.40), microbiological limits (Ph. Eur.2.6.12 and 2.6.13). All analytical methods have been adequately validated.

Batch analysis results are provided for 10 batches (7 pilot batches and 3 production scale batches) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. These batches were made with raltegravir manufactured at four different sites. The 3 production scale batches were manufactured at the proposed commercial manufacture site for the bulk blend.

Stability of the product

Stability data of 3 pilot size batches of finished product stored under long term conditions for 24 months at 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. The batches were manufactured with 3 different lots of active substance from two different sources.

Samples were tested for appearance, assay, degradation products, moisture, microbial quality, in-use stability, water activity. The analytical procedures used are stability indicating.

In-use stability was assessed for 3 batches of finished product stored for 12 month at 30 ºC / 75% RH and 6 months at 40 ºC / 75% RH by transferring the contents of a sachet into a sample cup, adding 5 mL of water, dispersing the granules and holding the suspension in the sample cup for six hours. The sample is then tested for assay and degradation products. Suspension stability was demonstrated.

The lack of photostability data has been accepted based on the fact that no evidence of photolysis is reported for the active substance and on the fact that the product is packaged in light protecting foil sachets.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Comparability exercise for finished medicinal drug product

N/A

Adventitious agents

No excipients derived from animal or human origin have been used. Assurance has been provided that the magnesium stearate is of vegetable origin only.

GMO

N/A

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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 a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product manufacturing process. However, no design spaces were claimed for the manufacturing process of finished product.

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.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

No new non-clinical studies have been performed in support of this application to extend the use of raltegravir to the treatment of paediatric patients of 4 weeks to less than 2 years of age.

Pharmacokinetics

During a definitive study, raltegravir was administered to the juvenile rat (n= 43 or 44/sex/group) via oral gavage at 0, 50, 200, or 600 mg/kg/day from post-natal day (PND) 5 to post-natal week (PNW) 8.

In females, the systemic exposures to the parent compound were slightly higher than those observed in males; however, the observed differences were not significant. Absorption of raltegravir was rapid, whereby the mean C_{max} was observed at 0.5 hours post-dose. Plasma elimination appeared to be

biphasic and overall, drug elimination was rapid, whereby the mean concentrations were less than 2% of their respective C_{max} values at 24 hours post-dose. In general, exposures to raltegravir increased in a less than proportional manner with dose.

The systemic exposures to the predominant metabolite, L-001277512, were similar in males and females. The mean C_{max} was observed at 0.5 hours post-dose. Plasma elimination appeared to be biphasic (as for the parent compound) and overall, elimination was rapid, whereby the mean concentrations were no greater than 8% of their respective C_{max} values at 24 hours post-dose. In general, AUC values for the metabolite increased in a less than proportional manner with dose and C_{max} values were similar across the dose range evaluated. The mean exposures to the metabolite were up to ~2-fold higher than those for the parent compound.

Overall, the mean C_{max} at 600 mg/kg/day observed during post-natal Week 7 was similar to that observed during a 5-week repeated-dose study in adult animals.

Toxicology

Raltegravir was administered to the juvenile rat (n= 43 or 44/sex/group) via oral gavage at 0, 50, 200, or 600 mg/kg/day from post natal day (PND) 5 to post natal week (PNW) 8. A total of 19 deaths were reported during the study; however, none of the deaths were considered to be treatment-related. The applicant suggested that there was no evidence of toxicity based on the incidence of mortality, the observed physical signs, body weights and developmental signs and haematology, serum biochemistry, ophthalmologic, behavioural assessment, and reproductive performance parameters.

Treatment-related histopathological findings consisted of vacuolation of the non-glandular mucosa at the limiting ridge at ≥200 mg/kg/day as well as inflammation which occurred at ≥200 mg/kg/day and 600 mg/kg/day in males and females, respectively. This difference is thought to be related to the absolute amount of drug deposited directly on the stomach mucosa, which is higher in males (due to body weight). Both vacuolar and inflammatory changes were considered reversible following cessation of treatment for approximately 6 weeks. The mucosal epithelial vacuolation and associated increased inflammation were consistent with raltegravir-induced irritation (very slight) to the limiting ridge of the non-glandular stomach. Moreover, the observed findings in juvenile animals were consistent with those observed in adult rats. Based on the histopathological results, the no-effect level for treatment related changes in juvenile rats was 50 mg/kg/day.

2.3.1. Ecotoxicity / environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP/4447/00], a full environmental risk assessment (ERA) has been submitted. The ERA report (dated June 2013) was signed off by Joan Griffith Tell, PhD who is employed by Merck & Co. Inc and has the appropriate training and experience in ecotoxicology.

The maximum dosage of Raltegravir granules for suspension is 100 mg/day administered orally, twice daily. Other forms and patient populations are allowed higher doses. The typical adult dose is 400 mg administered orally, twice daily with or without food. During coadministration with rifampin, the recommended dosage of Raltegravir is 800 mg twice daily with or without food (for a total of 1600 mg/day). For this assessment, in accordance with the guidance, the highest allowable dose is used.

Table 1. Summary of main study results

Substance (INN/Invented Name):					
CAS-number (if available):					
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 determined			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)
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 (0.25xPEC_{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

2.3.2. Conclusion on the non-clinical aspects

No new non-clinical studies have been performed in support of this application to extend the use of raltegravir to the treatment of paediatric patients from the age of 4 weeks to < 2 years. The data provided are considered to be sufficient to support the proposed use of raltegravir in paediatric patients from the age of 4 weeks to < 2 years.

Data from the ERA provided suggests that raltegravir and/or its metabolites will not constitute a risk to the environment.

2.4. Clinical aspects

Data relevant to the granules for suspension (GFS) come from the following two studies:

Protocol	Dose(s) of Raltegravir Studied	Final Dose Selected	Number Receiving Raltegravir	Population	Key Purpose
Study 068	A: 400 mg raltegravir FMI poloxamer tablet B: 400 mg (4 x 100 mg) raltegravir CT C: 400 mg raltegravir OG 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**: Weight based to approximately 6 mg/kg BID; 200 - 600 mg BID	400 mg BID for patients 12-18 years and 6-11 years and ≥ 25 kg.	87	Treatment-experienced pediatric patients	PK and short term safety for dose finding; safety and efficacy with long term dosing
	Chewable Tablet: 2-<12 years Weight based to approximately 8 and 6 mg/kg BID	Approximately 6 mg/kg BID (max 300 mg BID)	39	Treatment-experienced pediatric patients	
	Granules for suspension: Weight based to approximately 6 mg/kg BID	for patients 2-11 years. Approximately 6 mg/kg BID	26	**Cohort IV**: preventive therapy for maternal-infant transmission and/or for treatment of HIV infection. **Cohort V**: Preventive therapy for maternal-infant transmission	

2.4.1. Introduction

GCP

A routine GCP inspection was conducted. The final report was dated 3 January 2014 and was forwarded to the Rapporteur on 7 January 2014. The inspection covered two sites in Johannesburg and one in Brazil. The inspection revealed no critical but 11 Major Findings.

Regarding the Major Findings, with some occurring at each of the sites, a number were isolated and did not reflect a systemic issue.

The major findings in monitoring, data management and clinical study report are interlinked and taking them together these non-compliances could affect the data quality. It should be noted that:

- Monitoring was based on a risk based approach and therefore only a proportion of the data were subjected to SDV (in some sites it could be less than a quarter).
- The sponsor relied on investigator site process for data entry. There was no QC check of the CRF against the data entered into the database to monitor data entry errors by the monitor. Only automated edit checks and ad hoc searches were performed by the sponsor. All grade 3 or above SAEs and laboratory abnormalities were recorded separately and correctly accounted for.

– The protocol deviation list in the clinical study report was only a data dump extracted from the monitoring visit reports.

The combinations of the Major Finding in monitoring, data management (lack of QC of data) and lack of process for clinical study reporting does not give confidence that the data for the submission was adequately assured. However, the inspectors could verify that adherence was adequately monitored and that the dosing, PK samplings, sample handling and the reporting of grade 3 or above EAEs and SAEs were adequate. The assessors should be mindful of the poor data management processes, the lack of SDV and the ongoing data verification/cleansing post submission.

Based on the findings in this report, provided the CHMP accept the limitations mentioned, the inspectors can recommend that data from P1066 study to be used for further assessment. The inspectors have no recommendations for any follow up inspection for this application.

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

Both clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. These trials were conducted following appropriate Good Clinical Practice guidelines and considerations for the ethical treatment of patients that were in place at the time the trials were performed. Data presented in this raltegravir paediatrics application (4 weeks to <2 years) and information presented in this Clinical Overview were subject to audit by Merck Worldwide Quality Assurance Resources groups based on approved Standard Operating Procedures (SOPs) in effect at the time of the audit.

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.

2.4.2. Pharmacokinetics

In studies 068 and 022 plasma samples were analysed for raltegravir concentrations by the University of Alabama at Birmingham (Birmingham, AL). The analytical method used for the determination of raltegravir in human plasma was 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. Bioanalytical reports have been provided.

The formulations used in the two studies were:

- Adult tablets (100, 200 and 400 mg erodible tablet formulation). Only the 400 mg poloxamer tablet is actually approved for use.
- Chewable tablets [CT] (25, 50 and 100 mg unscored); only the 25 mg and 100 mg presentations were approved. The 100 mg CT used in study 068 was the same as that used in study 022.
- Oral granules for suspension (100 mg dissolved in 5 mL water to give 20 mg/mL) [GFS]

Study 068

This open label cross over study compared the three formulations intended for use in study P022 and also evaluated the effect of food on absorption after dosing with the CT. Subjects each received 4 single dose (400 mg) treatments (see footnote to table below) in a randomised order with at least 4 days of washout between each administration. PK samples were obtained over 72 h after each dosing.

- Treatments A (adult tablet), B (CT) and C (GFS) were administered in the fasting state.

- Treatment D (CT) was administered after a high fat breakfast of 827 kcal and 57% fat content.

The AUC0-∞ and Cmax observed with the CT were higher than obtained with the marketed adult tablet and the two formulations were not bioequivalent.

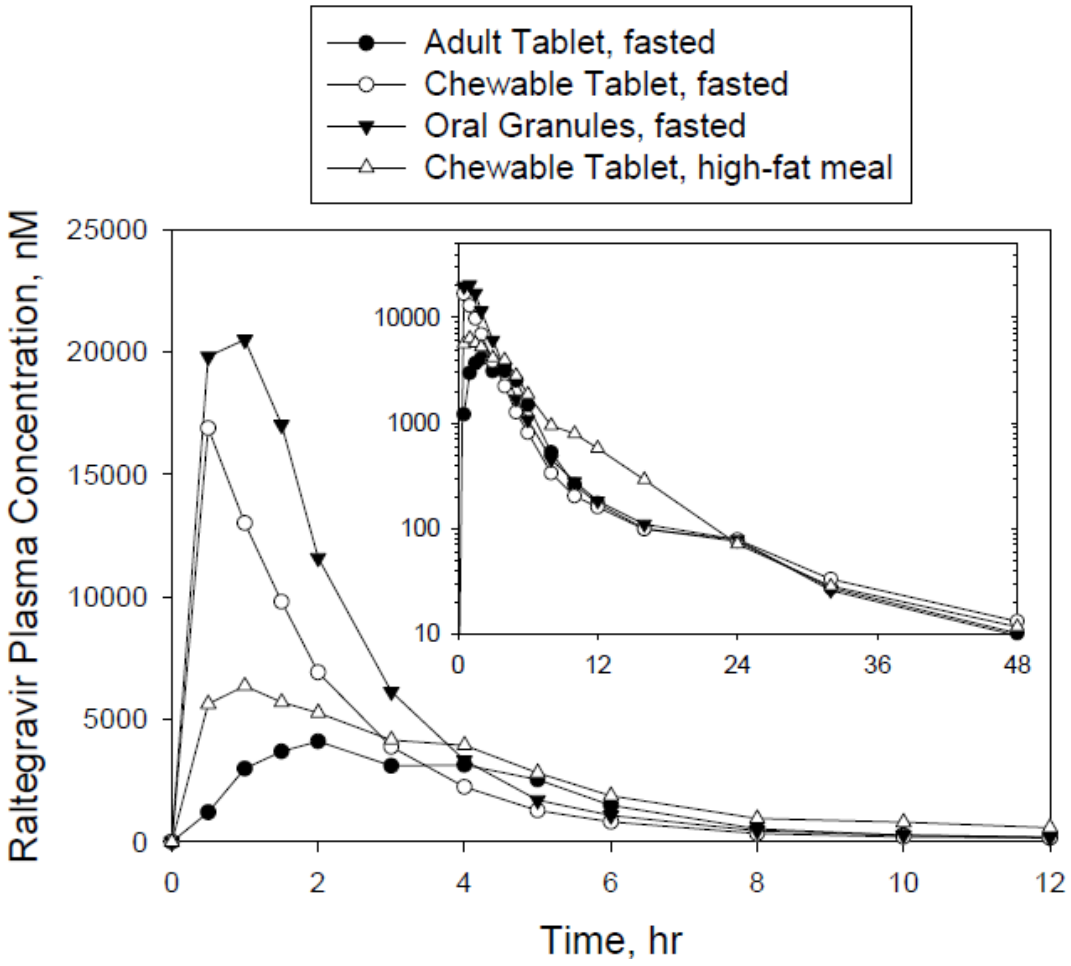
The oral suspension was not bioequivalent to the marketed adult tablet or to the chewable tablet. The GMRs for $AUC_{0-\infty}$ and C_{max} observed with GFS were 2.6-fold and 4.6-fold higher than those obtained with the adult tablet and 1.5-fold and 1.4-fold higher than those obtained with the CT. The geometric mean C_{12h} for the GFS was comparable to the values for the adult tablet and CT in the fasting state.

Table 2. Summary statistics of MK-0518 plasma PK following single dose administration of the MK-0518 OG formulation, the MK-0518 poloxamer formulation and the MK-0518 EC formulation in healthy adult subjects

Pharmacokinetic Parameter (Units)	N	Treatment A† GM	Treatment B† GM	Treatment C† GM	Treatment D† GM	Comparison	GMR (90% CI)	rMSE‡
C_{12hr} (nM)§	12	149	134	162	387	Treatment C/Treatment A	1.09 (0.84 , 1.41)	0.3794
						Treatment C/Treatment B	1.20 (0.92 , 1.56)	
						Treatment D/Treatment B	2.88 (2.21 , 3.75)	
						Treatment B/Treatment A	0.90 (0.70 , 1.18)	
$AUC_{0-\infty}$ (μM•hr)§	12	19.2	34.2	50.4	32.3	Treatment C/Treatment A	2.62 (2.17 , 3.17)	0.2748
						Treatment C/Treatment B	1.47 (1.22 , 1.78)	
						Treatment D/Treatment B	0.94 (0.78 , 1.14)	
						Treatment B/Treatment A	1.78 (1.47 , 2.15)	
C_{max} (μM)§	12	5.00	16.1	23.2	6.14	Treatment C/Treatment A	4.64 (3.41 , 6.30)	0.4425
						Treatment C/Treatment B	1.44 (1.06 , 1.95)	
						Treatment D/Treatment B	0.38 (0.28 , 0.52)	
						Treatment B/Treatment A	3.22 (2.37 , 4.38)	
T_{max} (hr)□	12	4.0	0.5	1.0	1.0			
$t_{1/2I}$ (hr)¶		1.5 (0.3)	1.7 (0.2)	1.6 (0.3)	2.0 (0.6)			
$t_{1/2T}$ (hr)¶	12	9.0 (5.9)	9.3 (5.1)	10.0 (3.2)	9.2 (3.8)			

† Treatment A = 400 mg MK-0518, poloxamer (administered fasted).
Treatment B = 400 mg MK-0518, EC (administered fasted).
Treatment C = 400 mg MK-0518, OG in a liquid suspension (administered fasted).
Treatment D = 400 mg MK-0518, EC (administered with a high-fat meal).
‡ rMSE: Root mean square error on natural log-scale. When multiplied by 100, it provides an estimate of the pooled within-subject coefficient of variation.
§ Back-transformed least squares mean and confidence interval from mixed effects model performed on the natural log-transformed values.
□Median values presented for T_{max}.
¶ Harmonic mean (jack-knife standard deviation) values presented for t1/2I and t1/2T. For t1/2I, the N's for Treatments A, B, C, and D are 11, 12, 12, and 10, respectively.

Figure 1 Arithmetic mean raltegravir plasma concentration-time profiles following single-dose administration of the RAL adult tablet, paediatric CT (fasted or fed) and oral granules in a liquid suspension to healthy adult, male and female subjects (N=12; inset = semilog scale)



Administration of the CT with a high-fat meal (D) gave (compared with CT in fasting state B) an increase in C_{12hr} (GMR 2.88 [90% CI 2.21, 3.75]), decrease in C_{max} (0.38 [0.28, 0.52]), delay in T_{max} (median 0.5 h fasted and 1 h fed) but comparable $AUC_{0-\infty}$ (0.94 [0.78, 1.14]). Dosing of the adult and CT formulations is recommended without regard to food in the respective SmPCs. Nevertheless, due to the increased variability in PK when dosing in the fed state the protocol for study 022 (see below) required dosing in the fasted state on days when full concentration-time PK profiles were obtained from Cohorts I-III. This allowed a direct comparison to adult PK data that were collected in the fasted state.

The MAH stated that the GFS formulation uses the same coated granule that is in the CT so that after the tablet is chewed the formulations would essentially present to the stomach in a similar fashion, albeit with less flavors and sweeteners in the GFS. On this basis the MAH concludes that because the PK profiles of the CT and the GFS are similar there will be a clinically insignificant food effect on the GFS. Note that in contrast to Cohorts I-III, the intensive sampling PK data used for final dose selection in Cohorts IV and V were obtained without regard to food.

Study 022

The new paediatric PK data in the current X44G application come from Cohorts IV and V of study 022 in children and adolescents. The study design is described in detail in the section on efficacy. Cohorts IV and V were the last age groups to be enrolled and received 6 mg/kg GFS twice daily.

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

For each of the three formulations the aim was to identify a dose regimen that would provide approximately the same plasma exposure to that achieved in adults using 400 mg poloxamer tablets BID. The initial protocol set a target minimum exposure for each cohort comprising a GM $AUC_{0\text{-}12h}$ 14 to 25 µM·hr and concurrent GM C_{12h} exceeding 33 nM (i.e. the IC95). Additionally, for safety reasons, the maximum $AUC_{0\text{-}12h}$ was to be < 45 µM·hr, which represents half the $AUC_{0\text{-}24h}$ observed when 1600 mg was administered in Phase I adult studies.

Subsequently, taking into account the additional information on the importance of C_{12hr} for efficacy based on study 071 (400 mg BID vs. 800 mg QD in adults) the criteria used for dose selection in Cohorts IV and V were modified to target a GM $AUC_{0\text{-}12h}$ between 14 and 45 µM·hr and an approximate GM C_{12hr} ≥ 75 nM. Dose adjustments for any subject with an $AUC_{0\text{-}12hr}$ ≥ 63 µM·hr were considered by the protocol team on a case by case basis and a repeat intensive PK visit was required.

Intensive PK sampling was to be performed for all subjects in Stage I of each cohort. Initial intensive PK visits occurred between Days 5 and 12 following the first raltegravir dose. At these visits there was witnessed dosing at approximately 12 h after the previous dose and without regard to food.

- **Cohort IV -** 1 mL blood was collected at pre-dose and at 0.5, 1, 2, 4 and 12 hours post dose.
- **Cohort V** - 1 ml blood was collected pre-dose, at 0.5 h, between 3-5 h and between 8-10 h.

A population PK model was used to determine if covariates (e.g. age, weight and sex) affected raltegravir PK and to derive estimated PK parameters $AUC_{0\text{-}12hr}$, C_{max} and C_{12hr} at steady state for each patient.

Sparse sampling was performed for all subjects in Stages I and II. Sparse sampling in Cohorts IV and V occurred between 10 and 14 h post-dose at Weeks 4 and 12. At Weeks 8 and 24 two samples were collected 2 h apart between 0.5 and 6 h (Week 8) or between 6 and 12 h (Week 24) post-dose.

Results

Intensive sampling PK data were initially obtained from four subjects in the mini-cohorts of each of Cohorts IV and V and from a total of 8 subjects in each Cohort.

In Cohort IV using 6 mg/kg BID the GM $AUC_{0\text{-}12hr}$ (19.8 µM·hr) and $C_{12\ hr}$ (108.2 nM) were within the target ranges. Two individual subjects had C_{12h} < 75 nM (51 and 64 nM) and one other subject had AUC < 14 µM·hr (11 µM·hr) but no subject exceeded the upper limit set for the GM AUC (45 µM·hr).

Table 3. Pharmacokinetic results for subjects in the mini-cohort IV

PID	Dose mg	Weight kg	Dose Mg/kg	Sex 1 M 2F	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL	C_{max} (µM)	Obs T_{last} (hr)	Mod TI_{last} (hr)	$C_{12\,h}$ (ng/ml)	$C_{12\,h}$ (nM)	AUC_{all} hr*mg/L	C_{min} (ng/mL	Cl_{ss_F} (l/hr)	Vz_F (l)	AUC_{12} hr*mg/L	AUC_{12} µMxh
801399E	80	12.8	6.3	2	2.1	0.5	9148.9	20.6	11.8	11.8	33.6	75.6	13.9	33.6	5.8	17.1	13.9	31.2
801526B	40	7.3	5.5	1	2.6	0.5	3854.8	8.7	11.0	11.0	44.3	99.7	7.9	44.3	5.0	19.1	7.9	17.8
801528J	50	8.1	6.2	1	1.9	2.0	2967.2	6.7	11.0	11.0	77.4	174.2	9.7	77.4	5.1	14.4	9.8	21.9
8501806G	60	9.7	6.2	1	2.2	0.5	10061.9	22.6	12.0	12.0	22.7	51.1	12.5	5.0	4.8	15.1	12.5	28.0
N	4	4	4		4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	57.5	9.5	6.0		2.2	0.9	6508.2	14.6	11.5	11.5	44.5	100.1	11.0	40.1	5.2	16.4	11.0	24.8
SD	17.1	2.4	0.3		0.3	0.8	3613.9	8.1	0.5	0.5	23.6	53.2	2.7	29.9	0.4	2.1	2.7	6.0
Min	40	7.3	5.5		1.9	0.5	2967.2	6.7	11.0	11.0	22.7	51.1	7.9	5.0	4.8	14.4	7.9	17.8
Median	55	8.9	6.2		2.1	0.5	6501.9	14.6	11.4	11.4	39.0	87.6	11.1	39.0	5.1	16.1	11.1	25.0
Max	80	12.8	6.3		2.6	2.0	10061.9	22.6	12.0	12.0	77.4	174.2	13.9	77.4	5.8	19.1	13.9	31.2
CV%	29.7	25.8	5.8		13.5	85.7	55.5	55.5	4.7	4.7	53.1	53.1	24.6	74.6	7.8	13.0	24.3	24.3
GM	55.7	9.3	6.0		2.2	0.7	5696.4	12.8	11.4	11.4	40.2	90.5	10.7	27.5	5.2	16.3	10.8	24.2

Subject 801525E was excluded due to the pre-exiting Kwashiorkor syndrome

Table 4. Pharmacokinetic results for all subjects in full cohort IV

PID	Dose mg	Weight kg	Dose Mg/kg	Sex 1 M 2F	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL	C_{max} (µM)	Obs T_{last} (hr)	Mod TI_{last} (hr)	$C_{12\,h}$ (ng/Ml)	$C_{12\,h}$ (nM)	AUC_{all} hr*mg/L	C_{min} (ng/mL	Cl_{ss_F} (l/hr)	Vz_F (l)	AUC_{12} hr*mg/L	AUC_{12} µMxh
2020164L	40	6.5	6.2	1.0	2.4	1.0	2133.4	4.8	12.0	12.0	75.7	170.3	6.8	75.7	5.9	20.0	6.8	15.3
382192K	80	12.4	6.5	2.0	7.2	0.5	10943.3	24.6	12.0	12.0	103.7	233.3	11.9	17.7	6.7	69.5	11.9	26.8
801399E	80	12.8	6.3	2.0	2.1	0.5	9148.9	20.6	11.8	11.8	33.6	75.6	13.9	33.6	5.8	17.1	13.9	31.2
801526B	40	7.3	5.5	1.0	2.6	0.5	3854.8	8.7	11.0	11.0	44.3	99.7	7.9	44.3	5.0	19.1	7.9	17.8
801528J	50	8.1	6.2	1.0	1.9	2.0	2967.2	6.7	11.0	11.0	77.4	174.2	9.7	77.4	5.1	14.4	9.8	21.9
801531L	30	5.6	5.4	1.0	4.4	0.5	3578.9	8.1	9.1	12.0	28.3	63.7	6.7	12.8	4.5	28.6	6.7	15.1
8501394B	30	5.5	5.5	2.0	3.8	1.1	2775.8	6.2	11.8	11.8	49.0	110.3	5.0	49.0	6.0	32.5	5.0	11.3
8501806G	60	9.7	6.2	1.0	2.2	0.5	10061.9	22.6	12.0	12.0	22.7	51.1	12.5	5.0	4.8	15.1	12.5	28
N	8	8	8		8	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	51.3	8.5	5.9		3.3	0.8	5683	12.8	11.3	11.7	54.3	122.3	9.3	39.4	5.5	27.0	9.3	20.9
SD	20.3	2.9	0.4		1.8	0.5	3685	8.3	1.0	0.4	28.4	64.0	3.2	27.4	0.7	18.3	3.2	7.2
Min	30	5.5	5.4		1.9	0.5	2133.4	4.8	9.1	11.0	22.7	51.1	5.0	5.0	4.5	14.4	5.0	11.3
Median	45	7.7	6.2		2.5	0.5	3716.9	8.4	11.8	11.9	46.7	105.0	8.8	39.0	5.4	19.5	8.8	19.9
Max	80	12.8	6.5		7.2	2.0	10943.3	24.6	12.0	12.0	103.7	233.3	13.9	77.4	6.7	69.5	13.9	31.2
CV%	39.6	34	7.1		54.1	64.7	64.8	64.8	8.9	3.8	52.3	52.3	34.4	69.6	13.5	67.8	34.3	34.3
GM	47.9	8.1	5.9		3.0	0.7	4714.9	10.6	11.3	11.7	48.1	108.2	8.8	28.9	5.4	23.4	8.8	19.8

The data from the mini-cohort of Cohort V gave GM an individual values within the required range. In May 2012 the protocol was amended to allow enrolment of up to 8 additional subjects in Cohort V Stage 1 to provide intensive sampling data and 4 had been enrolled when the study was closed to recruitment in February 2013. Three of these supplemental subjects in Cohort V provided intensive sampling data while taking 6 mg/kg while the fourth discontinued prior to the sampling day.

For the total Cohort V the GM $AUC_{0\text{-}12\,h}$ (22.3 µM·hr) and C_{12h} values (116.6 nM; estimated from prior concentrations using the population PK model for the GFS formulation) fell within the predefined targets. There was one subject with an individual AUC < 14 µM·hr (10.5 µM·hr) but no subject had a value that exceeded 45 µM·hr. Three others had individual C12h < 75 nM (36, 50 and 62 nM).

The graphical spread of AUC and C_{12h} values by age and weight did not show any appreciable difference between Cohorts IV and V. The final dose selected was 6 mg/kg for both Cohorts IV and V.

As shown in the next tables the actual doses administered using the GFS ranged from 5.38 to 6.45 mg/kg in Cohort IV and 5.10 to 7.14 mg/kg in Cohort V.

From these tables, the CHMP noted that with a suspension containing 20 mg/mL the actual doses were based on measurements to the nearest half millilitre. There is no consistent relationship between actual mg/kg and AUC. In particular, the two youngest infants aged 1 and 2 months received 5.36 and 6.15 mg/kg, respectively, and had corresponding AUCs of 39.7µM.h (the highest value in Cohorts IV and V) and 16.4 µM.h (in the lowest part of the range but above the minimum required).

Table 5. Pharmacokinetic results for all subjects in supplemental cohort V

PID	Dose mg	Weight kg	Dose Mg/kg	Sex 1 M 2F	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL	C_{max} (µM)	Obs T_{last} (hr)	Mod TI_{ast} (hr)	$C_{12\,h}$ (ng/Ml)	$C_{12\,h}$ (nM)	Predose Conc(nM)	AUC_{all} hr*mg/L	C_{min} (ng/mL	Cl_{ss}_F (l/hr)	Vz_F (l)	AUC_{12} hr*mg/L	AUC_{12} µMxh
382232C	25.0	4.5	5.6	1.0	4.7	1.0	5975.0	13.4	12.0	12.0	77.9	175.3	298.8	13.7	110.4	1.8	12.3	13.7	30.8
801539G(21)	40.0	6.9	5.8	1.0	111.1	1.0	5346.1	12.0	12.0	12.0	27.7	62.3	44.8	11.4	19.9	3.5	560.6	11.4	25.7
8503642B	30.0	5.3	5.7	2.0	2.5	1.0	2306.2	5.2	12.0	12.0	39.9	89.8	116.6	8.6	39.9	3.5	12.5	8.6	19.3
N	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	31.7	5.5	5.7	1.3	39.4	1.0	4542.4	10.2	12.0	12.0	48.5	109.1	153.4	11.2	56.7	2.9	195.1	11.2	25.3
SD	7.6	1.2	0.1	0.6	62.1	0.0	1962.0	4.4	0.0	0.0	26.2	58.9	131.0	2.6	47.5	1.0	316.5	2.6	5.8
Min	25.0	4.5	5.6	1.0	2.5	1.0	2306.2	5.2	12.0	12.0	27.7	62.3	44.8	8.6	19.9	1.8	12.3	8.6	19.3
Median	30.0	5.3	5.7	1.0	4.7	1.0	5346.1	12.0	12.0	12.0	39.9	89.9	116.6	11.4	39.9	3.5	12.5	11.4	25.7
Max	40.0	6.9	5.8	2.0	111.1	1.0	5975.0	13.4	12.0	12.0	77.9	175.3	298.8	13.7	110.4	3.5	560.6	13.7	30.8
CV%	24.1	22.3	1.7	43.3	157.6	1.7	43.2	43.2	0.2	0.2	54.0	54.0	85.4	22.9	83.8	32.8	162.2	22.9	22.9
GM	31.1	5.5	5.7	1.3	10.9	1.0	4192.0	9.4	12.0	12.0	44.2	99.4	116.0	11.0	44.4	2.8	44.1	11.0	24.8

Table 6. Pharmacokinetic results for all subjects in full cohort V

PID	Dose mg	Weight kg	Dose Mg/kg	Sex 1 M 2F	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL	C_{max} (µM)	Obs T_{last} (hr)	Mod TI_{ast} (hr)	$C_{12\,h}$ (ng/Ml)	$C_{12\,h}$ (nM)	Predose Conc (nM)	AUC_{all} hr*mg/L	C_{min} (ng/mL)	Cl_{ss}_F (L/hr)	Vz_F (L)	AUC_{12} hr*mg/L	AUC_{12} µMxh
2020158D	30.0	4.2	7.1	1.0	8.1	0.5	4406.8	9.9	8.1	12.0	45.0	101.3	76.5	11.0	34.0	2.7	32.0	11.0	24.7
2020159B	30.0	5.6	5.4	2.0	3.1	1.5	6075.2	13.7	8.1	12.0	46.4	104.3	71.3	15.3	31.7	2.0	8.9	15.3	34.3
2020161F	30.0	5.4	5.6	2.0	9.1	1.1	4970.4	11.2	8.5	12.0	164.4	369.9	144.5	15.5	64.2	1.9	25.5	15.5	34.9
2020171E	30.0	5.1	5.9	1.0	25.8	0.5	5034.2	11.3	8.5	12.0	16.0	36.0	6.9	6.4	5.0	4.7	173.3	6.4	14.5
2020176F	40.0	6.5	6.2	1.0	6.5	1.0	3500.7	7.9	8.5	12.0	22.1	49.7	79.9	7.3	22.1	5.5	51.6	7.3	16.4
382232C	25.0	4.5	5.6	1.0	4.7	1.0	5975.0	13.4	12.0	12.0	77.9	175.3	298.8	13.7	110.4	1.8	12.3	13.7	30.8
801532J	20.0	3.7	5.4	2.0	12.1	0.5	5591.3	12.6	8.0	12.0	83.8	188.4	66.8	17.7	29.7	1.1	19.7	17.7	39.7
801535D	40.0	7.5	5.4	1.0	2.6	0.5	799.6	1.8	8.0	12.0	98.7	222.0	121.7	4.7	54.1	8.6	32.2	4.7	10.5
801538I	30.0	5.9	5.1	1.0	7.4	1.2	3283.7	7.4	8.0	12.0	83.8	188.5	165.4	6.9	73.5	4.4	46.8	6.9	15.5
801539G(2)	40.0	6.9	5.8	1.0	111.1	1.0	5346.1	12.0	12.0	12.0	27.7	62.3	44.8	11.4	19.9	3.5	560.6	11.4	25.7
8503642B	30.0	5.3	5.7	2.0	2.5	1.0	2306.2	5.2	12.0	12.0	39.9	89.8	116.6	8.6	39.9	3.5	12.5	8.6	19.3
N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	31.4	5.5	5.7	1.4	17.5	0.9	4299.0	9.7	9.2	12.0	64.1	144.3	108.5	10.8	44.0	3.6	88.7	10.8	24.2
SD	6.4	1.1	0.6	0.5	31.7	0.3	1661.9	3.7	1.8	0.0	43.4	97.8	77.7	4.3	29.7	2.1	163.1	4.3	9.7
Min	20.0	3.7	5.1	1.0	2.5	0.5	799.6	1.8	8.0	12.0	16.0	36.0	6.9	4.7	5.0	1.1	8.9	4.7	10.5
Median	30.0	5.4	5.6	1.0	7.4	1.0	4970.4	11.2	8.5	12.0	46.4	104.3	79.9	11.0	34.0	3.5	32.0	11.0	24.7
Max	40.0	7.5	7.1	2.0	111.1	1.5	6075.2	13.7	12.0	12.0	164.4	369.9	298.8	17.7	110.4	8.6	560.6	17.7	39.7
CV%	20.3	20.8	9.7	37.0	180.8	37.3	38.7	38.7	19.3	0.1	67.7	67.7	71.6	40.2	67.5	59.1	184.0	40.2	40.2
GM	30.8	5.4	5.7	1.3	8.2	0.8	3821.2	8.6	9.1	12.0	51.8	116.6	80.5	9.9	34.4	3.1	36.8	9.9	

Table 7 makes a comparison across the five Cohorts. The data obtained from Cohorts IV and V resemble the GM and %CV observed in children taking the CT. As observed previously the GM AUC values are comparable across the age range included in P022 while the GM C12h values are lower for the groups that received either CT or GFS vs. those who received the adult tablets.

Table 7. Summary of Raltegravir Pharmacokinetic Parameters Following Administration of Final Recommended Doses in IMPAACT Protocol 1066

Age	Cohort	Formulation	Final Recommended Dose	N†	Mean Weigh t (kg)	Mean Dose (mg)	Mean Dose (mg/kg)	Geometric Mean (%CV) AUC $_{0\text{-}12hr}$ (µM*hr)	Geometric Mean (%CV) C_{12hr} (nM)
12 to 18 years	I	Adult tablet	400 mg BID	11	43.55	390.91	9.28	15.71 (98)	332.63 (78)
6 to < 12 years	IIA	Adult tablet	400 mg BID, for patients weighing ≥25 kg	11	31.54	400.00	13.45	15.84 (120)	246.09 (221)
6 to < 12 years	IIB	Chewable tablet	6 mg/kg BID, maximum of 300 mg BID	10	36.36	230.00	6.47	22.58 (34)	129.60 (88)
2 to <6 years	III	Chewable tablet	6 mg/kg BID, maximum of 300 mg BID	12	14.24	89.58	6.24	17.95 (59)	71.16 (55)
6 months to <2 years	IV	Granules for Suspension	6 mg/kg BID	8	8.49	51.3	5.93	19.8 (34)	108.2 (52)
4 weeks to <6 months	V	Granules for Suspension	6 mg/kg BID	11	5.50	31.4	5.70	22.3 (40)	116.6 (68)

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

Individual trough values < 45 nM (rather than <75 nM – the revised minimum target – for which numbers are reported above) occurred in 0/8 in Cohort IV and 1/11 (9%) in Cohort V.

Table 8. Geometric Mean Ctrough Values and Corresponding Proportion of Patients below 45 nM Ctrough for Each Cohort (I-V) of IMPAACT Protocol 1066 and Both Treatment Arms of Protocol 071 (QDMRK)

Study	Cohort: (Formulation, Age) / Study Arm	Dose	Geometric Mean C_{trough} in nM (%CV)	N	n < 45 nM	% of patients < 45 nM
IMPAACT Protocol 1066	Cohort I: Adult tablet, 12 to18 years	400 mg BID	332.63 (78)	8	0	0%
	Cohort IIA: Adult tablet, 6 to <12 years	400 mg BID	246.09 (221)	8	1	13%
	Cohort IIB: Chewable tablet, 6 to <12 years	Approx. 6 mg/kg BID	129.60 (88)	10	0	0%
	Cohort III: Chewable tablet, 2 to < 6years	Approx. 6 mg/kg BID	71.16 (55)	12	2	17%
	Cohort IV: GFS, 6 months to <2 years	Approx. 6 mg/kg BID, according to proposed dosing table	108.2 (52)	8	0	0%
	Cohort V: GFS, 4 weeks to <6 months	Approx. 6 mg/kg BID, according to proposed dosing table	116.6 (68)	11	1	9%
Merck Protocol 071 (QDMRK)	400 mg BID	400 mg BID	257 (167)	20	1	5%
	800 mg QD	800 mg QD	40 (111)	22	12	55%

In Stage II there were 6 additional subjects enrolled into Cohort IV and none into Cohort V. Three non-model based exposure summary measures were calculated based on the observed sparse concentration data as follows:

- **GM of All Observed Concentration (Call)**
- **GM C12hr**
- **Minimum of All Observed Concentrations (Cmin)**

In Cohorts IV and V 23 subjects had values for Call, C_{min} and GM C_{12hr}.

Table 9. Summary Statistics for Non-Model Based Raltegravir Pharmacokinetic Parameters Calculated from Sparse Concentration Data for Cohorts IV and V in IMPAACT Protocol 1066 (Values BLOQ substituted with ½ LOQ, or 11 nM)

PK Parameter	N †	Geo Mean	% CV	Median	Min	Max
Cohort IV						
C_{all} (nM)	13	246	67	354	48	803
GM C_{12hr} (nM)	13	73	74	87	11	268
C_{min} (nM)	13	39	85	36	11	156
Cohort V						
C_{all} (nM)	10	254	69	280	40	752
GM C_{12hr} (nM)	10	132	89	153	38	581
C_{min} (nM)	10	75	90	71	11	312

Note: raltegravir was administered with an optimized background regimen
† N = Number of patients with PK data.

Table 10. Geometric Mean (%CV) Values for Non-model based Raltegravir Pharmacokinetic parameters Calculated from Sparse Concentration Data (All Cohorts, 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	58 (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)
IV	13	246 (67)	13	73 (74)	13	39 (85)
V	10	254 (69)	10	132 (89)	10	75 (90)

The POP-PK model was a 2-compartment linear model with first order absorption based on P068 and P022 data from all subjects who received the GFS and CT formulations. Age, weight, BMI, BSA and gender were considered as covariates in the model (age, weight and BSA were highly correlated). The final model included an effect of weight on clearance, inter-compartmental flow rate and volume of distribution. Allometric scaling was used with a power of 0.75 for clearance and inter-compartmental flow rate and a power of 1 for volume of distribution. While maturation functions were explored to describe the influence of UGT1A1 activity on clearance in the youngest children incorporation of such a function did not improve the model fit vs. just including the effect of weight on clearance and volume of distribution. The MAH states that this is likely due to UGT1A1 activity being sufficiently high by 4 weeks of age to allow the clearance to be adequately described by a relationship with weight.

Post-hoc estimates of individual model parameters for patients in Cohorts IV and V were obtained using the final model and used to derive estimates of $AUC_{0\text{-}12hr}$, Cmax, and C_{12hr} at steady state for each subject. The MAH concluded that the estimates from the final model were generally consistent with expectations from the non-model based analysis described above and the analysis of intensive PK data.

Table 11. Summary Statistics for Raltegravir Population PK Parameters Following Administration of Multiple Oral Doses of Pediatric Granules for Suspension Formulation of Raltegravir 6 mg/kg BID -Sparse PK for Cohorts IV and V in IMPAACT Protocol 1066

PK Parameter	N †	Geo Mean	% CV	Median	Min	Max
Cohort IV						
$AUC_{0\text{-}12hr}$ (μM*hr)	8	18.5	34	19.0	11.7	29.6
C_{max} (μM)	8	8.4	61	7.0	3.7	17.7
C_{12hr} (nM)	8	149.1	88	150.9	45.9	585.0
Cohort V						
$AUC_{0\text{-}12hr}$ (μM*hr)	11	21.6	47	20.5	13.0	50.2
C_{max} (μM)	11	7.3	39	8.9	2.1	61.0
C_{12hr} (nM)	11	140	117	133.8	43.5	904.9

Note: raltegravir was administered with an optimized background regimen
† N = Number of patients with PK data.

Taste Evaluation

An assessment of taste for the GFS was conducted using a questionnaire that was administered to care-givers either at Week 4 or at an early discontinuation visit, if patient discontinued earlier than Week 4. Some care-givers completed more than one taste evaluation, in which case the most recent assessment was used in the analysis. Overall 88% of the 26 care-givers completed at least one taste evaluation. The overall taste was considered average, good or very good by 74% and 83% reported no problems with taking the GFS. Vomiting or spitting was reported by 17%.

Table 12. Summary of responses on Raltegravir GFS Taste Evaluation (Cohort IV and V); All Available Data

	Response Options	**Number (%) of Assessments (N=23)**
Provided Taste Assessment	Primary caregiver	23 (100)
Overall Taste Assessment	Bad	6 (26.1)
	Average	8 (34.8)
	Good	7 (30.4)
	Very good	2 (8.7)
Child/caregiver reported problems taking dose	Yes	4 (17.4)
	No	19 (82.6)
Problem with patient refusing dose?	Approximately half of all doses	1 (4.3)
	Never	3 (13)
Problem with patient vomiting/spitting up?	Infrequently	4 (17.4)
Problem with patient gagging?	Infrequently	2 (8.7)
	Never	2 (8.7)

N = Number of patients with at least one taste assessment. Some patients/caregivers provided more than one taste assessment; however only the most recent assessment is displayed.

2.4.3. Pharmacodynamics

PK/PD analysis

The following efficacy responses as documented in study 022 were considered for the PK/PD analysis:

- At least 1 log drop in HIV RNA or HIV RNA < 400 copies/mL at Week 24
- HIV RNA <50 copies/mL at Week 24

To assess the effect of PK parameter (GM C_{12hr} or GM C_{all}) 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. No statistically significant PK/PD associations were observed for the various combinations of sparse PK parameters and <50 copies/mL at Week 24 in the analyses of data from Cohorts IV and V. When data were pooled across all five Cohorts statistically significant PK/PD associations were observed for all combinations of sparse PK parameters and efficacy measures when samples with values BLOQ were substituted with ½ LLOQ (i.e. 5 ng/mL or 11 nM) in the calculation of C_{all} and GM C_{12hr}.

Table 13. Population PK parameters as a predictor for ARV responses (PK parameters were calculated with BLOQ values treated as ½ the LLOQ)

	n[§]	N[§]	Odds Ratio (95% CI)[†]	p-Value[†]
Patients in Cohorts IV and V in IMPAACT P1066				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at Week 24				
Geo Mean of C12hr (nM) from Sparse PK data	19	21	--------[‡]	---
Geo Mean of All Observed Conc. (nM) from Sparse PK data	19	21	--------[‡]	---
HIV RNA <50 copies/mL at Week 24				
Geo Mean of C12hr (nM) from Sparse PK data	9	20	10.5 (0.44, 248)	0.146
Geo Mean of All Observed Conc. (nM) from Sparse PK data	9	20	28.3 (0.43, 1880)	0.118
Patients in All Cohorts I to V				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at Week 24				
Geo Mean of C12hr (nM) from Sparse PK data	95	124	3.34 (1.39, 8.02)	0.007
Geo Mean of All Observed Conc. (nM) from Sparse PK data	108	142	3.84 (1.77, 8.36)	<.001
HIV RNA <50 copies/mL at Week 24				
Geo Mean of C12hr (nM) from Sparse PK data	66	123	3.57 (1.66, 7.68)	0.001
Geo Mean of All Observed Conc. (nM) from Sparse PK data	77	141	3.20 (1.55, 6.58)	0.002

† Logistic regression with PK parameters (in log10 scale) and following covariates: baseline HIV RNA (log_{10} copies/mL).
§ N: number of patients with both PK and efficacy data. n: number of patients (out of N) with events.
‡ The reliable estimate of Odds Ratio with corresponding p-value cannot be obtained due to the low number of subjects that failed this criteria.

When BLOQ samples were treated as missing in the calculation of Call and GM C12hr no statistically significant PK/PD associations were observed for the various combinations of sparse PK parameters and efficacy measures in the pooled analysis, suggesting that the concentration ranges in Cohorts IV and V fall at the top of the exposure-response curve.

In the viral dynamics model a simple Emax model was used to describe the dependence of viral inhibition on drug exposure with an in-vivo EC50 estimated from study 071 (3.5 ng/mL or 8 nM). The raltegravir concentration versus time profile was converted to a profile of percent viral inhibition versus time. By calculating the AUIC the average inhibition over the dosing interval was determined, from which a concentration can be calculated which would result in this same level of average inhibition over

the dosing interval as if the concentration were held constant over the interval. This concentration is what the Sponsor terms the Equivalent Constant Concentration (ECC) and is the PK parameter which is used as the input in the viral dynamics model.

In order to demonstrate that the PK profiles observed for Cohorts IV and V would be anticipated to result in efficacy similar to that obtained in adults with 400 mg BID and in paediatric subjects in Cohorts I-III, the full PK profiles for those dosed with the final recommended dose were used to calculate a distribution of steady state ECC values for each Cohort and the model was used to simulate the anticipated long-term efficacy for a combination regimen of raltegravir + NRTIs in treatment naïve HIV-infected patients with these PK profiles. The results were then compared to the observed results from the 400 mg BID arm of study 071 and from Cohorts I-III in P022. The mean ECC values and corresponding %CVs for each Cohort and for study 071 are shown in Table 14.

Table 14. Calculated GM steady state EEC values and corresponding %CV for each cohort (I-V) of IMPAACT protocol 1066 and both treatment arms of protocol 071 (QDMRK)

Study	Cohort: (Formulation, Age) / Study Arm	N	Dose	ECC Geometric Mean and %CV (ng/mL)	Percent Inhibition at GM ECC (%CV)
IMPAACT Protocol 1066	Cohort I: Adult tablet, 12 to18 years	8	400 mg BID	235 (93.9%)	98.5% (2.3%)
	Cohort IIA: Adult tablet, 6 to <12 years	8	400 mg BID	134 (120.5%)	97.5% (5.6%)
	Cohort IIB: Chewable tablet, 6 to <12 years	10	Approx. 6 mg/kg BID	156 (58.9%)	97.8% (1.1%)
	Cohort III: Chewable tablet, 2 to <6 years	12	Approx. 6 mg/kg BID	92 (47.5%)	96.3% (2.7%)
	Cohort IV: GFS, 6 months to <2 years	8	Approx. 6 mg/kg BID, according to proposed dosing table	115 (47.5%)	97.1% (1.5%)
	Cohort V: GFS, 4 weeks to <6 months	11	Approx. 6 mg/kg BID, according to proposed dosing table	119 (80.2%)	97.1% (2.9%)
Merck Protocol 071 (QDMRK)	400 mg BID	20	400 mg BID	217 (108.3%)	98.4% (2.5%)
	800 mg QD	22	800 mg QD	49 (90.2%)	93.3% (7.6%)

Figure 2 Simulated proportion of patients with viral loads <50 copies/mL over 96 weeks of treatment from patients in IMPAACT protocol 1066 (cohort I-V) and protocol 071 (QDMRK)

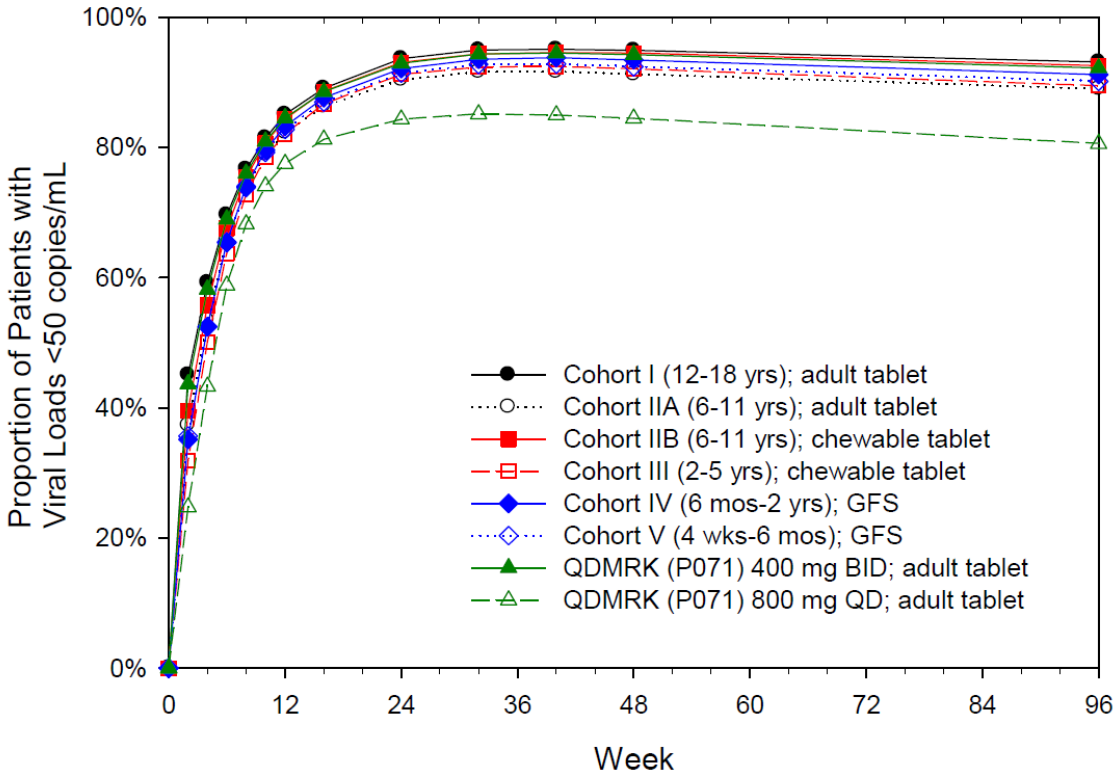
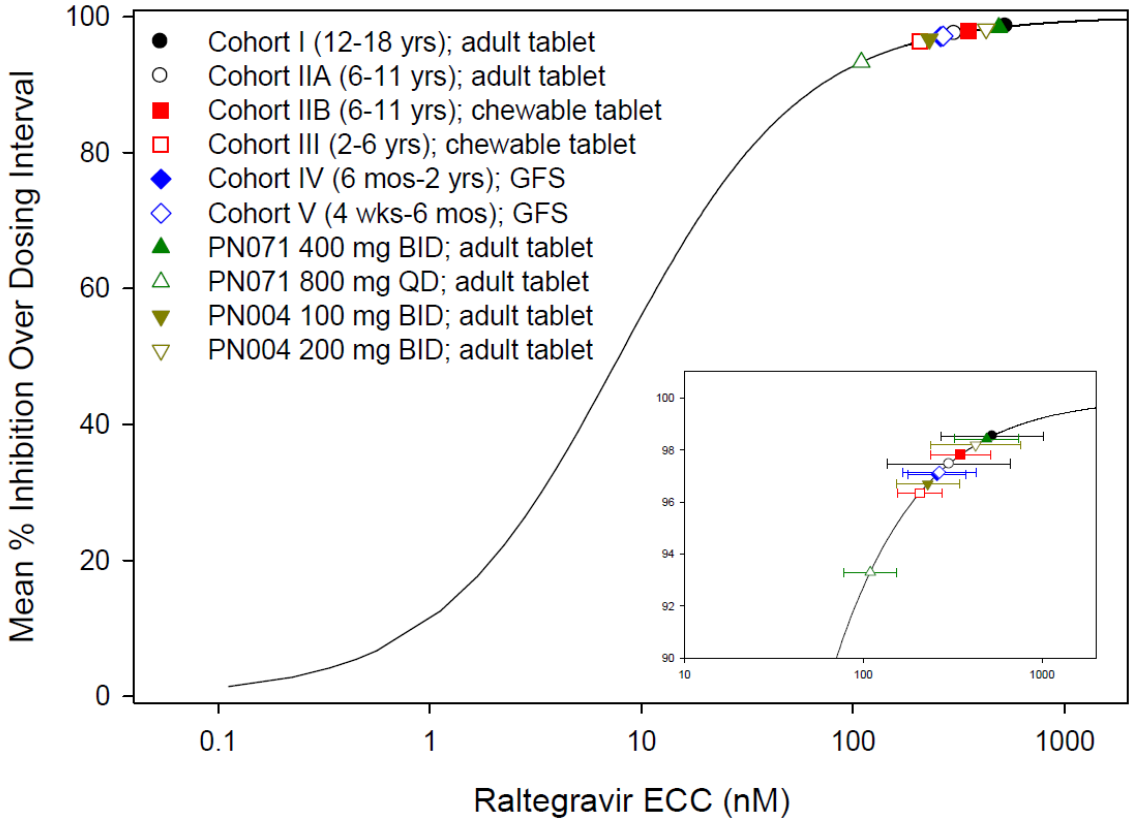


Figure 3 GM ECC and percent inhibition over the dosing interval for IMPAACT protocol 1066 and Merck protocol 071. Inset error bars represent 95% CI of ECC values (intensive PK data)



The Applicant concluded that the PK profiles observed with 6 mg/kg GFS in Cohorts IV and V should result in anti-viral efficacy very similar to that observed in adults taking the 400 mg BID dose.

Conclusions on pharmacodynamics

The PK/PD analysis has been conducted along the same lines as the analysis that was finally provided for the CT data. The non-model-based analyses that when BLOQ samples were treated as missing in the calculation of Call and GM C_{12hr} no statistically significant PK/PD associations were observed for the various combinations of sparse PK parameters and efficacy measures in the pooled analysis, suggesting that the concentration ranges in Cohorts IV and V fall at the top of the exposure-response curve.

In the viral dynamics model the mean ECC values and corresponding %CVs for each Cohort and for study 071 indicated similar findings for the GFS and CT formulations and both gave results that were less variable than the adult tablet. ECC values for all paediatric cohorts were more similar to those observed in the 400 mg BID arm of study 071 than the 800 mg QD arm.

The analyses broadly support the Applicant's conclusion that the PK profiles observed with 6 mg/kg GFS in Cohorts IV and V should result in anti-viral efficacy very similar to that observed in adults taking the 400 mg BID dose using the poloxamer tablets.

2.4.4. Discussion on clinical pharmacology

P068 showed that the CT and the GFS exhibited less PK variability compared to the adult tablet, likely reflecting the differences in bioavailability. Whereas AUC was 2.6-fold higher for the GFS, Cmax was 4.6-fold higher and C12hr was not substantially increased vs. adult tablets. This implies faster absorption for the GFS, which would be expected to result in a greater peak to trough fluctuation during steady-state dosing. However, intensive sampling showed that individual C12h values in Cohorts IV and V uncommonly fell below 75 nM and in only one case below 45 nM.

Due to the results of study 071 the targets set for Cohorts IV and V were GM AUC0-12hr between 14 and 45 μM·hr and GM C12hr ≥ 75 nM. The increase in the GM C_{12hr} target was based on the finding that in 071 the 400 mg BID and 800 mg QD regimens gave comparable $AUC_{0\text{-}24\ hr}$ but mean trough concentrations were 5-6 fold higher with BID dosing and correlated with the antiviral effect, such that subjects with values < 45 nM had the highest rate of virological failure. Aiming for a GM C_{12hr} > 75 nM would result in the majority of subjects having individual values > 45 nM.

The intensive and sparse PK analyses from P022 showed that ~ 6 mg/kg delivered via the GFS without regard to food (i.e. fasted state dosing on sampling days was not required) gave similar overall exposures compared to the adult tablet when given to older children but there was a higher C_{max} and lower trough concentrations (GM C12hr ~ 108 to 117 nM for the GFS vs. 250 to 340 nM for the adult tablet). The PK profiles were comparable between the GFS in Cohorts IV and V and the CT in Cohorts IIB and III with GM AUC values 18-23 μM•hr (CT) and 20-22 μM•hr (GFS) and GM C12hr values of 71-130 nM and 108-117 nM, respectively.

Unlike the previous data from cohorts from older age groups, there were no obvious trends in PK by gender and gender was not a significant covariate in the population PK model. The intensive PK analysis showed a trend for oral clearance to increase with weight (and with age, which is highly correlated with weight) in the younger age groups, before levelling off in the older and heavier paediatric patients. This is consistent with the results of the population PK analysis of the GFS and CT, which indicate that raltegravir clearance and volume of distribution are a function of weight (again

highly correlated with age) across the range studied in Cohorts IIB, III, IV and V. This provides further justification for the weight-based dosing using the chewable tablet/GFS in the younger (11 years and under) and less heavy (weight <25 kg) children but a fixed dose of 400 mg twice daily using the adult tablet for the adolescents (12 to 18 years) and heavier children (weight > 25 kg).

While the GM C_{min} values were 39 nM for Cohorts IV and 75 nM for Cohort V the range indicated that some subjects had values on occasion that were BLOQ (10 ng/mL or 22 nM), which were assigned a value of 11 nM (1/2 BLOQ) in some analyses.

The intensive sampling data include 801525E (excluded from Cohort IV due to Kwashiorkor syndrome) and 8503642B (Cohort V) who inadvertently received 100 mg instead of 30 mg BID for 5 days pre-sampling.

In Cohort IV the intensive sampling data showed that the Kwashiorkor subject had two instances of < 10 ng/mL (BLOQ; 22 nM) at 0h and at 12 h post-dose and another subject had one instance BLOQ at 0h only. Note that these BLOQ values would have followed ingestion of the last non-witnessed dose scheduled for the previous evening. The subject with a sample BLOQ at 12 h after the witnessed dose had a concentration at 4 h that was well into the range of all other subjects, suggesting more rapid clearance of raltegravir between 4-12 h post-dose. If correct, then the BLOQ at 0h may not be due to non-adherence. The subject with BLOQ only at 0h had the lowest measurable 12 h concentration and again this may mean that BLOQ was not due to non-adherence.

In Cohort V two subjects had 0h concentrations <BLOQ and these same two subjects had the lowest concentrations at 8-10 h. Hence it is possible that the BLOQ values do not represent non-adherence.

Sparse sampling data showed that two subjects in Cohort IV had BLOQ values at Week 4 only, which could represent non-adherence. One in each Cohort had a BLOQ at Week 12 only - the Cohort V subject had rather typical values at all other visits while the Cohort IV subject had no sample for 3/6 instances, which makes it difficult to comment further. Overall, there were few instances of values BLOQ in Cohorts IV and V. Not all of these BLOQ value may represent non-adherence. The intensive sampling data suggest that perhaps the subjects involved had faster clearance in the latter part of the dosing interval. This could represent natural variability but it may also be pertinent to understand whether the BSA of these children or the concomitant medications they were taking could be associated with the findings.

The clearance of raltegravir in humans is mainly via UGT1A1-mediated glucuronidation. UGT1A1 demonstrates polymorphism but dose adjustment is not required for subjects with reduced UGT1A1 activity. In the responses to X24G the MAH reported studies to show that adult levels of UGT1A1 are attained by three to six months of age and that no differences in infant vs. adult transcript levels of UGT1A1 or UGT2B7 were observed when infant samples were placed into three age brackets (6-12, 13-18 and 19-24 months). The table and graphical display of the Cohort V PK data by age showed the highest AUC in the youngest infant even though the actual dose given was 5.36 mg/kg. The possible effects of UGT levels in infants aged < 6 months should be addressed, taking into account that the age range in cohort V was 4-19 weeks but the mean and median were ~14-15 weeks.

The evaluation of taste in adults was not favourable. In children aged < 2 years it is very difficult to understand how caregivers could evaluate the taste of the GFS. Spitting out the medicine or refusing it does not necessarily mean that the taste is poor just as swallowing it without apparent reaction does not mean it tastes good. Overall the CHMP places no reliance on the care-givers assessment. The only critical point is whether they were able to get the children to take the dose when scheduled and swallow it without vomiting. On this basis alone it seems likely that the GFS is an acceptable formulation. Overall, the PK data support a dose of 6 mg/kg but there are a few issues to address.

Additional issues during the assessment

The MAH was asked to further explore the actual doses administered to children with C_{12hr} and/or AUC values that fell below the population targets or below < 45 nM at trough, as listed in the table.

Table 15 does not show an obvious trend when comparing the actual doses administered on a per kg basis in these subjects (5.35-6.17 mg/kg) compared to the range of doses received in the rest of the subjects in Cohorts IV and V (5.10-7.14 mg/kg). The two subjects with AUC_{0-12hr} less than 14 uM*hr (PID 8501394 in Cohort IV and PID 801535 in Cohort V; Table 1) demonstrated adequate C_{12hr} (110 and 222 nM, respectively). However, since even in the "intensive sampling" patients the data points are inevitably limited, the C_{max} and to some extent the other values can only be regarded as estimates.

Table 15. Individual Listing of Dose Administered, Demographics, and Pharmacokinetic Parameters for Subjects with Individual C12hr and AUC0-12hr Values Below the GM Targets Following Intensive PK Sampling in Cohorts IV and V in IMPAACT P1066

Patient ID (PID)	Cohort	Age (months)	Dose (mg)	Weight (kg)	Dose (mg/kg)	$AUC_{0-12hrr}$ (µM·h)	C_{max} (µM)	T_{max} (hr)	C_{12hr} (nM)
801531	IV	6	30	5.58	5.38	15.1	8.1	0.5	**64**§
8501394	IV	6	30	5.5	5.45	**11.3**	6.2	1.05	110
8501806	IV	8	60	9.73	6.17	28	22.6	0.5	**51**
2020171	V	4	30	5.1	5.88	14.5	11.3	0.5	**36**§
2020176	V	2	40	6.5	6.15	16.4	7.9	1	**50**§
801535	V	4	40	7.47	5.35	**10.5**	1.8	0.5	222§
801539	V	4	40	6.89	5.81	25.7	12	1.03	**62**

§ Model-based C12hr values derived from population PK model using model-estimated elimination rate constant and observed 8 hour concentration
Target GM AUC0-12hr values were >14 µM•hr and <45 µM•hr; Target GM C12hr values were >75 nM. Bolded values are outside of the geometric mean targets.

Table 16 lists the children with at least one sparse sampling value BLOQ. Only 1 of the 4 subjects (PID 8501806) with a BLOQ sparse PK sample also had a C_{12hr} value below the GM target during intensive PK, as shown in Table 1. This patient's AUC0-12hr was on the higher end of the range, at 28 uM*hr. Furthermore, 3 of 4 patients showed favourable virologic efficacy as shown by the steep decline in HIV RNA (copies/mL) from baseline to the week with a BLOQ value: PID 382192 (BL: 135,016; Week 4: 1,880), PID 2020164 (BL: 10,000,000; Week 4: 8,637), PID 8501806 (BL: 18,385; Week 12: 51,560) and PID 801538 (BL: 10,000,000; Week 12: 1,290).

Table 16. Listing of Individuals, Dose Administered, and Time at Which BLOQ Concentration Values Were Observed in Cohorts IV and V in IMPAACT P1066 Following Sparse PK Sampling

		Intensive PK Parameters (Stage I)		Associated with Sparse PK BLOQ Concentrations (Stage II)					
PID	Cohort	AUC_{0-12hr} (μM·h)	C_{12h} (nM)	Weight (kg)	Dose (mg/kg)	Week	Time Since Last Dose (hr)	Baseline HIV RNA (copies/mL)	HIV RNA (copies/mL) at BLOQ time point
382192	IV	26.8	233	12.40	6.45	4	13.65	135,016	1,880
2020164	IV	15.3	170	6.50	6.15	4	10.17	10,000,000	8,637
8501806	IV	28.0	51	9.73	6.17	12	12.83	18,385	51,560
801538	V	15.5†	188†,§	5.88	6.80	12	12.32	10,000,000	1,290

§ Model-based C_{12hr} values derived from population PK model using model-estimated elimination rate constant and observed 8 hour concentration
† For PID 801538, a dose of 30 mg was administered during the intensive PK sampling.

Note that PID 8501806 actually had an increase in viral load from an unusually low baseline (18,385) to 51,560 at Week 12. The intensive sampling PK data from this patient suggested no problem with absorption based on levels in the early samples but showed an unusually fast decline from 4 h to 12 h. This patient, who was 8 months old, could have had unusually high UGT levels that could have been the result of induction by one or more concomitant medications.

Indeed, all seven of the children listed in Table 1 were taking LPV/r during the study. However, since 65% of all patients in the study were taking LPV/r it is not possible to draw any conclusions about an association between use of LPV/r and virological response from these observations.

With regard to UGT levels, which are reported to reach adult levels at around 3-6 months of age, the MAH stated that Data from Cohorts IV and V suggested at most a weak trend between raltegravir AUC and age. However, the claim cannot be regarded as substantiated when there is no discussion of factors other than age that could impact on raltegravir clearance. There is a need to further explore the potential reasons for PK values BLOQ or, at least, below the pre-defined population thresholds (which can be used as a benchmark) as well as C_{12h} values < 45 nM.

The question arose from the prior responses, in which it was considered that the MAH had not considered whether some patients could have had faster clearance that could be related to their level of UGT expression and whether induction of UGT by co-administered medications (such as lopinavir/ritonavir; LPV/r; Kaletra; which was taken by 65% of patients in the study) could have influenced PK.

The CHMP considered the MAH's responses adequate; however no assessment of the real reasons for the variability between subjects and within subjects over time was provided. The CHMP considered to not pursuing this issue further.

The revisions to section 4.2 of the SmPC further clarified the use of the GFS up to a maximum 100 mg BID. Although the MAH could have calculated GFS doses for higher weights to allow an alternative to the CT in heavier children there is no major objection to this limit.

However, an additional point concerned the fact that the US FDA approved the GFS formulation in December 2013. The dose recommendations approved in the US are not exactly those used in the study and as proposed for the EU SmPC since they have been simplified into weight bands that round up to nearest half or whole millilitre volumes. The tabulation is also useful since it displays the doses

for the GFS and CT in parallel (note that the doses for the CT are the same between the approved EU and US prescribing information).

During the responses to questions, the MAH had revised the dosing table for the oral suspension so that dosing limits were based on weights and not additionally restricted by age. This was considered appropriate. It was also clarified that children of 12-20 kg could take either the GFS or the CT depending on preference. The dosing table, based on the study, was as follows:

Recommended Dose* for ISENTRESS Granules for Oral Suspension in Pediatric Patients at least 4 weeks of Age

Body Weight (kg)	Dose	Volume of Suspension to be administered
3.0 to < 3.7	20 mg twice daily	1 mL twice daily
3.7 to < 4.6	25 mg twice daily	1.25 mL twice daily
4.6 to < 6.0	30 mg twice daily	1.5 mL twice daily
6.0 to < 7.6	40 mg twice daily	2 mL twice daily
7.6 to < 9.1	50 mg twice daily	2.5 mL twice daily
9.1 to < 11.6	60 mg twice daily	3 mL twice daily
11.6 to < 14.0	80 mg twice daily	4 mL twice daily
14.0 to < 20.0	100 mg twice daily	5 mL twice daily

*The weight-based dosing recommendation for granules for oral suspension is based on approximately 6 mg/kg/dose twice daily.

However, it was noted that the dose recommendations approved in the US were not exactly those used in the study and as proposed for the EU SmPC since they have been simplified into weight bands that round up to nearest half or whole millilitre volumes as follows:

Recommended Dose* for ISENTRESS For Oral Suspension and Chewable Tablets in Pediatric Patients Weighing Less than 25 kg

Body weight (kg)	Volume (Dose) of Suspension to be administered	Number of Chewable Tablets
3 to less than 4	1 mL (20 mg) twice daily	
4 to less than 6	1.5 mL (30 mg) twice daily	
6 to less than 8	2 mL (40 mg) twice daily	
8 to less than 11	3 mL (60 mg) twice daily	
11 to less than 14†	4 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	5 mL (100 mg) twice daily	1 x 100 mg twice daily
20 to less than 25		1.5 x 100 mg‡ twice daily

*The weight-based dosing recommendation for the chewable tablet and oral suspension is based on approximately 6 mg/kg/dose twice daily [see Clinical Pharmacology (12.3)].
†For weight between 11 and 20 kg either formulation can be used.
Note: The chewable tablets are available as 25 mg and 100 mg tablets.
‡The 100 mg chewable tablet can be divided into equal halves.

The tabulation appeared to be potentially very useful because it displayed the doses for the GFS and CT in parallel (the doses for the CT are the same between the approved EU and US prescribing information).

Since the US table along with the parallel dosing for oral suspension and CT seemed appealing the MAH was asked to explain how the US simplified dose recommendations were derived and to discuss why they had not been proposed for the EU SmPC.

The modifications to the oral suspension regimens as adopted in the US will mostly slightly increase the dose, which is better for efficacy. The small modifications do not seem at all likely to impact on safety, taking into account also that a relationship between plasma exposures and specific AEs has not been identified.

Therefore, the CHMP considered that the US version is an improvement and that the most recent modifications that have been made by the MAH to all three SmPCs (i.e. poloxamer tables, CT and suspension) are accepted.

2.4.5. Conclusions on clinical pharmacology

The PK/PD analysis has been conducted along the same lines as the analysis that was finally provided for the CT data. The non-model-based analyses that when BLOQ samples were treated as missing in the calculation of Call and GM C_{12hr} no statistically significant PK/PD associations were observed for the various combinations of sparse PK parameters and efficacy measures in the pooled analysis, suggesting that the concentration ranges in Cohorts IV and V fall at the top of the exposure-response curve.

In the viral dynamics model the mean ECC values and corresponding %CVs for each Cohort and for study 071 indicated similar findings for the GFS and CT formulations and both gave results that were less variable than the adult tablet. ECC values for all paediatric cohorts were more similar to those observed in the 400 mg BID arm of study 071 than the 800 mg QD arm.

The analyses broadly support the MAH's conclusion that the PK profiles observed with 6 mg/kg GFS in Cohorts IV and V should result in anti-viral efficacy very similar to that observed in adults taking the 400 mg BID dose using the poloxamer tablets.

2.5. Clinical efficacy

The Applicant submitted a report on study 022 (also referred to as P1066 or IMPAACT) dated 6 June 2013. This open-label study was conducted between 2007 and 2013 and subjects were enrolled at 43 sites across N. and S. America and Southern Africa. The data cut-off date for the preparation of the current study report was the LPLV date 7 February 2013. The updated report provided data up to maximum Week 48 for Cohorts IV and IV and longer-term data up to maximum Week 240 on subjects previously enrolled into Cohorts I, IIA, IIB and III.

Study 022

This was a multi-centre, 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, PK and efficacy of raltegravir when administered in combination with an optimised background regimen (OBR). Subjects were stratified into six cohorts based on five age groups and three formulations as follows:

Cohort I: 12 to < 19 years - adult tablets

Cohort IIA: 6 to < 12 years - adult tablets

Cohort IIB: 6 to < 12 years - chewable tablets (CT)

Cohort III: 2 to < 6 years - chewable tablets

Cohort IV: 6 months to < 2 years - oral granules for suspension (GFS)

Cohort V: 4 weeks to < 6 months - oral granules for suspension

The study consisted of sequential Stages I and II within each Cohort. In Stage I the background ARV was optimised after sampling for PK evaluation. The starting dose of raltegravir was administered to the first 4 in each cohort (i.e. a mini-cohort) before expanding to the full cohort and then to the next youngest cohort. PK and short-term safety were again assessed before deriving a final dose

recommendation for Stage II, which involved raltegravir dosing for 48 weeks with an optimised background ARV regimen.

Eligibility for inclusion in Cohort IV required therapy to interrupt maternal-infant transmission and/or treat HIV infections. Eligibility for inclusion in Cohort V required therapy to interrupt maternal-infant transmission but no other anti-HIV treatment. 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.

Cohorts IV and V received oral granules for suspension twice daily at 6 mg/kg. The oral granules (100 mg) were suspended in 5 mL of water for a 20 mg/mL final concentration.

Efficacy measurements included HIV RNA, CD4 cell counts and percentages and viral resistance testing. In Cohorts IV and V all HIV RNA determinations used the Abbott Real Time HIV-1 platform. HIV RNA was measured at screening, entry, Weeks 1, 4, 8, 12, 24, 36 and 48 at the 14-day post therapy follow-up visit and at any early discontinuation visits. During long-term follow-up HIV RNA was measured every 4 months (± 6 weeks) for up to 5 years from enrolment.

The All Treated population included all who received a dose of raltegravir. The Final Dose population included those who received only the final selected dose. In Cohorts IV and V all subjects received the final dose. Subjects reaching 2 years of age and after 48 weeks could switch from the GFS to the CT but were still included in all Cohort IV and V displays. However, at the time of database lock no Cohorts IV and V subjects had transitioned to the CT.

The modified 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.

Results for Cohorts IV and V

There were 26 treated subjects, including 18 enrolled at three sites in S. Africa, of which 23 completed at least 24 weeks of treatment and 21 completed the Week 48 visit or had discontinued before that date.

Table 17. Overall disposition of patients by cohort (IV and V)

	Cohort IV (N=15) N (%)	Cohort V (N=12) N (%)	Total (N=27) N (%)
Total	15 (100)	12 (100)	27 (100)
Treated	14 (93.3)	12 (100)	26 (96.3)
Non-Treated	1 (6.7)	0 (0)	1 (3.7)
Patients completed Week 24*	14 (93.3)	9 (75)	23 (85.2)
Patients completed Week 48**	14 (93.3)	7 (58.3)	21 (77.8)
Off study drug	1 (6.7)	2 (16.7)	3 (11.1)
Died	1 (6.7)	0 (0)	1 (3.7)
Protocol defined toxicity	0 (0)	1 (8.3)	1 (3.7)
Not able to attend clinic	0 (0)	1 (8.3)	1 (3.7)
Off study	1 (6.7)	1 (8.3)	2 (7.4)
Death	1 (6.7)	0 (0)	1 (3.7)
Subject/parent not able to get to clinic	0 (0)	1 (8.3)	1 (3.7)

N = Number of patients in each cohort.
n (%) = Number (percent) of patients in each subcategory.
*Patient was on study treatment to at least Rel Day 127.
**Patient was on study treatment to at least Rel Day 295.

The mean baseline $\log_{10}$ plasma HIV RNA was 5.7 $\log_{10}$ copies/mL and 18 (69.2%) had > 100,000 copies/mL vs. only 8.3% in Cohorts I-III. Just over half (57.7%; 15/26) were infected with non-clade B but 5 had no viral subtype designation. Three were classified as CDC clinical category B HIV infection and three as category C. Almost all had at least one secondary diagnosis (11/14 Cohort IV and 11/12 Cohort V, mostly involving infections and infestations, including three cases of AIDS encephalopathy in Cohort IV and the most common diagnosis was oral candidiasis (34.6%).

All 14 in Cohort IV had been previously treated with ARV for a mean of 20.1 weeks, and had received a mean of 2.1 prior agents. Most Cohort IV subjects had previously used NRTIs (64.3%) and NNRTIs (57.1%, all as nevirapine) while 35.7% had received PIs (35.7%) all as lopinavir/ritonavir. Most Cohort V subjects had received prior NNRTI (91.7%, all as nevirapine), 25% had received prior NRTI (all as zidovudine) and none had prior use of PIs. No data are available on the mother's PMTCT regimens.

Based on GSS the baseline treatment contained 2 or more active ARV agents in 13/14 in Cohort IV while the other subject had no GSS available at baseline. In Cohort V baseline treatment contained 2 or more active ARV agents in 7/12 (58.4%) while GSS was missing for 5 subjects. At study entry the ARV was adjusted or initiated according to treatment history and baseline resistance data (or using data from the maternal virus if available). The most frequently reported (25%) ARVs used included lamivudine (100%), abacavir (73.1%), lopinavir/ritonavir (65.4%) and zidovudine (26.9%). LPV/r was used in 12 Cohort IV and 5 Cohort V subjects.

Based on sachet counts, 80.7% had at least 90% adherence to raltegravir during the study, and none had < 70% adherence in this age group that required care-givers to ensure dosing.

Based upon the OF approach > 85% in each cohort had ≥1 log drop in HIV RNA or HIV RNA < 400 copies/mL at Week 24. There were 6/13 (46.2%) and 3/8 (37.5%) in respective cohorts with < 50 copies/mL at Week 24. The mean drop in HIV RNA was by 3.1 $\log_{10}$ copies/mL, the mean CD4 cell count increased by 500 cells/mm^3 and the mean CD4 percentage increased by 7.5%. The response rates using the NC=F approach were the same as for the OF approach at week 24.

Table 18. Efficacy analysis by cohort (IV and V); week 48; observed failure approach

Parameter	Cohort IV (N=14)		Cohort V (N=8)		Total (N=22)	
	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	13/14	92.9 (66.1, 99.8)	4/6	66.7 (22.3, 95.7)	17/20	85 (62.1, 96.8)
Proportion of patients with HIV RNA <50 copies/mL	7/13	53.8 (25.1, 80.8)	3/6	50 (11.8, 88.2)	10/19	52.6 (28.9, 75.6)
Proportion of patients with HIV RNA <400 copies/mL	10/14	71.4 (41.9, 91.6)	4/6	66.7 (22.3, 95.7)	14/20	70 (45.7, 88.1)
Proportion of patients with HIV RNA below the limit of quantification	8/14	57.1 (28.9, 82.3)	3/6	50 (11.8, 88.2)	11/20	55 (31.5, 76.9)
	mean	(95 % CI)	mean	(95 % CI)	mean	(95 % CI)
Change from baseline in plasma HIV RNA (log10copies/mL)	-2.8	(-3.8, -1.7)	-2.6	(-5.2, 0)	-2.7	(-3.6, -1.8)
Change from baseline in CD4 cell count (cells/mm3)	278.8	(-185.6, 743.2)	989.5	(81.1, 1897.9)	492.0	(86.3, 897.7)
Change from baseline in CD4 percent	6.4	(1.4, 11.3)	11.1	(3.8, 18.4)	7.8	(3.9, 11.6)

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 Week 48 results did not show any interpretable changes from Week 24. The NC=F results included only one extra subject and were closely comparable to the OF approach. Sustained responses were observed in 85% (17/20; OF) and 81% (NC=F; 17/21) at week 48. Not all subjects had reached Week 48 but of those who did 13/14 in Cohort IV and 4/6 in Cohort V still met the response criteria.

Proportions with < 50 copies/mL increased gradually up to Weeks 24 and 36 reaching just over 50% in each cohort and overall by Week 48.

Proportions with < 400 copies/mL increased more quickly within the first 8 weeks, representing very substantial early drops in viral load

In these young paediatric subjects the mean and median baseline CD4 counts were around 1500 cells/mm^3 although the range was from 131-3648 cells/mm^3. In Cohort IV the increases in CD4 counts were generally of lesser magnitude than Cohort V but the difference from baseline reached ~300 cells/mm^3 by Week 8 and then hovered between 200-400 cells/mm^3 up to Week 48. Despite the considerable variability in Cohort V data there was also a very rapid increase in the first 4-8 weeks of treatment.

The mean change from baseline in CD4 percent over time reflected the early increment in the absolute CD4 cell counts. The overall data indicated that mean changes did not exceed ~10%.

Outcomes by baseline characteristics were not explored for Cohorts IV and V due to the small numbers enrolled.

In Cohort IV there were 4 subjects with virological failure (as defined in the protocol) that occurred between Weeks 24 and 48 and all were rebounders. Based on sachet counts adherence was over 90% in these 4 subjects who failed. No subject in Cohort V had a virological failure. One additional Cohort IV subject experienced rebound at Week 96.

Resistance

Table 19. RAL resistance data for virologic failures patients – cohorts IV and V; all available data

	Cohort IV (N=2) n (%)	Cohort V (N=0) n (%)	Total (All Cohorts) (N=2) n (%)
Number (%) With Mutation at Amino Acid 143, 148 or 155	1 (50.0)	0 (0)	1 (50.0)
With Mutation at Amino Acid 143	0 (0)	0 (0)	0 (0)
With Mutation Y143C	0 (0)	0 (0)	0 (0)
With Mutation Y143H	0 (0)	0 (0)	0 (0)
With Mutation Y143R	0 (0)	0 (0)	0 (0)
With Mutation at Amino Acid 148	0 (0)	0 (0)	0 (0)
With Mutation Q148H	0 (0)	0 (0)	0 (0)
With Mutation Q148K	0 (0)	0 (0)	0 (0)
With Mutation Q148R	0 (0)	0 (0)	0 (0)
With Mutation at Amino Acid 155	1 (50.0)	0 (0)	1 (50.0)
With No Mutation at either Amino Acid 143, 148 or 155	1 (50.0)	0 (0)	1 (50.0)
With Other Known RAL Resistance Mutations†	0 (0)	0 (0)	0 (0)
With No Other Known RAL Resistance Mutations	1 (50.0)	0 (0)	1 (50.0)

†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.

Because of limited blood volumes genotypic data are available for 2/4 subjects with virological failure. Virus from one subject had a mutation at AA155 (without other raltegravir associated resistance mutations) but the other virus tested had no known raltegravir mutations. No baseline phenotypic data were available for those who failed therapy and had resistance testing. The virus with the mutation at AA155 showed reduced phenotypic susceptibility at the time of failure.

Long Term Efficacy for Cohorts I-III

For the evaluation of long-term efficacy data from Cohorts I-III (subjects aged 2 - < 18 years at enrolment) separate analyses were performed for the Final Dose population (96) and the All Treated population (126).

By the 07-Feb-2013 cut-off date all subjects in Cohorts I, IIA and IIB had completed the Week 144 study visit or had already discontinued. For the Cohort III Final Dose subset 50% (10/20) had completed treatment at least up to Week 144. Across the 96 Final Dose subjects 64 (66.7%) had completed treatment at least up to Week 144 and 7 had completed to Week 240. Among the 35 (36.5%) subjects that had discontinued treatment by the data cut-off the most common reason was

non-adherence (13 in Cohort I; 13.5%). Overall 17/96 (17.7%) had discontinued the study altogether and the most common reason was unwillingness to adhere to study requirements (7 in Cohort I; 7.3%).

Based on the OF approach in Cohorts I-III after 144 weeks of treatment 62% had at least one log drop in HIV RNA or HIV RNA <400 copies/mL, 47.9% had <50 copies/mL and 57.7% had < 400 copies/mL. These overall rates are driven by the relatively low percentages in the largest Final Dose Cohort (I) with higher rates in the small numbers in each of the younger Cohorts. The overall mean increases at Week 144 from baseline in CD4 cell count and percent were 58.1 cells/mm3 and 4.6%, respectively. The negative mean change in counts in two Cohorts seems to be driven by one or a few individuals based on the range.

Using the NC=F approach for the Final Dose population the proportion meeting the response criteria falls to 52% and, as for the OF, is lowest in the adolescents (Cohort I). Also, 40% had < 50 copies/mL and 48% < 400 copies/mL.

The All Treated population for both methods of analysis gave results across Cohorts that were similar to those reported for the Final Dose population. The table presents virological failures up to Week 144 for Cohorts I-III in the All Treated population.

Of the 49 who had failed by Week 144 and had genotypic data there were 18 subjects across all cohorts with viruses that displayed signature raltegravir genotypic mutations. Six of the 31 viruses with non-signature raltegravir mutations had other mutations known to confer raltegravir resistance and 25 had mutations with no known raltegravir resistance.

Phenotypic sensitivity (IC50 fold change compared to the wild-type reference) of viruses isolated at baseline and after virological failure showed that baseline samples displayed mean and median IC50 fold-change of 1.0 and 1.0 (range 0.7 to 1.5), respectively, indicating phenotypic susceptibility. After virological failure there were mean and median fold-changes in IC50 of 34.8 and 1.0 (range 0.6 to 150.2). Per Monogram Biosciences, a fold change IC50>1.5 is above the technical assay cut-off and suggests the possibility of true raltegravir resistance.

Finally, an appended table lists all the raltegravir phenotypic and genotypic resistance data for those who failed in Cohorts I-III up to the February 2013 cut-off date. Compared to the Table shown above for Weeks 0-144 the assessor counted:

- 33 in Cohort I of which 2 were non-responders (vs. 25 shown above)
- 10 in Cohort IIA of which all were rebounders (vs. 9 shown above)
- 8 in Cohort IIB of which one was a non-responder (vs. 7 shown above)
- 9 in Cohort III of which 2 were non-responders (vs. 8 shown above)

Therefore the total number that failed in Cohorts I-III increases from 49 to 60 but most of the difference is in the adolescents. Almost all those who failed had previously met the criteria for a virological response and were therefore classed as rebounders.

2.5.1. Discussion on clinical efficacy

Cohorts IV and V

Initiation of a regimen containing raltegravir achieved a very marked drop in viral load and by Week 24 20/22 met the response criteria although only 9/21 (43%) had < 50 copies/mL. Despite the relatively high baseline CD4 counts (*vs*. older HIV infected) in the majority of subjects in these Cohorts the mean

CD4 cell count increased by 500 cells/mm3. There was no substantial change by Week 48 (but only 7/12 in Cohort V had data available to Week 48 in the CSR) by which time 10/19 with data had < 50 copies/mL.

The numbers in these two youngest Cohorts are too small to draw firm conclusions regarding efficacy and the Applicant did not look at outcomes by various factors due to the total study sample size. However, it is notable that at Week 24 across the Final Dose subjects in Cohorts I, IIA, IIB and III the OF approach showed that 71.6% met the response criteria while the proportion with <50 copies/mL was 53.7%. Also, the two pivotal Phase 3 studies in treatment-experienced adults gave response rates at the HIV RNA <50 copies/mL level for raltegravir plus OBT that were 62% at Week 48 and 57% at Week 96. Therefore, broadly speaking, the data for Cohorts IV and V are in keeping with those in older subjects.

There have been 5 subjects in Cohort IV with rebound from Week 36 onwards but there are too few data to interpret the possible reasons. In addition, there are few data on the range of rebound rates that can be expected in this age group that could be used to place the results in some perspective. The high risk for de novo class resistance during suboptimal treatment should be more emphasized in the SmPC, therefore the CHMP considered that the subheading “resistance” in section 5.1 needed an update to reflect that clinical practice full cross resistance to elvitegravir, and for a substantial proportion a negative impact on the efficacy of dolutegravir can be observed. In addition, it was considered necessary to indicate the number of patients with virological failure in the efficacy outcomes tables in the SmPC.

Cohorts I-III

Overall 64/96 (66.7%) Final Dose subjects had data at least up to Week 144. Among 35 subjects that had discontinued treatment by the data cut-off the most common reason was non-adherence (13 in Cohort I; 13.5%). Also, 17/96 (17.7%) had discontinued the study altogether and the most common reason was unwillingness to adhere to study requirements (7 in Cohort I; 7.3%). This picture points to some of the difficulties in treating adolescent subjects.

Generally, for those who were followed up the rates with virological response (62%) and < 50 copies/mL (47.9%) do not point to marked loss of efficacy vs. Week 48. In the Final Dose population 49 had failed by Week 144 but the difference vs. Week 48 was mainly driven by Cohort I. Overall, 18 of the subjects with genotypic data had viruses that displayed signature raltegravir genotypic mutations. Almost all those who failed had previously met the criteria for a virological response and were therefore classified as rebounders.

2.5.2. Conclusions on the clinical efficacy

Study 022 was not designed to provide definitive evidence of efficacy. For Cohorts I-III it was observed that the response rates and the percentages that achieved < 50 copies/mL and sustained these responses to at least Week 48 were in keeping with several other studies using different regimens in children of these age groups. For Cohorts IV and V it can only be observed in such small numbers and with limited follow-up that the data do not point to any major concerns. Taking together the PK, PK/PD and efficacy data, such as they are, a dose of approximately 6 mg/kg could be accepted.

The doses achieved using the protocol will fairly closely approximate 6 mg/kg for body weights up to about 11.6 kg. There is more variability between 11.6 to 14 kg (80 mg vs. calculated 70-84 mg) and for the 14-20 kg range the dose of 100 mg is rather more of a compromise vs. the calculated doses, which would be from 84-120 mg. Since no child switched to the CT but weights and doses did increase the applicant justified these mg/kg dose ranges vs. the target of ~6 mg/kg based on the actual

numbers who received these doses and their PK data. The applicant proposal for parallel dosing for oral suspension and CT seemed appealing. The modifications to the oral suspension regimens will mostly slightly increase the dose, which is better for efficacy. The small modifications do not seem at all likely to impact on safety, taking into account also that a relationship between plasma exposures and specific AEs has not been identified.

Therefore, the CHMP considered that the modifications that have been made by the MAH to all three SmPCs (i.e. poloxamer tables, CT and suspension) are acceptable.

2.6. Clinical safety

2.6.1. Introduction

The primary purpose of this paediatric application was to provide 24 and 48 week data from IMPAACT P1066 in children aged from 4 weeks to <2 years (n=26) that demonstrate the favourable safety profile of raltegravir GFS at doses proposed dosing recommendations.

The main focus of this application was on new safety data from Cohorts IV and V. Longer-term safety data from the Final Dose population of Cohorts I-III (67 adult tablet and 33 CT) was also provided.

The approach in the safety evaluation for infants and toddlers included in Cohorts IV and V was similar to that used in the paediatric application in children from 2 to 18 years. A review of the overall adverse event profile, serious adverse events (SAE), adverse events Grade 3 or greater, events considered by the investigator as potentially related to raltegravir use, and events leading to treatment discontinuation was included. A review of safety by demographic subgroup (i.e., gender, race and ethnicity) was not performed due to the modest size of the study population.

Experience with off-label paediatric use of raltegravir was limited to the commercially available adult 400 mg tablet. A literature review of paediatric raltegravir use was also conducted and in addition, the Applicant reviewed the post-marketing safety database for reports of paediatric use, from 31-Dec-2010 through 31-Dec-2012.

Patient exposure

For Cohorts IV and V the exposure up to the February 2013 cut-off date is shown below.

Number of Patients on Study Drug by Dose and Actual Duration of Treatment by Formulation - Granules for Suspension; All Available Data as of Feb 07, 2013

Dose	<=4 wks	>4 - <=12 wks	>12 - <=24 wks	>24 - <=48 wks	>48 - <=72 wks	>72 - <=96 wks	>96 - <=120 wks	>120 - <=144 wks	>144 wks	Total	Range of Days on Study Drug	Mean Number of Days on Study Drug
Any Dose	1	2	1	2	8	9	3	0	0	26	(7, 791)	448
20mg BID	0	1	0	0	0	0	0	0	0	1	(29, 29)	29
25mg BID	1	0	0	0	0	0	0	0	0	1	(28, 28)	28
30mg BID	2	8	0	0	0	0	0	0	0	10	(28, 84)	56
40mg BID	1	10	3	2	0	0	0	0	0	16	(7, 225)	90
50mg BID	3	4	1	8	1	0	0	0	0	17	(8, 337)	155
60mg BID	0	0	5	7	3	1	0	0	0	16	(85, 590)	250
80mg BID	0	1	5	4	1	0	0	0	0	11	(58, 396)	174
100mg BID	1	2	0	1	0	1	0	0	0	5	(5, 622)	211

Although some patients may have taken two or more different dosages, they have been counted only one time each, on the 'ANY DOSE' row.

For Cohorts I and IIA (adult tablet) and Cohorts IIB and III (CT) the mean (range) number of days on raltegravir was 1052 (28 to 1702) days and 948 (250 to 1317) days, respectively. Overall, 39/67 (58.2%) and 18/33 (54.5%) in respective Cohorts exceeded 144 weeks. Total daily doses in Cohorts IIB and III ranged from 75 to 300 mg twice daily.

Adverse events

In Cohorts IV and V by Week 24 all subjects had at least one clinical AE and 7 had at least one SAE.

Summary of clinical adverse events by cohort (IV and V); Week 0-48

	Cohort IV (N=14) n (%)	Cohort V (N=12) n (%)	Total (N=26) n (%)
With one or more clinical adverse events	14 (100)	12 (100)	26 (100)
With no clinical adverse event	0 (0)	0 (0)	0 (0)
With one or more serious clinical adverse events	6 (42.9)	2 (16.7)	8 (30.8)
With one or more serious drug related* clinical adverse events	0 (0)	1 (8.3)	1 (3.8)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	1 (8.3)	1 (3.8)
With one or more Grade 3 or greater clinical adverse events	4 (28.6)	2 (16.7)	6 (23.1)
With one or more Grade 3 or greater drug related* clinical adverse events	0 (0)	1 (8.3)	1 (3.8)

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 raltegr avir.
Complete Week 48 data (Patient was on study treatment to at least Rel Day 295) is available for 58.3% (7/12) of Cohort V patients.

By Week 48 one additional subject had at least one SAE and one additional subject had at least one Grade 3 AE. Up to February 2013 one subject had a SAE of gastroenteritis at Day 415 and died on Day 418. This subject had reported Grade 3 wheezing and dyspnoea prior to Week 24 and then had Grade 3 gastroenteritis along with Grade 3 diarrhoea and vomiting reported on Day 415.

Up to Week 24 the most frequently reported AEs were cough (53.8%), nasal congestion (42.3%), diarrhoea (38.5%), rash (38.5%), pyrexia (30.8%), pharyngitis (30.8%) and rhinorrhoea (30.8%).

Among all AEs some events might be considered as CDC Category A events for mildly symptomatic HIV infection in infants/toddlers (<2 years of age), although these were not formally assessed as such. These events include respiratory disorders, otitis media, failure to thrive, dermatitis, oral candidiasis, pneumonia, lymphadenopathy and hepatomegaly.

Up to Week 48 there were small increases in numbers reporting some specific AEs but the general pattern of commonest AEs remained the same as shown below.

All Clinical Adverse Events by Cohort (IV and V); (Incidence >=15% in One or More Cohorts); Weeks 0-48

	Cohort IV (N=14)	Cohort V (N=12)	Total (N=26)
System Organ Class **Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Number of patients with one or more adverse events	14 (100)	12 (100)	26 (100)
Blood and lymphatic system disorders	5 (35.7)	1 (8.3)	6 (23.1)
Ear and labyrinth disorders	3 (21.4)	3 (25)	6 (23.1)
Ear congestion	0 (0)	2 (16.7)	2 (7.7)
Eye disorders	3 (21.4)	1 (8.3)	4 (15.4)
Gastrointestinal disorders	10 (71.4)	8 (66.7)	18 (69.2)
Diarrhoea	6 (42.9)	6 (50)	12 (46.2)
Vomiting	4 (28.6)	2 (16.7)	6 (23.1)
General disorders and administration site conditions	6 (42.9)	5 (41.7)	11 (42.3)
Pyrexia	6 (42.9)	5 (41.7)	11 (42.3)
Infections and infestations	13 (92.9)	6 (50)	19 (73.1)
Gastroenteritis	3 (21.4)	2 (16.7)	5 (19.2)
Otitis media	4 (28.6)	2 (16.7)	6 (23.1)
Pharyngitis	5 (35.7)	3 (25)	8 (30.8)
Investigations	3 (21.4)	1 (8.3)	4 (15.4)
Metabolism and nutrition disorders	3 (21.4)	3 (25)	6 (23.1)
Failure to thrive	2 (14.3)	2 (16.7)	4 (15.4)
Respiratory, thoracic and mediastinal disorders	11 (78.6)	10 (83.3)	21 (80.8)
Cough	8 (57.1)	7 (58.3)	15 (57.7)
Dyspnoea	3 (21.4)	1 (8.3)	4 (15.4)
Nasal congestion	4 (28.6)	8 (66.7)	12 (46.2)
Rhinorrhoea	4 (28.6)	5 (41.7)	9 (34.6)
Skin and subcutaneous tissue disorders	4 (28.6)	8 (66.7)	12 (46.2)
Rash	3 (21.4)	7 (58.3)	10 (38.5)
Rash generalized	0 (0)	2 (16.7)	2 (7.7)

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.
Adverse event terms are from MedDRA Version 15.1.
Although a patient may have had two or more occurrences of a specific adverse event, the patient is counted only once for that adverse event. If a patient has more than one adverse event within a System Organ Class, the patient is counted once for each specific adverse event but only once in the System Organ Class row.
Complete Week 48 data (Patient was on study treatment to at least Rel Day 295) is available for 58.3% (7/12) of Cohort V patients.

Grade 3 or greater clinical adverse events had been reported by 6 subjects (23.1%) at Week 48. One of these events (staphylococcal abscess) occurred between Weeks 24 and 48. This subject also had a SAE of abdominal abscess.

Grade 3 or Greater Clinical Adverse Events by Cohort (IV and V); (Incidence >0% in One or More Cohorts); Weeks 0-48

	Cohort IV (N=14)	Cohort V (N=12)	Total (N=26)
System Organ Class **Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Number of patients with one or more adverse events	4 (28.6)	2 (16.7)	6 (23.1)
Blood and lymphatic system disorders	1 (7.1)	0 (0)	1 (3.8)
Iron deficiency anaemia	1 (7.1)	0 (0)	1 (3.8)
Gastrointestinal disorders	0 (0)	1 (8.3)	1 (3.8)
Diarrhoea	0 (0)	1 (8.3)	1 (3.8)
Infections and infestations	3 (21.4)	2 (16.7)	5 (19.2)
Bronchiolitis	1 (7.1)	0 (0)	1 (3.8)
Gastroenteritis	0 (0)	1 (8.3)	1 (3.8)
Otitis media	1 (7.1)	0 (0)	1 (3.8)
Pneumocystis jiroveci pneumonia	0 (0)	1 (8.3)	1 (3.8)
Staphylococcal abscess	1 (7.1)	0 (0)	1 (3.8)
Respiratory, thoracic and mediastinal disorders	1 (7.1)	0 (0)	1 (3.8)
Dyspnoea	1 (7.1)	0 (0)	1 (3.8)
Wheezing	1 (7.1)	0 (0)	1 (3.8)
Skin and subcutaneous tissue disorders	0 (0)	1 (8.3)	1 (3.8)
Dermatitis allergic	0 (0)	1 (8.3)	1 (3.8)
Drug eruption	0 (0)	1 (8.3)	1 (3.8)
Vascular disorders	0 (0)	1 (8.3)	1 (3.8)
Hypovolaemic shock	0 (0)	1 (8.3)	1 (3.8)

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.
Adverse event terms are from MedDRA Version 15.1.
Although a patient may have had two or more occurrences of a specific adverse event, the patient is counted only once for that adverse event. If a patient has more than one adverse event within a System Organ Class, the patient is counted once for each specific adverse event but only once in the System Organ Class row.
Complete Week 48 data (Patient was on study treatment to at least Rel Day 295) is available for 58.3% (7/12) of Cohort V patients.

There were 2 drug-related Grade 3 or greater events that occurred in a single subject up to the data cut-off date and both occurred by Week 24. These events of drug eruption (diagnosis) and allergic dermatitis (symptom) occurred in a 17-week old child in Cohort V with onset on Day 7. The events were considered possibly drug related and resulted in discontinuation. However, this child also had *Pneumocystis jiroveci* pneumonia [PCP] (considered not related to study therapy) 1 day prior to the onset of the drug-related rash and concomitant treatment included other agents that are associated with rash (including benzyl penicillin, cefotaxime, vancomycin and co-trimoxazole) as well as the ARV. Also the MAH considered that immune reconstitution syndrome (IRS) could explain new onset of PCP within one week of starting therapy and immediately before the episode of rash.

AEs of special interest included:

- Eight (30.8%) reported metabolism and nutrition disorders, including 9 occurrences of decreased appetite and failure to thrive but none was Grade 3 or greater.
- One infant who had received BCG at birth had *Mycobacterium bovis* (BCG) IRS reported 4 weeks after initiating raltegravir, abacavir and lamivudine. The subject had no significant clinical or laboratory abnormalities (Grade 2 or higher) at the time of diagnosis and the event was not considered serious or drug related. It had resolved by Week 24 despite continuing study treatment.
- Skin and subcutaneous tissue disorders were reported in 13/26 (50%) up to February 2013. Those with rash were taking NRTIs and other agents such as co-trimoxazole and none was taking darunavir.

- Two non-serious AEs of pruritus were reported (eye pruritus and ear pruritus) but were not Grade 3.
- Two subjects had Grade 2 ALT elevations and one had a Grade 2 AST elevation that did not worsen or result in study drug discontinuation.
- There was one non-serious AE of hepatomegaly that was not Grade 3 or greater.
- Gastrointestinal disorders were reported in 18 (69.2%) up to February 2013. The most frequently reported were diarrhoea (14/26, 53.8%) and vomiting (7/26, 26.9%).

In Cohorts I, IIA, IIB and III (Final Dose) up to Week 144 clinical AEs of Grades 1–4 were reported by 92.7% and 21.9% reported at least one SAE (including the previously reported subject with 3 drug-related SAEs of abnormal behaviour, psychomotor hyperactivity and insomnia that did not lead to discontinuation). There were 7 new SAEs and 10 new AEs of at least Grade 3 reported since Week 48 but none was considered drug-related. No subjects had discontinued due to AEs or died.

The most frequently reported AEs were cough (58.3%), pyrexia (47.9%), rhinorrhoea (38.5%), nasal congestion (37.5%), vomiting (29.2%), oropharyngeal pain (28.1%) and headache (27.1%).

Grade 3 or greater clinical adverse events were reported by 26% in Cohorts I-III and 12 additional subjects reported such AEs after Week 48. Overall 15.6% reported such AEs in the Infections and Infestations SOC and the most frequently reported (3%) included pyrexia, pneumonia, and influenza-like illness.

Serious adverse event/deaths/other significant events

In Cohorts IV and V SAEs had been reported by 7 subjects up to Week 24 and 8 by Week 48. Dyspnoea was reported in 2 but all other SAEs were reported in a single subject.

Serious Clinical Adverse Events by Cohort (IV and V); (Incidence >0% in one or more cohorts); Weeks 0-48

System Organ Class Preferred Term	Cohort IV (N=14) n (%)	Cohort V (N=12) n (%)	Total (N=26) n (%)
Number of patients with one or more adverse events	6 (42.9)	2 (16.7)	8 (30.8)
Blood and lymphatic system disorders	1 (7.1)	0 (0)	1 (3.8)
Anaemia	1 (7.1)	0 (0)	1 (3.8)
Infections and infestations	2 (14.3)	1 (8.3)	3 (11.5)
Abdominal abscess	1 (7.1)	0 (0)	1 (3.8)
Gastroenteritis	1 (7.1)	0 (0)	1 (3.8)
Pneumocystis jiroveci pneumonia	0 (0)	1 (8.3)	1 (3.8)
Metabolism and nutrition disorders	2 (14.3)	0 (0)	2 (7.7)
Hypoglycaemia	1 (7.1)	0 (0)	1 (3.8)
Hypokalaemia	1 (7.1)	0 (0)	1 (3.8)
Respiratory, thoracic and mediastinal disorders	3 (21.4)	0 (0)	3 (11.5)
Asthma	1 (7.1)	0 (0)	1 (3.8)
Dyspnoea	2 (14.3)	0 (0)	2 (7.7)
Skin and subcutaneous tissue disorders	0 (0)	1 (8.3)	1 (3.8)
Rash erythematous	0 (0)	1 (8.3)	1 (3.8)
Vascular disorders	0 (0)	1 (8.3)	1 (3.8)
Hypovolaemic shock	0 (0)	1 (8.3)	1 (3.8)

One of these SAEs was the Grade 3 drug-related allergic rash, which led to discontinuation of study drug (see above). Raltegravir was discontinued as it was believed to be related to the worsening rash but other ARVs were continued. The generalised erythematous rash was reported as recovered/resolved after one week and PCP (severe) after two weeks.

From 24-48 weeks there was only one additional SAE – the case of abdominal abscess considered not related (see above). One further SAE was reported up to the cut-off date. This was the case mentioned above of gastroenteritis resulting in death.

In Cohorts I, IIA, IIB and III by Week 144, 21/96 Final Dose subjects had reported at least one SAE. There were 7 new SAEs reported since Week 48. None was considered related to raltegravir by the investigator or led to discontinuation. By the cut-off date, 29 (23%) All Treated subjects had reported SAEs, mostly in the Infections and Infestations SOC (19 subjects). The previously reported case of agitation not considered to be related to study therapy had since been admitted to a detention centre and discontinued from study therapy. There were no drug related SAEs reported after Week 144.

Laboratory findings

In Cohorts IV and V laboratory AEs of any grade were reported by 88.5% of subjects by Week 24 but no-one discontinued. Laboratory SAEs were reported in 2 (7.7%) but were not considered drug related. Grade 3 or greater laboratory AEs occurred in 4 subjects.

One subject in Cohort IV had two AES with onset on Day 76 (non-drug related SAE of hypoglycaemia, non-drug related AE of blood bilirubin increased, Grade 3 drug-related AE of blood glucose decreased and Grade 3 drug-related AE of blood bilirubin increased). After database lock, the site updated the causality for both Grade 3 events to non-treatment related.

Up to Week 48 there was one additional laboratory AE in a Cohort V subject, which was non-serious and not of Grade 3 or 4. Up to the cut-off date the laboratory safety profile on review of all available Cohort IV and V data was generally similar across both cohorts to those at Weeks 24 and 48. Laboratory AEs were reported in 92.3% and the most frequently reported included blood potassium increased (38.4% [10/26]; 9/10 were Grade 1), neutrophil count decreased (34.6% [9/26]); no Grade 4) and blood sodium decreased (30.8% [8/26]; all Grade 1).

Grade 3 or greater laboratory AEs were reported in 4 (15.4%) subjects up to Week 24 of which two involved neutrophil count decreased. None of these was considered serious. No additional Grade 3 or greater laboratory adverse events were reported between Week 24 and the data cut-off date.

Laboratory SAEs were reported in 2 Cohort IV subjects (7.7%) by Week 24. One was the case with increased blood bilirubin mentioned above and the other involved lipase increased that led to a temporary interruption of study therapy. On Day 11 there was Grade 4 lipase (Grade 2 at baseline) originally reported as drug related but due to confounding co-infections with CMV and EBV the investigator ultimately determined that the increased lipase was not related to raltegravir. No additional laboratory SAEs were reported between Week 24 and the cut-off date. Analyses of all data showed that mean values of ALT and AST modestly decreased in Cohorts IV and V, whereas there were modest increases in haemoglobin, platelets and absolute neutrophil counts to Week 48. There were no specific abnormal laboratory values of clinical relevance observed in Cohorts IV and V.

In Cohorts I, IIA, IIB and III laboratory AEs of any grade (Grades 1–4) were reported by 94.8% of Final Dose subjects. There were 10 subjects with laboratory events reported since Week 48 and in 5/10 these were Grade 3 or greater. There were no new drug related Grade 3 or drug related laboratory SAEs and no discontinuations or deaths due to laboratory AEs.

Adverse events leading to discontinuation

In Cohorts IV and V two subjects (7.7%) discontinued from the study due to AEs. One was the Cohort V subject who discontinued due to a serious Grade 3 allergic rash. The second was the Cohort IV subject who died due to gastroenteritis.

In Cohorts I, IIA, IIB and III two (2.1%) subjects in the Final Dose population discontinued due to a drug related AE. One was the case who died on Day 597 due to pneumonia and the second was the case who discontinued due to Grade 4 agitation. There was a further subject who discontinued due to Grade 3 renal failure (not serious and not drug related) that occurred on Day 1443 of study therapy, after a report of a Grade 3 septic shock (serious and not related) that occurred on Day 1436 of study therapy. There were no other discontinuations due to clinical or laboratory AEs among All Treated subjects by the cut-off date.

2.6.2. Discussion on clinical safety

The additional safety data reported in the youngest age groups do not give rise to any new or major concerns. In the older children there were no new concerns raised by the longer-term exposure data. The tables of subject disposition as shown in the section on efficacy demonstrate that very few subjects have discontinued due to AEs.

2.6.3. Conclusions on clinical safety

The safety data provided in the youngest age groups do not give rise to any new or major concerns. In the older children there were no new concerns raised by the longer-term exposure data. Very few subjects discontinued due to adverse events.

2.6.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk management plan

2.7.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan version 10.0.

PRAC Advice

The PRAC considered the updates to Risk Management Plan relating to a new formulation, namely, granules for suspension for use in paediatric patients aged 4 weeks to less than 2 years of age as acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of safety concerns	
Important Identified Risks	• Immune reconstitution inflammatory syndrome • Drug resistance • Drug interaction with rifampin and other strong UGT1A1 inducers • Extent of pharmacokinetic (PK) variability and impact, if any, on • pharmacodynamics (PD) • Serious Rash • Drug interaction with magnesium and/or aluminum antacids
Important Potential Risks	• Malignancies • Increase in liver enzymes • Lipodystrophy/Fat maldistribution • Increase in CPK with clinical manifestations; myopathy, rhabdomyolysis • Depression, suicidal ideation, suicidal behaviors • Medication Error related to potential substitution of pediatric formulations for non-chewable (adult) tablets (pediatric formulations and non-chewable tablets are not bioequivalent)
Missing Information	• Potential exposure during pregnancy • Long-term safety data • Populations studied • Populations insufficiently studied/not studied: • Exposure in neonates less than 4 weeks of age

Summary of safety concerns	
	• Exposure in elderly patients • Exposure in patients with severe hepatic impairment

Pharmacovigilance plans

The PRAC, having considered the updated data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan remain sufficient to monitor the effectiveness of the risk minimisation measures

Ongoing and planned studies in the PhV development plan

Study / Activity	Safety concern address	Date for Submission (target dates)
Observational studies		
Observational post authorization safety study (058) (Category 3)	Malignancy, selected clinically important liver outcomes, lipodystrophy, all-cause mortality, long-term safety data	The final study report is expected by 31- DEC- 2014.
Observational post authorization safety study (EPO8025.006) (Category 3)	Malignancy, selected clinically important liver outcomes, lipodystrophy, all-cause mortality, serious rash, selected clinically important muscle outcomes, long-term safety data	The final study report is expected by 31- DEC- 2014.
Collaboration with the D:A:D Cohort Study (Category 3)	Monitored risks include cardiovascular risk; however, the study outcomes are not specific to raltegravir.	The MAH will support the collaboration until 2017 at which time the obligation will be completed.
Clinical studies		
Study 022 (Category 3)	Long term safety data in populations studied pediatric patients ages 4 weeks to 18 years.	Submission 31 Dec 2017
Study 022- chewable tablet Ctrough substudy (Version 3.0, LOA #4) (Category 3)	Exposure in neonates less than 4 weeks of age	Submission 31- DEC- 2017.
Study 083 (ex-US) (Compassionate access program)	Long term safety data in populations studied pediatric patients ages 4 weeks to <12 years.	SAE's are being collected and reported in the PSUR.
Study 135 (US) (Compassionate access program)	Long term safety data in populations studied pediatric patients ages 4 weeks to <12 years.	SAE's are being collected and reported in the PSUR.
Registry		
Antiretroviral Pregnancy Registry (Category 3)	Exposure during pregnancy	Provided every 6 months

Risk minimisation measures

Summary of Safety Concerns and Risk Minimization Activities

Safety Concern	Routine Risk Minimization Measures	Additional measure
Important Identified Risks		
IRIS	Listed as class labeling warning in Section 4.4 and 4.8 of the SmPC. Package leaflet—Section 2, What you need to know before you take ISENTRESS and Section 4, Possible side effects	None
Drug resistance	Listed under SmPC Sections 4.4 and 5.1. Package leaflet—Section 3, How to take ISENTRESS.	None
Drug interactions with rifampin and	Listed under SmPC Sections 4.4 and 4.5.	None

Safety Concern	Routine Risk Minimization Measures	Additional measure
other strong UGT1A1 inducers	Package leaflet—Section 2, What you need to know before you take ISENTRESS	
Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD)	Listed under SmPC Sections 4.4, 4.5 and 5.2.	None
Serious rash	Listed under SmPC Section 4.4 and 4.8. Package leaflet—Section 2, What you need to know before you take ISENTRESS and Section 4, Possible side effects	None
Drug interaction with magnesium and/or aluminum antacids	Listed under SmPC Section 4.4 and 4.5 Package leaflet—Section 2, What you need to know before you take ISENTRESS	None
Important potential risks		
Malignancies	Listed under SmPC Section 4.8. Package leaflet—Section 4, Possible side effects	None
Increase in liver enzymes	Listed under SmPC Section 4.8. Package leaflet—Section 4, Possible side effects	None
Lipodystrophy/Fat Maldistribution	Listed under SmPC Section 4.8. Package leaflet—Section 4, Possible side effects	None
Increase in CPK with clinical manifestations; myopathy, rhabdomyolysis	Listed under SmPC Section 4.4 and 4.8. Package leaflet—Section 2, What you need to know before you take ISENTRESS and Section 4, Possible side effects	None
Depression, Suicidal ideation, Suicidal behaviours	Listed under SmPC Section 4.4 and 4.8. Package leaflet—Section 2, What you need to know before you take ISENTRESS and Section 4, Possible side effects	None
	Listed in SmPC Section 4.2, Posology and method of administration, of the SPC. Package leaflet—Section 3, How to take ISENTRESS	
Missing information		
Exposure during pregnancy	Listed in SmPC Section 4.6. Package leaflet—Section 2, What you need to know before you take ISENTRESS	None
Long-term safety data Populations studied Populations insufficiently studied/not studied	To be determined based on analysis of long-term safety data.	None
Exposure in neonates less than 4 weeks of age	SmPC Section 4.2 notes that safety and efficacy has not been established in patients below 4 weeks of age. Lack of PK in this population is discussed in Section 5.2. Package leaflet—Section 2, What you need to know before you take ISENTRESS	None
Exposure in elderly patients	SmPC Section 4.2 includes information about limited information in the elderly. PK information is included in Section 5.2.	None
Exposure in patients with severe hepatic impairment	SmPC Section 4.2 includes dosing recommendations in patients with hepatic impairment. The SmPC also includes language in Section 4.4 related to patients with severe hepatic impairment. Package leaflet—Section 2, What you need to know before you take ISENTRESS	None

The CHMP endorsed this advice without changes.

2.8. Update of the Product information

A Product Information was introduced for ISENTRESS 100 mg granules for oral suspension.

Updates affect the Product Information for ISENTRESS 400 mg film-coated tablets as well as the ISENTRESS 100 mg and 25 chewable tablets. The changes to the product Information are presented as new text underlined and deleted text marked as strikethrough.

As a consequence of this new indication, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated.

4.1 Therapeutic indications

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, toddlers and infants from the age of ~~2 years~~4 weeks (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration

Children and adolescents
If at least 25 kg, ~~T~~the recommended dosage is 400 mg (one tablet) twice daily. If unable to swallow a tablet, consider the chewable tablet.~~for adolescents (12 to 18 years), and children 6 to less than 12 years of age, weighing at least 25 kg~~

ISENTRESS is also available in a chewable tablet formulation for children ~~2 through 11to less than 12 years of age and~~ weighing at least 11~~2~~ kg and in granules for oral suspension formulation for infants and toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg. Refer to the chewable tablet and granules for oral suspension EU-SmPCs for additional dosing information.

The maximum dose of the chewable tablet is 300 mg twice daily. Because the formulations are not bioequivalent, ~~do not substitute~~ neither the chewable tablets nor the granules for oral suspension should be substituted for the 400 mg tablet (see section 5.2). The chewable tablets and the granules for oral suspension have not been studied in HIV-infected adolescents (12 to 18 years) or adults.
Paediatric population

Safety and efficacy of raltegravir in ~~children~~ infants below ~~2 years~~4 weeks of age have not yet been established. No data are available.

Method of administration

Oral use.

ISENTRESS 400 mg tablets can be administered with or without food.

~~It is not recommended to~~ The tablets should not be chewed, crushed or split t~~he 400 mg tablets~~ due to anticipated changes in the pharmacokinetic profile

4.8 Undesirable effects

~~§ One paediatric patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity and abnormal behaviour, this patient also had insomnia.~~

5.1 Pharmacodynamic properties

Resistance

Mutations conferring resistance to raltegravir generally also confer resistance to the integrase strand transfer inhibitor elvitegravir. Mutations at amino acid 143 confer greater resistance to raltegravir than to elvitegravir, and the E92Q mutation confers greater resistance to elvitegravir than to raltegravir. Viruses harbouring a mutation at amino acid 148, along with one or more other raltegravir resistance mutations, may also have clinically significant resistance to dolutegravir. ~~Preliminary data indicate that there is potential for at least some degree of cross-resistance to occur between raltegravir and other integrase inhibitors.~~

Clinical experience

Paediatric population

Children and adolescents 2 to 18 years of age~~2 to 18 Years of Age~~

Raltegravir has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 ~~through~~ to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2). Of the 126 patients, 96 received the recommended dose of ISENTRESS.

Infants and toddlers 4 weeks to less than 2 years of age 4 Weeks to less than 2 Years of Age

Raltegravir has also been studied in 26 HIV 1 infected infants and toddlers 4 weeks to less than 2 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2).

In these 26 infants and toddlers, the frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced a Grade 3 serious drug related allergic rash that resulted in treatment discontinuation.

Children and adolescents 2 to 18 years of age~~2 to 18 Years of Age~~

IMPAACT P1066 is a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 ~~through~~ to18 years of age. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 ~~through~~ to 18 years of age) or the chewable tablet formulation (2 ~~through~~ to less than 12~~11~~ years of age). Raltegravir was administered with an optimized background regimen.

Minor typo corrections and revisions to the title of Table 4 were introduced.

Infants and toddlers 4 weeks to less than 2 years of age

IMPAACT P1066 also enrolled HIV-infected, infants and toddlers 4 weeks to less than 2 years of age who had received prior antiretroviral therapy either as prophylaxis for prevention of mother to child transmission (PMTCT) and/or as combination antiretroviral therapy for treatment of HIV infection. Raltegravir was administered as granules for oral suspension formulation without regard to food in combination with an optimized background regimen that included lopinavir plus ritonavir in two-thirds of patients.

Table 5
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066 (4 weeks to less than 2 years of age)

Parameter	***N=26***
Demographics	
Age *(weeks), median [range]*	*28 [4 -100]*
Male Gender	*65 %*
Race	
Caucasian	*8 %*
Black	*85 %*
Baseline Characteristics	
Plasma HIV-1 RNA *(log_{10} copies/ml), mean [range]*	*5.7 [3.1 - 7]*

Parameter	**N=26**	
CD4 cell count (cells/mm^3), median [range]	1400 [131 -3648]	
CD4 percent, median [range]	18.6 % [3.3 – 39.3]	
HIV-1 RNA >100,000 copies/ml	69 %	
CDC HIV category B or C	23 %	
Prior ART Use by Class		
NNRTI	73 %	
NRTI	46%	
PI	19 %	
Response	**Week 24**	**Week 48**
Achieved ≥1 log_{10} HIV RNA drop from baseline or <400 copies/ml	91 %	85 %
Achieved HIV RNA <50 copies/ml	43 %	53 %
Mean CD4 cell count (%) increase from baseline	500 cells/mm^3 (7.5 %)	492 cells/mm^3 (7.8 %)
Virologic failure	**Week 24**	**Week 48**
Non-responder	0	0
Rebounder	0	4
Number with genotype available*	0	2

*One patient had a mutation at the 155 position.

5.2 Pharmacokinetic properties

Special populations

Paediatric population

Based on a formulation comparison study in healthy adult volunteers, the chewable tablet and granules for oral suspension have~~has~~ higher oral bioavailability compared to the 400 mg tablet. In this study, administration of the chewable tablet with a high fat meal led to an average 6 % decrease in AUC, 62 % decrease in Cmax, and 188 % increase in C12hr compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food. The effect of food on the granules for oral suspension formulation was not studied.

Table ~~5~~ 6 displays pharmacokinetic parameters in the 400 mg tablet (6 through 18 years of age), and the chewable tablet (2 through 11 years of age), and the granules for oral suspension, by body weight.

Table 5 has been replaced by Table 6 below

Table ~~5~~6: Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in Section 4.2

Body weight	**Formulation**	**Dose**	**N***	**Geometric mean (%CV†) AUC_{0-12hr} (µM•hr)**	**Geometric mean (%CV†) C_{12hr} (nM)**
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 (121 %)	233 (157 %)
≥25 kg	Chewable tablet	Weight based dosing, see dosing tables for the chewable tablet	9	22.1 (36 %)	113 (80 %)

11 to less than 25 kg	*Chewable tablet*	*Weight based dosing, see dosing tables for the chewable tablet*	*13*	*18.6 (68 %)*	*82 (123 %)*
3 to less than 20 kg	*Oral suspension*	*Weight based dosing, see dosing table for granules for oral suspension*	*19*	*24.5 (43 %)*	*113 (69 %)*
**Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.* *†Geometric coefficient of variation.*					

The pharmacokinetics of raltegravir in ~~children~~ infants under ~~2 years~~ 4 weeks of age has not been established.

Package Leaflet

1. What Isentress is and what it is used for

When Isentress should be used

Isentress is used to treat adults, adolescents ~~and,~~ children, toddlers and infants ~~2 years~~ 4 weeks of age and older who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

3. How to take Isentress

- *It is very important that this medicine is taken exactly as directed.*
- *~~As children get older, gain weight or are able to swallow whole tablets, the doctor may want to prescribe a different daily dose and/or a different tablet.~~*

How much to take
Dose for children of 2 through 11 years of age
The doctor will work out the right dose of the chewable tablet based on the age and weight of the child. This dose must not exceed 300 mg twice a day. The doctor will tell you how many chewable tablets the child must take.
- *Do not change the dose, or stop taking this medicine, or switch between the chewable tablets and the 400 mg tablet, without first talking with your doctor, pharmacist or nurse.*

ISENTRESS is also available in a 400 mg tablet for use in adults, adolescents and ~~childrenaged 12 years and older, and in children aged 6 through 11to less than 12 years of age~~ weighing at least 25 kg and able to swallow a tablet; and as granules for oral suspension for use in infants and toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg.

- *Do not switch between the chewable tablet, granules for oral suspension or 400 mg tablet without first talking with your doctor, pharmacist or nurse.*
- *~~As c~~Children should keep scheduled doctor's visits because their Isentress dosage should be adjusted as they get older, grow or gain weight. ~~or are able to chew a tablet,~~ Their doctor may also want to prescribe ~~a different daily dose and/or a different tablet~~ the 400 mg tablet when they are able to swallow a tablet.*

Instructions of the preparation of Isentress granules for oral suspension were introduced.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Portugal.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Raltegravir has been shown to be effective in adults. Subject to identification of suitable dose regimens it could be expected that raltegravir would contribute in a similar fashion to regimens used in subjects aged < 18 years. The virological responses observed in study 022, including the two youngest age Cohorts, are generally in line with data obtained in treatment-experienced adults.

Uncertainty in the knowledge about the beneficial effects

Study P022 was not designed to provide definitive efficacy data. It is not possible to match exactly the adult plasma profile using 400 mg poloxamer tablets when dosing children aged < 2 years with GFS. To a considerable extent the expectation of efficacy is based on the results of study 071 and the evidence that points to the importance of C_{12h}. While these concentrations are lower in the younger children the actual data suggest that the majority of them should achieve and maintain values above the proposed cut-off provided they adhere to the regimen.

Risks

Unfavourable effects

At present the data suggest a comparable safety profile in children aged < 2 years as has been observed in older children, adolescents and adults. There are no new concerns raised.

Uncertainty in the knowledge about the unfavourable effects

The numbers of subjects aged < 18 years exposed to raltegravir are very limited and the duration of reporting is relatively short for the subjects aged < 2 years. However, the longer-term data from the older children do not currently suggest the onset of new AEs emerging with time.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Benefit-risk balance

Overall the data suggest a favourable benefit-risk balance for children aged from 4 weeks up to a cut-off weight of 20 kg (i.e. maximum GFD dose of 100 mg BID).

Discussion on the 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 the GFS formulation in children aged from 4 weeks up to a cut-off weight of 20 kg (i.e. maximum GFD dose of 100 mg BID). Satisfactory virological and immunological response rates were observed in 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 compared to that of older children and adults. 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 Isentress GFS in patients aged from 4 weeks and up to a maximum dose of 100 mg BID is considered to be favourable.

4. Recommendations

Final Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk/benefit balance of the extension of Marketing Authorisation for ISENTRESS granules for oral solution 100 mg in the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral therapy (ART)-experienced paediatric patients from the age of 4 weeks is favourable and therefore recommends the granting of the marketing authorisation subject to the current conditions below.

In addition, CHMP recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s)

Variation(s) accepted		**Type**
C.I.6.a - OpnionAccepted.	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Grouping of a line extension application to introduce a new pharmaceutical form (100 mg granules for oral suspension) and a type II variation to extend the indication to toddlers and infants from 4 weeks to less than 2 years of age. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and separate SmPC is introduced for the new pharmaceutical form. The Package Leaflet and Labelling are updated in accordance. In addition, minor updates are made to SmPC sections 5.1 and 6.1, Labelling and the PL. Furthermore, the product information is brought in line with the latest QRD version 9.3.

The requested group of variations proposed amendments to the SmPC, <Annex II>, Labelling and Package Leaflet.

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

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/99/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Grouping of a line extension application to introduce a new pharmaceutical form (100 mg granules for oral suspension) and a type II variation to extend the indication to toddlers and infants from 4 weeks to less than 2 years of age. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and separate SmPC is introduced for the new pharmaceutical form. The Package Leaflet and Labelling are updated in accordance. In addition, minor updates are made to SmPC sections 5.1 and 6.1, Labelling and the PL. Furthermore, the product information is brought in line with the latest QRD version 9.3.

The requested group of variations proposed amendments to the SmPC, Labelling and Package Leaflet.

Summary

Please refer to the CHMP AR EMEA/H/C/000860/X/44/G.