15 November 2012
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

INTELENCE

International non-proprietary name: **etravirine**

Procedure No. **EMEA/H/C/000900/X/0018/G**

Note

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

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Product information

Name of the medicinal product:	INTELENCE
Applicant:	Janssen-Cilag International N V Turnhoutseweg 30 BE-2340 Beerse Belgium
Active substance:	etravirine
International Nonproprietary Name/Common Name:	etravirine
Pharmaco-therapeutic group (ATC Code):	Non-nucleoside reverse transcriptase inhibitors (J05AG04)
Therapeutic indication(s):	INTELENCE, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients and in antiretroviral treatment-experienced paediatric patients from 6 years of age (see sections 4.4, 4.5 and 5.1). The indication in adults is based on week 48 analyses from 2 where INTELENCE was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir. The indication in paediatric patients is based on 48-week analyses of a single-arm, Phase II trial in antiretroviral treatment-experienced paediatric patients (see section 5.1).
Pharmaceutical form:	Tablet
Strength:	25 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	120 tablets

List of abbreviations

3TC	lamivudine
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ARV	antiretroviral
AUC	area under the plasma concentration-time curve
AUC_{12h}	area under the plasma concentration-time curve over 12 hours at steadystate
AUC_{last}	area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration
b.i.d.	bis in die (twice daily)
BMI	body mass index
C_{0h}	trough concentration at steady-state
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
DRV	darunavir
DBP	diastolic blood pressure
EC_{50}	50% effective concentration in cell-based assays
ECG	electrocardiogram
EMA	European Medicines Agency
ETR	etravirine
EU	European Union
FC	fold change in EC_{50}
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
HAART	highly active antiretroviral therapy
HDPE	high-density polyethylene
HIV(-1)	human immunodeficiency virus (type 1)
HPLC	high performance liquid chromatography
HPMC	hydroxypropylmethylcellulose (hypromellose)
IAS	International AIDS Society
ICH	International Conference on Harmonization
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IR	infrared spectrometry
LS	least squares
LPV	lopinavir

MedDRA	SMQ Standardized Medical Dictionary for Drug Regulatory Affairs Query
MTCT	mother to child transmission
NC=F	non-completer equals failure
NNRTI	non-nucleoside reverse transcriptase inhibitor
Non-VF	non-virologic failure
NRTIs/NtRTIs	nucleo(side)/(tide) reverse transcriptase inhibitors
NVP	nevirapine
OBR	optimized background regimen
PEG	polyethylene glycol
PENTA	Paediatric European Network for the Treatment of AIDS
Ph.Eur.	European Pharmacopoeia
PI	protease inhibitor
PIANO	Pediatric study of Intelence As a NNRTI Option
PP	polypropylene
RAL	raltegravir
RAM	resistance associated mutation
RH	relative humidity
RNA	ribonucleic acid
rtv	co-administered low-dose ritonavir
SAE	serious adverse event
SBP	systolic blood pressure
SmPC	summary of product characteristics
SOC	System Organ Class
SQV	saquinavir
TLOVR	time to loss of virologic response
TMC	Tibotec Medicinal Compound
USA	United States of America
• XRD	x-ray diffraction

1. Scientific discussion

1.1. Introduction

Intelence (etravirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). On 28 August 2008, the European Commission issued a conditional Marketing Authorisation (MA) for Intelence based on a positive Opinion adopted by the CHMP on 26 June 2008 for the following indication:

"INTELENCE, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients.

This indication is based on week 48 analyses from 2 randomised, double-blind, placebo-controlled Phase III trials in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, where INTELENCE was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir"

The indication was based on Week 24 analyses from 2 randomized, double-blind, placebo-controlled phase III studies (DUET-1 and DUET-2) in highly pre-treated patients with viral strains harboring mutations of resistance to NNRTIs and PIs, where ETR was investigated in combination with a background regimen which included DRV/rtv. These studies showed that ETR is able to provide an adequate virologic response in this patient population, however additional clinical data was considered necessary by the CHMP to further substantiate the durability of virologic response and to confirm the use of ETR in combination with ritonavir-boosted PIs other than DRV/rtv. Consequently, a conditional MA with specific obligations was issued.

In order to address the lacking data the applicant, at the time of the initial MA, undertook specific obligations.

Intelence is available as 100 and 200 mg film-coated tablet. The recommended dose of Intelence is 200 mg taken orally twice daily following a meal.

1.2. Quality aspects

1.2.1. Introduction

Intelence 25 mg immediate release tablets are presented as white to off-white, oval scored tablets with "TMC" on one side, containing 25 mg etravirine. The tablets are un-coated, can be divided into equal doses and are water dispersible.

The list of excipients can be found in section 6.1 of the SmPC. The tablets are presented in white, high-density polyethylene (HDPE) bottles with child-resistant, polypropylene (PP) closures lined with an induction seal. Two silica gel pouches are added as desiccant. Each bottle contains 120 tablets.

1.2.2. Active Substance

Etravirine, the active substance in Intelence 25 mg tablets is identical to the active substance in the authorized Intelence 100 mg and 200 mg tablets (EU/1/08/468/001-002). The crystalline drug substance is classified as a BCS class IV compound. During the drug product manufacturing process, the crystalline drug substance is transformed into the amorphous form to allow absorption of the active substance *in vivo*. For information on the active substance reference is made to Module 3.2.S of the marketing authorisation of the 100 mg and 200 mg strengths and subsequent quality variations. The active substance specifications are the same as for the 100 mg and 200 mg tablets.

1.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim was to develop a paediatric formulation for Intelence, suitable for use in children and adolescents from 6 years up to 18 years. In order to provide the HIV-1 infected children and adolescents with the appropriate dose regimen of etravirine, an additional tablet strength of 25 mg had to be developed. The proposed 25 mg tablet is scored and allows flexible and accurate dosing (dose increments of 12.5 mg) in paediatric patients in case this would be needed in the future. A tablet breakability test has been performed. The paediatric tablet is dose and weight proportional to the commercially available 100 mg tablet. The two products were compared in a bioequivalence study. The 25 mg tablet can be dispersed in water or in water and subsequently diluted with either orange juice, milk products or prepared instant infant formula.

The 25 mg tablet contains the same excipients as the 100 mg tablet: hypromellose (stabilizer), microcrystalline cellulose (carrier/filler), colloidal anhydrous silica (glidant), croscarmellose sodium (disintegrant), magnesium stearate (lubricant) and lactose monohydrate (filler). These excipients are standard excipients for immediate release formulations. The excipients are all of pharmacopoeial grade and acceptable for use in the paediatric population. For a discussion on the results of the taste acceptability test, reference is made to the clinical part of this assessment report.

A study was performed to evaluate the in-use compatibility of the 25 mg tablets when dispersed in different types of beverages. The results showed that the tablet should be dispersed in water only in case the patient is unable to swallow the tablet. A recommended dispersion procedure has been included in section 6.6 of the SmPC.

No formulation changes have been made between the Intelence 25 mg tablets tested in the paediatric clinical trials, the registration/validation batches tablets, and the proposed commercial tablets. All batches were manufactured at the proposed commercial manufacturing site.

The suitability of the container closure system used for drug product has been established through stability testing. The chosen container closure system is similar to the one used for the commercially available 100 mg tablets. The bottle size and amount of desiccant were adjusted to the size of the 25 mg tablets.

Adventitious agents

The only excipient of animal origin used in the manufacture of the drug product is lactose monohydrate. It is confirmed that the lactose is produced only from milk sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet according to the Note for Guidance on Minimising

the Risk of Transmitting Animal Spongiform Encephalopathy Via Human and Veterinary medicinal products.

Manufacture of the product

Intelence 25 mg tablets are dose and weigh proportional to the commercially available Intelence 100 mg tablets and the manufacturing process is based on that of the 100 mg tablets. The main manufacturing steps are: preparation of the spraying solution, spray drying, post drying, blending, roller compaction, blending and tablet compression.

The upstream process (spray suspension preparation, spray drying and post drying) is identical to that of the 100 mg tablets; the process includes a design space for the spray drying and post-drying. The spray dried drug substance is considered as an intermediate product and an adequate control monograph has been proposed.

The downstream process includes: mixing of the spray dried dispersion with a portion of croscarmellose sodium, roller compaction of the mixture, addition and mixing of the other excipients, addition of the external phase, tableting and packaging. Two process flows and batch sizes (160 and 560 kg) are used in the downstream process. The 25-mg tablets can be prepared from a 160 kg final blend or from a portion of the 560 kg final blend prepared for the 100-mg tablets. For the smaller batch size (160 kg), the downstream process is identical to that of the commercially available 100 mg tablets, apart from the scale, the size of the blending bins and the compression process step. For the larger batch size (560 kg), the 25 mg tablets are produced starting from the final blend prepared for the commercially available 100 mg tablets. A target portion of 70 kg of this final blend is transferred to a separate blending bin, blended again and compressed into 25 mg tablets.

The applicant has identified the critical manufacturing steps in the manufacturing process, and has adequate in-process controls in place. The manufacturing process has been adequately validated and demonstrates to reproducibly produce a finished product of the intended quality.

Batch analysis data have been presented for three validation batches and for clinical trial batches and demonstrate that the tablets can be manufactured reproducibly according to the agreed finished product specification.

Product specification

The Intelence 25 mg tablets release specifications include tests for appearance (visual inspection), identity (HPLC, IR), assay (HPLC - 95.0%-105.0% of label claim), chromatographic purity (HPLC), dissolution, water content, uniformity of dosage units (Ph. Eur.), crystallinity (XRD) and microbiological purity (Ph. Eur.). A crystallinity test has been added to the release specifications because the crystalline form of the drug substance is not absorbed in vivo.

The finished product specifications are standard for immediate release tablets. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products are acceptable from the safety point of view. Batch analysis results comply with the predefined specifications and confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data have been provided for three batches of 25 mg tablets, which have been stored up to 24 months at 25°C/60%RH and 30ºC/75%RH and 6 months at 40°C/75%RH, according to the ICH requirements.

These batches were manufactured at the proposed manufacturing site, Janssen- Cilag S.p.A., Latina, Italy and packed in the primary packaging proposed for marketing. The parameters tested and analytical methods used in the stability studies are identical to those used for the release specifications apart from identification, crystallinity and uniformity of dosage units which are tested only at release, and the tablet breakability test (Ph.Eur.) which is only performed at the end of shelf-life.

Supportive data are provided after 3 months storage at 50°C and after 8 hours exposure to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

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

In addition, an in-use stability study simulating the daily use of the medication by the patient (8 weeks at 25ºC/60%RH and 30ºC/75%RH) was performed at the start and the end of shelf life. During the simulation of the in-use test, an increase in water content was observed and out of specification results were recorded on samples stored at 30°C/75%. As the water content is a critical parameter regarding the recrystallization of the active substance (and hence the in vivo absorption), the in-use shelf life after first opening of 8 weeks had to be reduced to only 6 weeks The CHMP recommends the applicant to perform a new in-use stability study using a larger quantity of desiccant or to consider a change of primary packaging (blister) in order to extent the in-use shelf life from 6 weeks to 8 weeks.

The applicant confirmed their plans to conduct additional development studies to further prove the robustness of the formulation and packaging configuration with the aim to extend the in-use stability. A protocol for this study is under development and would include both open dish and simulated in use conditions for tablets that contain a high water content with the aim to demonstrate that the water content does not impact crystallinity. Alternatively, the applicant will consider performing a new in use stability study using additional desiccant in the current bottle. If the data from these studies does not allow an extension of the in use period, the 6 week in use period will be maintained.

1.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Intelence 25 mg tablet is a paediatric formulation for Intelence. The 25 mg tablet is manufactured using the same active substance as for the authorised Intelence 100 mg and 200 mg tablets and the manufacturing process is based on that of the 100 mg tablets. The 25 mg tablet contains the same excipients as the 100 mg.

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

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

1.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

1.2.6. Recommendation for future quality development

The CHMP recommends the applicant to conduct additional development studies (open dish, simulated in use or larger quantity of desiccant) with the aim to support an extension of the in use stability from 6 weeks to 8 weeks.

1.3. Non-clinical aspects

1.3.1. Introduction

The applicant submitted a nonclinical overview which integrates the results from all relevant nonclinical studies in support of the use of ETR for the treatment of HIV-1 infection in paediatric subjects. No new non-clinical juvenile studies were performed as part of this application.

1.3.2. Pharmacology

ETR only weakly interacted with glycine-1 transporter binding sites (inhibition constant (K_i) was 5.4 µM (2.4 µg/mL)). At concentrations of 1 (0.44 µg/mL) and 10 µM (4.4 µg/mL) ETR was found to have inhibitory effects on nicotinergic nerve-smooth muscle function, but was devoid of muscarinic effects.

The secondary pharmacodynamics and safety pharmacology program revealed no relevant effects of ETR on in vitro and in vivo cardiovascular electrophysiological parameters, respiratory parameters, neurobehavior, motor activity or any other body functions.

1.3.3. Pharmacokinetics

Pharmacokinetic data revealed low to intermediate transepithelial intestinal permeability of ETR. Following oral administration peak plasma concentrations were generally reached within 4 hours in all species.

Tissue distribution and the elimination from plasma were rapid. The human profile of metabolites was reflected in the species tested and the animal pharmacokinetic data in general reflected the clinical data, albeit at lower levels in some species.

In all species, the contribution of metabolic elimination to the overall disposition of ETR was quantitatively limited as in the plasma and feces of animals and humans unchanged ETR was more abundant than any metabolite.

ETR was predominantly excreted unchanged via the feces in all species. Urinary elimination of ETR was negligible.

1.3.4. Toxicology

Regarding the acute toxicity studies, in mice, there were no relevant effects following oral administration of ETR base or ETR HBr in PEG400 vehicle at doses up to 1000 mg/kg. Similarly, there was no effect of ETR base in PEG400 vehicle administered by subcutaneous injection to mice at doses

of up to 320 mg/kg. In rats, there were no relevant effects following oral administration of ETR base or ETR HBr in PEG400 vehicle at doses up to 1000 mg/kg. Similarly, there was no effect of ETR base in PEG400 vehicle administered by subcutaneous injection to rats at doses of up to 320 mg/kg, other than slight skin irritation/necrosis at the site of injection in 1 female given the highest dose. In dogs, the single dose oral toxicity was determined using spray-dried ETR formulated tablets or as an aqueous suspension in a study comprised of 3 phases. A dose-escalation phase up to 160 mg/kg was followed by a 5-day repeated dose phase at 120 mg/kg/day using tablets. In the third phase, dogs were given 350 mg/kg/day of spray-dried ETR in an aqueous suspension by oral gavage for 5 consecutive days in fasted or fed conditions. No relevant toxicity findings were observed.

Liver changes seen in rodents occurred at exposures below those in the clinic at the recommended therapeutic dose. In the dog, repeated dosing with spray-dried ETR resulted also in liver changes (increases in transaminases, microgranuloma and minor inflammatory changes, and inspissated bile in gall bladder). In rodents, changes in the coagulation parameters were also noted, more pronouncedly in mice relative to rats. In mice and following dietary administration only, disturbances in the coagulation parameters led to mortality, hemorrhagic cardiomyopathy and hemothorax in male animals only.

Genotoxicity tests, in vitro and in vivo, have shown ETR to be free of genotoxic potential, with and without liver metabolic activation system. These tests included in vitro gene mutation assays (Ames test and mouse lymphoma test), an in vitro chromosomal aberration test (human lymphocytes) and an in vivo chromosomal aberration test (mouse bone marrow micronucleus test; up to a single dose of 2000 mg/kg).

Regarding the carcinogenicity studies, ETR was not carcinogenic in rats or in male mice. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in female mice. Administration of ETR did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

No relevant effects on male or female fertility were observed in this study performed with ETR HBr in PEG400 up to a dose level of 506 mg/kg/day. No relevant effects were observed in study with spray-dried ETR suspended in water and the NOAEL was roughly 500 mg/kg/day. In an embryo-fetal developmental toxicity study pregnant rats were dosed with ETR HBr in PEG400 up to 1000 mg/kg/day and this did not result in maternal or fetal toxicity. The fetal NOAEL was 1000 mg/kg/day and ETR is therefore considered not to be teratogenic in the rat. In an embryo-fetal developmental toxicity study ETR HBr formulated in alpha-tocopheryl polyethylene glycol succinate (TPGS)/HPMC was dosed in pregnant rabbits up to 750 mg/kg/day. ETR has shown no teratogenic potential. Therefore, an additional study was conducted using spray-dried ETR suspended in water and at doses up to 375 mg/kg/day. The maternal NOAEL was 125 mg/kg/day and fetal NOAEL was 375 mg/kg/day. No adverse effects were observed in a pre- and postnatal development study in the rat using spray-dried ETR at dose levels up to 500 mg/kg/day.

ETR was classified as “non sensitizing” in an *in vivo* guinea pig skin sensitization study and in a mouse local lymph node assay. ETR was also classified as “non irritant” in an *in vivo* rabbit skin irritation study. In an *in vitro* eye irritation assay, ETR in base form was considered to be a “mild” eye irritant, whereas in HBr-salt form, it was considered to be a “very severe” eye irritant. No effects were observed in an in vitro phototoxicity study.

Concerning the immunotoxicity aspects ETR HBr formulated in PEG400 was administered at doses of up to 600 mg/kg/day. There were no relevant effects of treatment with ETR and the immune response, as measured by IgM production, was not affected by treatment.

The mechanistic studies conducted with ETR suggested that the effect of ETR on clotting times and clotting factors in mice is mediated via a vitamin K pathway. The underlying mechanism for the cardiac lesions can be explained by the severely disturbed coagulation resulting in interstitial hemorrhagic diathesis within the myocardium and subsequent muscle degeneration and inflammation. The exact mechanism of ETR on the vitamin K pathway is not described and extrapolation to humans is still questionable.

1.3.5. Ecotoxicity / environmental risk assessment

As the partition coefficient octanol/water, log Pow, of ETR is 3.4, which is below 4.5, there was no assessment for Persistence, Bioaccumulation and Toxicity (PBT). The predicted environmental concentration of TMC125 in surface water ($PEC_{surfacewater}$) was calculated to be 0.013 µg/L. The predicted environmental concentration of TMC125 in groundwater ($PEC_{groundwater}$) was calculated to be 0.0032 µg/L.

Concerning the aquatic fate and effect assessment (Phase II Tier A), the ratios $PEC_{surfacewater}/PNEC_{water}$ and $PEC_{groundwater}$ /$PNEC_{groundwater}$ are below 1 and the ratio $PEC_{surfacewater}/PNEC_{microorganisms}$ is below 0.1. Consequently, no further testing in the aquatic compartment is necessary and it can be concluded that ETR and/or its metabolites are unlikely to represent a risk to the aquatic environment. The very low bioconcentration values (BCF) of 370.3 and 476.9 indicate that ETR does not bioaccumulate in aquatic organisms. The adsorption/desorption coefficients (K_{oc}) for activated sludge and soils indicates that ETR is immobile and will remain preferably in soil. Regarding the phase II Tier B, the ratio $PEC_{soil}/PNEC_{soil}$ is below 1.

In conclusion, ETR and/or its metabolites are considered unlikely to represent a risk to the terrestrial compartment.

1.3.6. Discussion on non-clinical aspects

The target organs reported in toxicity studies were: liver, thyroid and coagulation system. However, the liver effects resulted from enzymatic induction in rats, were observed at exposures at least 8-fold higher than the anticipated human exposure in dogs, and no clinically relevant changes over time were apparent in hepatic- or thyroid- related laboratory parameters in clinical trials. The thyroid effects were species-specific and associated with enzymatic induction. Concerning the coagulation system, in mice, coagulopathy was mediated by a mechanism involving vitamin K and further induced cardiomyopathy. No such effects were reported in either dogs or humans. The mouse is believed to be more sensitive to develop hemorrhagic cardiomyopathy due to a higher heart rate and thinner ventricular and atrial wall, relative to other species (dog, humans). However, it should be noted that the exact mechanism of ETR effect on the Vitamine K pathway is not known.

ETR and/or its metabolites are considered unlikely to represent a risk to the terrestrial compartment.

1.3.7. Conclusion on the non-clinical aspects

No non-clinical juvenile studies were performed by the applicant to support this application. This is considered acceptable because the effects noted on the liver and/or thyroid were species-specific or occurred at exposures higher than that expected in humans. In addition, no effects on growth or development of offspring in the reproductive toxicology studies have been observed. Therefore, the nonclinical data generated to date does not suggest a potential risk for paediatric subjects and supports the use of ETR in the paediatric population.

1.4. Clinical aspects

1.4.1. Introduction

GCP

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

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

A GCP inspection was performed in February 2012 on study TMC213 at the CHMP request. The inspectors' conclusion was that the conduct of the trial could be considered to be GCP compliant and that the data can be considered for evaluation and assessment for the present application.

- Tabular overview of clinical studies

Study	Phase	Design	Objective	population	Formulation and dose
TMC125-C173	I	open-label, randomized, single-dose, 3 periods crossover study	PK bioequivalence	Healthy adult volunteers	100 mg tablet 25 mg tablet
TMC125-C126	I	open-label, single arm study	PK	2 groups of HIV infected experienced paediatric subjects: ≥ 6 to <12 y.o. ≥ 12 to <18 y.o.	<u>Stage I</u> : 4 mg/kg/b.i.d for 7 days 100 mg tablet 25 mg tablet <u>Stage II</u> : 5.2 mg/kg/b.i.d for 7 days 100 mg tablet 25 mg tablet
TMC125-C213	II	open label, single arm study	PK safety efficacy	2 groups of HIV infected experienced paediatric subjects: ≥ 6 to <12 y.o. ≥ 12 to <18 y.o.	5 mg/kg/ b.i.d 100 mg tablet 25 mg tablet

1.4.2. Pharmacokinetics

Study TMC125-C173

Study TMC125-C173 was conducted in healthy subjects to evaluate the relative oral bioavailability of one single dose of the new 25 mg tablet (F066) with the marketed 100 mg tablet (F060). Moreover, oral biovailability of 100 mg tablet either swallowed or dispersed in water was tested. High inter subject variability was observed in the same range as previously known for ETR. Overall, comparable bio availabilities were observed between the 3 modes of administration of one dose of 100 mg of etravirine in adult (with one swallowed tablet of F060, with one F060 dispersed in water and 4 swallowed tablets of F066), with a minor trend for lower (15-20%) C_{max} with the paediatric F066 tablet as compared to the adult F060 tablet.

Study TMC125-C126

This was an open-label, Phase I trial conducted in 2 stages to evaluate the steady-state pharmacokinetics of ETR at 2 different weight-based target dose levels (4 mg/kg b.i.d. in Stage I and 5.2 mg/kg b.i.d. in Stage II) and to support a weight-based dosing recommendation for ETR in treatment-experienced HIV-1 infected paediatric subjects from 6 years to < 18 years of age.

In each stage:

- Patients were studied in 2 age groups: 6 to < 12 years old (Group 1) and ≥ 12 to ≤ 17 years old (Group 2),
- ETR was administered as the commercial 100-mg tablet (F060) and/or as the compositionally proportional 25-mg tablet (F066) for 7 days with an additional morning dose on day 8.

The results from study C126 indicated that the 4 mg/kg dose might be too limited in some patients (lower C_{min}) especially given the high variability and taking into account the genetic barrier of the drug. The 5.2 mg/kg dose (closer to a 400 mg/70 kg~5.7mg/kg dose in adult) would provide better confidence on the efficacy side. These data were reviewed by the CHMP through previous assessment of the Article 46 submission P46 029 (conclusion adopted in August 2010).

As part of the present application, the applicant provided data comparing the mean PK parameters in the overall paediatric population to historical adult values (data from study C228 and DUETs which were submitted as part of the initial marketing authorisation application). Comparative evaluation of the PK data plots in paediatric and adult population confirmed that the dose of 5 mg/kg/day was more adequate than the dose of 4 mg/kg/day to mimic the adult's exposures in paediatric patients. Of note, a trend for a lower exposure in adolescents compared to children and adults was observed.

Study TMC125-C213 (PIANO)

This study is an open-label, Phase IIb trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of ETR, administered on a weight-based dose of 5.2 mg/kg b.i.d. regimen, during 48 weeks of treatment with ETR, in combination with other antiretroviral (ARV) drugs, in treatment experienced HIV-1 infected paediatric subjects from 6 years to < 18 years of age (see Section 2.5 for further details).

Sparse PK sample were obtained at different times of the study and were used to elaborate a paediatric population pharmacokinetic model conjointly with data from the DUETs studies and study C126.

As a difference with the study C126, patients who were unable to swallow the tablets were authorised to disperse it in a glass of water. As in C126 study, almost all adolescents (93%) were dosed with the adult dose of 200 mg b.i.d. The population pharmacokinetic estimates for etravirine AUC_{12h} and C_{0h} from the 48 data for study C213 are summarised in the table below.

Table 1. Population pharmacokinetic estimates for etravirine (all doses combined) in treatment-experienced HIV-1 infected paediatric patients 6 years to less than 18 years of age (PIANO 48 week analysis)

Parameter	**N = 101**
AUC_{12h} (ng•h/ml)	
Geometric Mean ± Standard Deviation	3,729 ± 4,305
Median (Range)	4,560 (62 - 28,865)
C_{0h} (ng/ml)	
Geometric Mean ± Standard Deviation	205 ± 342
Median (Range)	287 (2 – 2,276)

1.4.3. Discussion on pharmacokinetics

As previously noted in adults, there is a high inter-subject variability concerning exposure parameters for ETR in the paediatric population.

Tables 2 and 3 present the PK data from the paediatric studies C126 and C213 in comparison with the PK data from previously conducted adult studies C228 and DUET.

Table 2. PK data in DUET trial, C228, C126, C213

Mean (SD)	DUET	C228	C126				C213	
	adults	adults	children	Ado.	children	Ado.	children	Ado.
	200 mg bid	200 mg bid	4 mg/kg bid		5.2 mg/kg bid		5.2 mg/kg bid (PK pop model	
AUC_{12h}	5506 (4710)	3713 (2069)	4989 (5189)	3299 (1468)	7713 (7160)	4219 (1575)	5764 (4044)	4874 (4487)
C_{oh}	393(391)	236(163)	238(202)	178(63)	453(442)	247(155)	381(321)	324(357)
C_{min}		185(128)	209(210)	161(70)	363(352)	210(120)		

Table 3. PK data in C126 and C213

difference in mean AUC (%) between paediatric data and adults data		**C126**					**C213**	
		children	Ado.		children	Ado.	children	Ado.
		4 mg/kg bid			5.2 mg/kg bid		5.2 mg/kg bid	
	AUC (mean)	4989	3299		7713	4219	5764	4874
DUET	5506	-9%	-40%		40%	-23%	5%	-11%
C228	3713	34%	-11%		108%	14%	55%	31%

The exposure in children with the 5.2 mg/kg b.i.d dose is higher (in C126 study) or similar (in C213 study) to the exposure observed in DUET studies conducted in adult patients. However, while the adolescents were receiving the adult dose, the exposure in this age group was lower than the one in adults. This might be explained by a lower adherence rate in adolescents; however the adherence data collected is limited and it cannot allow drawing formal conclusion (see section 2.5).

1.4.4. Conclusions on pharmacokintics

The pharmacokinetics of etravirine in 101 treatment-experienced HIV-1 infected paediatric patients, 6 years to less than 18 years of age and weighing at least 16 kg, showed that the administered weight-based dosages resulted in etravirine exposure comparable to that in adults receiving etravirine 200 mg b.i.d. when administered at a dose corresponding to 5.2 mg/kg b.i.d. Therefore the CHMP considered that the 5.2 mg/kg dose was satisfactory.

1.5. Clinical efficacy

1.5.1. Main study

TMC125-TiDP35-C213: A Phase II open-label trial to evaluate the safety, tolerability and antiviral activity of TMC125 in antiretroviral experienced HIV-1 infected children and adolescents.

Methods

TMC125-C213, also known as the Pediatric study of Intelence As a NNRTI Option (PIANO) study, was a Phase II, open-label study to assess the safety, tolerability, pharmacokinetics and antiviral activity of ETR during a 48-week treatment with ETR, when added to an investigator-selected optimized background regimen (OBR) in treatment-experienced pediatric HIV-1 infected subjects aged 6 to < 18 years.

The study consisted of a screening period with a maximum of 6 weeks, a 48-week treatment period, followed by a 4-week post-treatment follow-up period for subjects who were not continuing treatment with ETR in another study or program.

Study Participants

Main inclusion criteria were as following:

- Male or female subjects, aged between 6 and < 18 years;
- Body weight of at least 16 kg
- Subjects with documented HIV-1 infection
- HIV-1 plasma viral load at screening visit ≥ 500 copies/mL (assayed by Roche COBAS TaqMan).
- On a stable ART for at least 8 weeks at Screening and willing to stay on that treatment until Baseline.

Treatments

ETR was administered with food and dosed per body weight: 5.2 mg/kg b.i.d. up to a maximum of 200 mg b.i.d. (the dose recommended in adults).

- 16 to < 20 kg: 100 mg b.i.d. (4 x 25-mg tablets or 1 x 100-mg tablets)
- 20 to < 25 kg: 125 mg b.i.d. (5 x 25-mg tablets or 1 x 100-mg + 1 x 25-mg tablets)
- 25 to < 30 kg: 150 mg b.i.d. (6 x 25-mg tablets or 1 x 100-mg + 2 x 25-mg tablets)
- ≥ 30 kg: 200 mg b.i.d. (8 x 25-mg tablets or 2 x 100-mg tablets)

In combination with an investigator-selected OBR consisting of at least 2 ARV drugs (a boosted PI in combination with N[t]RTI(s); RAL use was permitted as part of the OBR; additional use of ENF was optional).

Objectives

The ***primary objective*** of this study was to evaluate the safety and tolerability of etravirine (ETR) in combination with other antiretrovirals (ARVs) over a 24-week treatment period in children and adolescents aged 6 to < 18 years.

The ***secondary objectives*** of this study were:

- To evaluate long-term safety and tolerability of ETR in combination with other ARVs over a 48-week treatment period in children and adolescents aged 6 to < 18 years;
- To assess population pharmacokinetic parameters and pharmacokinetic/pharmacodynamic relationships of ETR for antiviral activity and safety over 24 and 48 weeks of treatment in children and adolescents aged 6 to < 18 years;
- To evaluate the antiviral activity of ETR in combination with other ARVs over a 24-week and 48-week treatment period in children and adolescents aged 6 to < 18 years;
- To evaluate immunological changes (as measured by CD4 and CD8 cell count and CD4/CD8 ratio) over 24 and 48 weeks;
- To assess the evolution of the viral genotype and phenotype over 24 and 48 weeks.

Outcomes/endpoints

- Plasma Viral Load

The plasma viral load was measured by the Roche COBAS TaqmanTM HIV-1 test.

- Resistance Evaluations

At Screening only a genotype determination by means of vircoTYPE HIV-1 was performed. If the baseline phenotype was negative, a phenotype was performed by means of the Antivirogram on the screening sample.

- Pharmacokinetic Evaluations

At a number of visits throughout the study blood samples were taken to determine the ETR concentrations, and optionally PI concentrations. Plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. At Week 24 or at Premature Withdrawal, whichever came first, a sample was taken for CYP2C9 and CYP2C19 genotyping.

- Taste Questionnaire

Taste acceptability of ETR dispersed in water was assessed at Week 2 using a modified questionnaire form incorporating a 5-point hedonic facial scale.

- Adherence

Determination of adherence was based on two methods: pill counts at each visit and replies to question 7 of the PENTA Study Adherence Questionnaire for children/teenager and to question 10 of the Study Adherence Questionnaire for caregivers.

Sample size

The study population was planned to comprise 100 HIV-1 infected subjects. Efforts were made to include at least 30 subjects in each of the 2 age groups (6 to < 12 years and 12 to < 18 years), on a stable ARV regimen, who needed to change their ARV regimen because it was currently failing, with a confirmed HIV-1 plasma viral load ≥ 500 copies/mL.

Statistical methods

The primary population is the intent-to-treat (ITT) population, i.e. all subjects who had been enrolled and taken ETR at least once, regardless of their compliance with the protocol. In case of a substantial number of major protocol violation, an on-protocol analysis was to be performed.

Virologic response defined as:

- % of subjects with plasma viral load < 50 copies/mL at Week 24 (primary efficacy parameter),
- % of subjects with plasma viral load < 50 copies/mL at all other time points,
- % of subjects with plasma viral load < 400 copies/mL at all time points,
- % of subjects with at least 1 log10 drop in plasma viral load compared to Baseline at all time points.
- Change in plasma viral load from Baseline at all time points.

Data was analyzed using the following imputation methods:

Observed: no imputation done. This is the classical observed case analysis.

Imputed non-completer equals failure (NC=F): Subjects who dropped out of the study were considered as non-responders after discontinuation. Subjects with intermittent missing viral load values were considered responders only if the preceding visit indicate response. In all other cases, intermittent values were imputed with non-response.

Imputed TLOVR: responders/non-responders are defined according to the FDA Time To Loss Of Virologic Response algorithm32; a subject was considered a responder at a given time point if the subject showed virologic response at that time point and at the subsequent time point; a subject was considered a non-responder at a time point in the following situations:

- the subject discontinued at that time point;
- the subject showed a 'rebound' HIV RNA value at that time point and the subsequent time point;
- intermittently missing values were considered as response if the immediately preceding and following visits demonstrated response; in case the subject had not reached the next visit yet, no imputation was performed for the missing time points, unless the subject had discontinued the study;
- the subject showed a rebound at an earlier time point (irrespective of re-suppression of viral load).

Imputed TLOVR (non-VF censored): Similar to the TLOVR algorithm as defined above, but with the following difference: for subjects who dropped out for reasons other than virologic failure (non-VF), the values after discontinuation were not imputed (i.e. is left missing).

The NC=F imputation method was used for the calculation of the primary efficacy parameter.

The response rates together with their 95% CIs were calculated for all response parameters described above. Raw data and changes versus Baseline of log10 plasma viral load were descriptively and graphically presented. Time to first virologic response and time to loss of virologic response (for all definitions of virologic response as described above) were graphically presented by means of Kaplan-Meier curves.

The effect of baseline disease parameters and type and activity of the OBR was investigated through subgroup analyses and logistic regression models.

Definition of Lack of Response: Virologic failure (lack of response) is defined as:

- Plasma viral load decline of < 0.5 log10 from Baseline by Week 8;
- Plasma viral load decline of < 1.0 log10 from Baseline by Week 12.

Confirmation of virologic failure (lack of response) has to be done at the next planned visit or at an unscheduled visit. There has to be a minimum 2-week interval between plasma viral load assessments.

Definition of Loss of Response: Virologic failure (loss of response) is defined as 2 consecutive measurements of plasma viral load > 0.5 log10 above the nadir after a minimum of 12 weeks of treatment. Confirmation has to be done at the next planned visit or at an unscheduled visit. There has to be a minimum 2-week interval between plasma viral load assessments.

Results

Participant flow

In total, 41 investigators in 13 countries actively enrolled subjects in study C213. The highest proportion of study participants were from Thailand, Argentina and the United States, contributing 19.8%, 14.9% and 14.9% of the subjects in the overall study population, respectively.

In total, 178 subjects were screened, of whom 101 were enrolled, treated with ETR and as such included in the ITT population: 41 (40.6%) children (≥ 6 to < 12 years) and 60 (59.4%) adolescents (≥ 12 to < 18 years). Seventy-seven subjects were screened but were not treated (screening failure rate of 43% in both age groups).

Seventy-six (75.2%) subjects have completed the study (34 children and 42 adolescents) and 25 (24.8%) subjects have prematurely discontinued (7 children and 18 adolescents). The main reasons for premature treatment discontinuation were AE/HIV-related events (2 children and 6 adolescents) and non-compliance (3 children and 5 adolescents).

Recruitment

The study started on 6th August 2008 and ended on 30th August 2011.

Baseline data

The population is comprised of 41 children from 6 years of age and 60 adolescents. It is noted that 43% of the population were screening failure. Moreover, a higher rate of discontinuation was observed in adolescents as compared to adults (28% vs 15%), mainly driven by a higher rate of adverse events. Adolescents were included mainly in Thailand (27%) and in USA (20%), and children mainly in South Africa (20%) and Argentina (22%).

Paediatric patients enrolled in the study had a median CD4 cell count of 385/mm3 and a median HIV RNA level of approx 4 log/copies/ml. Patients with a low viral load (< 20 000 copies/mL) were the majority (62,4%) while patients with high VL (>100 000 copies) represented only 11% of the overall population.

As a reminder, in DUET studies in adults, the population was heavily pre-treated and at an advanced stage of the disease (60% being classified in CDC category C, with median viral load approx 4.8 log10 copies/ml and approx 100/mm3 median CD4).

Seventy two percent (72%) of adolescents has already received 6 or more ARV, while only 39% of children did so. All main classes (NNRTI, PI and NRTI) have already been used, the number of molecules in each class being accordingly greater among older patients over 12 years than in children. The majority of children and adolescents have previously received 1 NNRTI.

In this study, ETR had to be given in combination with an investigator OBR, which had to consist to at least 2 active antiretroviral including a boosted PI (either lopinavir, darunavir, atazanavir or saquinavir). The most frequently used PIs were DRV (approximately 51% in both groups of paediatric patients) and LPV (44% in children vs 35% in adolescent). Five adolescents were receiving the boosted PI atazanavir, the PK parameters of which could be significantly altered by ETR.

Fifty seven per cent (57.4%) and 87.1% of subjects had at least 3 IAS-USA NRTI and 3 PI RAMs detected at Baseline, respectively (17% with primary PI mutation). To put in perspective, in DUETs studies, baseline phenotypic sensitivity to at least 1 protease inhibitor was 77.5% of all subjects in DUET-1 and 75% of all subjects in DUET-2.

Outcomes and estimation

Virologic response

The sensitivity analyses for virologic response defined as the percentage of subjects with plasma VL < 50 copies/mL are summarized for the Week 24 and Week 48 time points in Table 4.

Table 4. Sensitivity Analyses for Virologic Response Defined as the Percentage of Subjects With Plasma VL < 50 Copies/mL at Week 24 and Week 48 –TMC125-C213 Week 48 Analysis

	Children ≥ 6 to < 12 years N = 41		Adolescents ≥ 12 to < 18 years N = 60		All subjects N = 101	
Analysis	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Week 24						
NC=F	41	24 (58.5)	60	29 (48.3)	101	53 (52.5)
TLOVR	41	24 (58.5)	60	28 (46.7)	101	52 (51.5)
TLOVR (non-VF censored)	39	24 (61.5)	55	28 (50.9)	94	52 (55.3)
Observed Case	39	24 (61.5)	53	28 (52.8)	92	52 (56.5)
Week 48						
NC=F	41	28 (68.3)	60	29 (48.3)	101	57 (56.4)
TLOVR	41	28 (68.3)	60	26 (43.3)	101	54 (53.5)
TLOVR (non-VF censored)	37	28 (75.7)	48	26 (54.2)	85	54 (63.5)
Observed Case	35	28 (80.0)	42	26 (61.9)	77	54 (70.1)

N = number of subjects; n = number of responders

The primary efficacy parameter was virologic response defined as the percentage of subjects with plasma viral load < 50 copies/mL at Week 24 calculated according to the NC=F imputation method. Based on this analysis, 52.5% of all subjects had a plasma viral load < 50 copies/mL at Week 24, with a better efficacy response observed in children (58.5%) than in adolescents (48.3%). At Week 48, the overall proportion of responders with VL < 50 copies/mL was slightly increased to 56.4%. The

proportion of responders had increased from 58.5% to 68.3% in children, whereas in adolescents, the proportion of responders remained the same (48.3%).

The percentage of subjects with virologic response defined as a plasma VL < 50 copies/mL according to the TLOVR algorithm at Week 48 was 53.5 (68.3% in children and 43.3% in adolescents).

At Week 48, 63.4% of all subjects had a confirmed plasma VL < 400 copies/mL, and 60.4% of all subjects had a confirmed ≥ 1 $\log_{10}$ decrease in plasma VL versus Baseline, calculated according to the TLOVR algorithm. Response rates in children were identical for the VL < 50 and < 400 copies/mL definition of response. In adolescents there was a 16.7% difference between the two definitions of response (43.3% VL < 50 copies/mL and 60.0% VL < 400 copies/mL).

Overall, these 48 weeks data speak in favour of a sustainability of the virologic suppression.

Change in Plasma Viral Load from Baseline

The change in log10 plasma VL from Baseline was calculated using the NC=F imputation method. A mean decrease in log10 plasma VL from Baseline was observed at all time points. At Week 48, the mean (SE) change in log10 plasma VL from Baseline was -1.53 (0.132) log10 copies/mL for all subjects, -1.67 (0.219) log10 copies/mL for children and -1.44 (0.163) log10 copies/mL for adolescents.

Immunologic outcome

An increase in absolute CD4 cell count was observed at all time points. The beneficial effect of ETR on restoration of the immune function was shown by a clear immunologic response versus Baseline at Week 24 and this was still observed at Week 48. At Week 48, the mean change in absolute CD4 cell count from Baseline was +156 x 10^6 cells/L overall; +178 x 10^6 cells/L in children and +141 x 10^6 cells/L in adolescents. The mean change in % CD4 at Week 48 was 5% overall, 6% in children and 4% in adolescents. Findings based on CD4/CD8 ratio were generally in line with those for % CD4. The mean increase from Baseline in CD4 cell count was higher in pediatric subjects in the TMC125-C213 study compared with the pooled DUET studies.

Comparison of the results in C213 to those in the pivotal DUET studies in adults

When comparing W24 results in C213 to those in the pivotal DUET studies in adults:

Table 5. Virologic responses (ITT – TLOVR), Change from Baseline in Log_{10} Viral Load (NC=F), and Change from Baseline in CD4 Percentage and Cell Count (NC=F) at Week 24 in the TMC125-C213 and pooled DUET studies

Study Age at Screening Treatment Group	TMC125-C213 6 to < 12 years ETR N = 41	TMC125-C213 12 to < 18 years ETR N = 60	TMC125-C213 6 to < 18 years ETR N = 101	Pooled DUET Studies ≥ 18 years ETR N = 599
Virologic parameters				
Viral load < 50 copies/mL at Week 24, n (%)	24 (58.5)	28 (46.7)	52 (51.5)	363 (60.6)
Viral load < 400 copies/mL at Week 24, n (%)	28 (68.3)	38 (63.3)	66 (65.3)	445 (74.3)
≥ 1 log_{10} decrease from Baseline at Week 24, n (%)	26 (63.4)	38 (63.3)	64 (63.4)	475 (79.3)
Change from Baseline in log_{10} viral load (copies/mL) at Week 24, mean (SE) and median (range)	-1.62 (0.21) -1.68 (-4.3; 0.9)	-1.44 (0.17) -1.68 (-4.0; 0.7)	-1.51 (0.13) -1.68 (-4.3; 0.9)	-2.37 (0.05) -2.78 (-4.6; 1.4)
Immunologic parameters				
Change from Baseline in CD4 cell count (x 10^6 cells/L), mean (SE) and median (range)	125 (33.0) 124 (-410; 718)	104 (17.5) 81 (-243; 472)	112 (16.9) 108 (-410; 718)	83.5 (3.64) 77.5 (-331; 517)
Change from Baseline in CD4 percentage, median (range)	4% (-9; 20)	3% (-4; 14)	4% (-9; 20)	3% (-7; 23)

When comparing W48 results in C213 to those in the pivotal DUET studies in adults:

Table 6. Virologic Response (ITT-TLOVR), Change from Baseline in Log10 Viral Load (NC=F), and Change from Baseline in CD4 Percentage and Cell Count (NC=F) at Week 48 Study TMC125-C213 and Pooled DUET Studies

Study	TMC125-C213			Pooled DUET Studies	
Age at Screening	6 to < 12 years	12 to < 18 years	All subjects	≥ 18 years	
Treatment Group	ETR N = 41	ETR N = 60	ETR N = 101	ETR N = 599	Not *de novo* ENF use ETR N=446
Viral load < 50 copies/mL at Week 48, n (%)	28 (68.3)	26 (43.3)	54 (53.5)	363 (60.6)	254 (57.0)
Viral load < 400 copies/mL at Week 48, n (%)	28 (68.3)	36 (60.0)	64 (63.4)	428 (71.5)	303 (67.9)
≥ 1 log_{10} decrease from Baseline at Week 48, n (%)	27 (65.9)	34 (56.7)	61 (60.4)	445 (74.3)	318 (71.3)
Change from Baseline in log_{10} viral load (copies/mL) at Week 48, mean (SE) and median (range)	-1.67 (0.22) -1.78 (-4.7;0.8)	-1.44 (0.16) -1.58 (-3.7; 0.4)	-1.53 (0.13) -1.61 (-4.7; 0.8)	-2.25 (0.06) -2.77 (-4.6; 0.7)	-2.13 (0.07) -2.68 (-4.6; 0.5)
Change from Baseline in CD4 cell count (x 10^6 cells/L), mean (SE) and median (range)	178 (39.7) 161 (-271; 1042)	141 (27.0) 76 (-249; 982)	156 (22.7) 82 (-271; 1042)	98.2 (4.61) 86.0 (-281; 671)	85.7 (5.03) 70.0 (-281; 653)
Change from Baseline in CD4 percentage, median (range)	7% (-12; 24)	3% (-8; 16)	5% (-12; 24)	4% (-11; 45)	3% (-11; 45)

The response rate in paediatric patients was close to that observed in adults from DUET Studies. The lower decrease from baseline in paediatric patients as compared to adults is related to the lower viral load at baseline in children in this study as compared to the DUET studies (3.6 vs 4.8 log copies/ml).

While having mostly received the adult dose, adolescents had a trend for lower virologic response, without clear explanation. Given the limitations of the adherence data collected (see below), the relation cannot be explored.

Resistance

HIV-1 genotypes and phenotypes were assessed as per protocol during treatment with ETR in combination with other ARV drugs in treatment-experienced, HIV-1 infected pediatric subjects 6 years to < 18 years of age. For the resistance analyses, virologic failures (rebounders and nonresponders) were defined using the TLOVR, non-VF censored, algorithm. The genotypic and phenotypic baseline versus endpoint profiles of the 41 virologic failures from the Week 48 analysis were evaluated.

At Week 48, 41 of 101 (40.6%) subjects were classified as virologic failures (TLOVR non-VF censored) (26.8% of children, 50.0% of adolescents). Twenty-nine (28.7%) subjects were non-responders (19.5% of children, 35.0% of adolescents) and 12 (11.9%) subjects were rebounders (7.3% of children, 15.0% of adolescents). Eight of the 12 rebounders did not pass beyond 400 copies/mL at confirmed failure.

At baseline, a higher mean viral load and median number of NNRTI RAMs were observed in the virologic failures compared to the non-virologic failures, but no substantial differences in baseline genotypic and phenotypic characteristics and ARV activity of the OBR were noted.

Development of resistance was assessed in virologic failures for which Baseline/Endpoint genotypic and phenotypic profiles were available at both Baseline and Endpoint (n = 23). The median ETR fold change in EC_{50} (FC) increased from 0.9 (ranging from 0.3 to 2.3) at Baseline to 3.6 (ranging from 0.8 to > 1598.8) at Endpoint. The median number of ETR RAMs increased from 0 (ranging from 0 to 2) to 1 (ranging from 0 to 4) and the median ETR weighted genotypic score increased from 0 (ranging from 0 to 2.5) to 1.5 (ranging from 0 to 6.5).

NNRTI RAMs emerging in at least 3 subjects who were virologically failing included Y181C (n = 8), V90I (n = 3), L100I (n = 3) and E138A (n = 3). These 4 NNRTI RAMs have been previously described as ETR RAMs and were also seen as emerging mutations in virologic failures in the adult DUET studies.

Both genotypic (i.e. emergence of 1 or more ETR RAM(s) and an increase in ETR weighted genotypic score from 0-2 at Baseline to > 2.5 at Endpoint) and phenotypic (i.e. an increase in ETR FC > 3.0 at Endpoint) development of resistance to ETR was observed in 9 out of the 23 virologic failures (39.1%) who had available genotype and phenotype data at Baseline and Endpoint. For 11 of 23 (47.8%) virologic failures, no development of resistance to ETR was observed, whereas in 3 of the 23 (13.0%) virologic failures ETR resistance was demonstrated by phenotype only.

The proportion of responders (< 50 copies/mL TLOVR [non-VF censored]) at Week 48 was greater among those with a lower baseline ETR FC. For subjects with ETR FC < 3,63.6% (42/66) responded and 50.0% (4/8) responded when ETR FC values were between 3 and 13. Similarly, a higher rate of virologic response was observed for subjects with a baseline ETR weighted genotypic score of 0-2 (52/77, 67.5%) compared to those with a baseline ETR weighted genotypic score of 2.5-3.5 (2/8, 25.0%). Note that the subgroups with reduced ETR sensitivity (either phenotypically or genotypically) were small.

Pharmacokinetic/pharmacodynamic relationship

The Week 48 analysis of study TMC125-C213, in which treatment-experienced HIV-1 infected pediatric subjects (6 years to < 18 years of age) were treated with ETR at a target weight-based dose of 5.2 mg/kg b.i.d. (up to a maximum of 200 mg b.i.d.), confirmed that ETR exposure was slightly higher in subjects with a virologic response (< 50 copies/mL) when compared with the non-responders. For subjects in the lowest ETR AUC_{12h} quartile (AUC ≤ 2704 ng.h/mL), the virologic response rate defined as achieving plasma VL < 50 copies/mL (TLOVR non-VF censored; 40.9%) at Week 48 was lower compared to subjects in higher ETR AUC_{12h} quartiles (range 66.7% to 76.2%). Similar results were observed with plasma trough concentration C_{0h}. Note that these findings should be interpreted with caution because the sample size limits the ability to draw firm conclusions.

Exploration of adherence and taste:

The proportion of subjects who were adherent (i.e. level of adherence > 95%) to ETR up to Week 24 as assessed by pill count was 44.4% (16 subjects) in children and 37.0% (20 subjects) in adolescents.

Taste acceptability of ETR dispersed in water was assessed at Week 2 using a modified questionnaire form incorporating a 5-point hedonic facial scale. The 5 response categories were (1) really good, (2) pretty good, (3) okay, (4) not good, and (5) terrible. Overall, 30% considered that the taste was “not good” or even “terrible”.

Mode of administration, palatability and impact on adherence, predictive factors of virologic failure

In study C213, the 25 mg tablet was administered alone in 3 children. All the other paediatric patients received either a combination of 100 and 25 mg tablets [24/41 (59%) of the children; 4/60 adolescents] or the 100 mg tablet [56/60 (93%) of the adolescents; 14/41 (34%) of the children]. Table 7 summarized the available data on adherence.

Table 7. Adherence in study C213

	Children	**Adolescent**
Patient is adherent according to pills count	16/ 44 (44,4%)	20/54 (37%)
Patient is Adherent according to questionnaire	31/40 (77.5%)	41/58 70.7%

Higher exposure is observed in subjects with higher adherence. However, it is noted that in observant patients (adherence > 95% assessed by pill count) mean AUC and mean C_{0h} remain higher in children than in adolescents.

Data by age strata concerning adherence (assessed by pill count more reliable than questionnaire) and virological failure (VF) at week 24 (see table 8) do not provided a clear understanding of the relationship between these two parameters: in VF, non adherence is an apparent major risk factor in adolescents but not clearly in children; in adherent patients, the difference between the two groups seems less marked.

Table 8. Adherence (assessed by pill count more reliable than questionnaire) and virological failure (VF) at week 24

	Children	**Adolescent**
Patient with VF	43% adherent (vs 57% non adherent)	25% adherent (vs 75% non adherent)
Patient non-adherent (pills count)	40 % VF (vs 60 % in success)	53 % VF (vs 47% in success)

An analysis performed on the all paediatric population identified lower exposure as a risk factor for virological failure.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9. Summary of Efficacy for trial C213

<table>
<tr><td colspan="3">Title: A Phase II open-label trial to evaluate the safety, tolerability and antiviral activity of TMC125 in antiretroviral experienced HIV-1 infected children and adolescents.</td></tr>
<tr><td>Study identifier</td><td colspan="2">TMC125-TiDP35-C213</td></tr>
<tr><td>Design</td><td colspan="2">Phase II, open-label study to assess the safety, tolerability, pharmacokinetics and antiviral activity of ETR during a 48-week treatment with ETR, when added to an investigator-selected optimized OBR comprising of a low-dose rtv-boosted PI (either [LPV, DRV, ATV or SQV) in combination with N[t]RTIs in treatment-experienced HIV-1 infected pediatric subjects. RAL use was permitted as part of the OBR. The OBR had to contain at least 2 active ARVs. The additional use of ENF was optional.</td></tr>
<tr><td></td><td>Duration of main phase:</td><td>48 weeks</td></tr>
<tr><td></td><td>Duration of Run-in phase:</td><td>Screening period of maximum 6 weeks</td></tr>
<tr><td></td><td>Duration of Extension phase:</td><td>4-week post-treatment period for those who were not continuing ETR in another study or program</td></tr>
<tr><td>Treatments group</td><td colspan="2">Treatment-experienced, HIV-1 infected paediatric subjects between the ages of 6 and < 18 years, on a stable regimen with a confirmed HIV-1 plasma viral load ≥ 500 copies/mL.
ETR was administered with food and dosed per body weight, i.e. 5.2 mg/kg twice daily (b.i.d.) up to a maximum of 200 mg b.i.d. (the dose recommended in adults).</td></tr>
<tr><td>Endpoints and definitions</td><td colspan="2">Primary endpoint: safety, tolerability, pharmacokinetics and antiretroviral activity of ETR.

It should be noted that, without any comparison, the efficacy evaluation was addressed only to a limited extent.</td></tr>
<tr><td>Database lock</td><td colspan="2">30th August 2011</td></tr>
<tr><td colspan="3"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="2">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="2">Intent to treat</td></tr>
<tr><td>Pharmacokinetic</td><td colspan="2"><table>
<tr><td>Parameter</td><td>N = 101</td></tr>
<tr><td>AUC_{12h} (ng•h/ml)</td><td></td></tr>
<tr><td>Geometric Mean ± Standard Deviation</td><td>3,729 ± 4,305</td></tr>
<tr><td>Median (Range)</td><td>4,560 (62 - 28,865)</td></tr>
<tr><td>C_{0h} (ng/ml)</td><td></td></tr>
<tr><td>Geometric Mean ± Standard Deviation</td><td>205 ± 342</td></tr>
<tr><td>Median (Range)</td><td>287 (2 – 2,276)</td></tr>
<tr><td colspan="2">The exposure in children with the 5.2 mg/kg b.i.d dose was comparable to the exposure observed in the studies conducted in the adult patients.</td></tr>
</table></td></tr>
<tr><td>Safety</td><td colspan="2">The safety data did not give rise to any new or major concerns.
Severe rashes are the main safety issue of ETR and have occurred in the</td></tr>
</table>

Title: A Phase II open-label trial to evaluate the safety, tolerability and antiviral activity of TMC125 in antiretroviral experienced HIV-1 infected children and adolescents.	
	adolescents and the children exposed to ETR as part of studies C213. The overall frequencies of "skin events of interest" were similar in adults and paediatric patients. Gender was identified as an important prognostic risk factor for the development of rash with female being more at risk than men.
Efficacy	Percentage of subjects with virologic response Plasma viral load < 50 copies/mL at Week 24 according to the NC=F imputation method: 52.5% of all subjects [children (58.5%); adolescents (48.3%)] Plasma viral load < 50 copies/mL at Week 48 according to the NC=F imputation method: 56.4% of all subjects [children (68.3%); adolescents (48.3%)] Plasma VL < 50 copies/mL according to the TLOVR algorithm at Week 48: 53.5 [children (68.3%); adolescents (43.3%)] Plasma viral load < 400 copies/mL at Week 48: 63.4% of all subjects Change in Plasma Viral Load from Baseline Mean (SE) change in log10 plasma VL from Baseline at Week 48: -1.53 (0.132) log10 copies/mL for all subjects Immunologic change Mean change in absolute CD4 cell count from Baseline at Week 48: +156 x 106 cells/L overall

1.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study TMC125-C213 was designed as an open-label, single arm study to evaluate the safety, tolerability, pharmacokinetics and antiretroviral activity of ETR in a treatment-experienced paediatric population.

The study design of the Phase II study TMC125-C213 is in line with current recommendations in the Guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02. Revision 2, 20 November 2008) which stipulate that extrapolation to children from efficacy data obtained in adults is acceptable if reliable pharmacokinetic data allow for proper dose recommendations.

Given the similarity of the disease in adults and children, the CHMP acknowledged that there is no need to duplicate the level of efficacy demonstration obtained in adults since the dose has been adequately selected on the basis of the adult exposure. However, it should be noted that, without any comparison, the efficacy evaluation was addressed only to a limited extent.

Efficacy data and additional analyses

In study C213, patients with a low viral load (< 20 000 copies/mL) were the majority (62,4%) while patients with high VL (>100 000 copies) represented only 11% of the overall population. In the DUET studies, the population was heavily pre-treated and at an advanced stage of the disease (60% being classified in CDC category C, with median viral load approx 4.8 log10 copies/ml and approx 100/mm3 median CD4).

Seventy two per cent (72%) of adolescents has already received 6 or more ARVs, while only 39% of children did so. All main classes (NNRTI, PI and NRTI) have already been used, the number of molecules in each class being accordingly greater among older patients over 12 years old. The majority of children and adolescents have previously received 1 NNRTI.

The primary efficacy parameter was virologic response defined as the percentage of subjects with plasma viral load < 50 copies/mL calculated according to the NC=F imputation method. Based on this analysis, 52.5% of all subjects had a plasma viral load < 50 copies/mL at Week 24, with a better efficacy response observed in children (58.5%) than in adolescents (48.3%). At Week 48, the overall proportion of responders with VL < 50 copies/mL was slightly increased to 56.4%.

The percentage of subjects with virologic response defined as a plasma VL < 50 copies/mL according to the TLOVR algorithm at Week 48 was 53.5 (68.3% in children and 43.3% in adolescents).

At Week 48, 63.4% of all subjects had a confirmed plasma VL < 400 copies/mL, and 60.4% of all subjects had a confirmed ≥ 1 $\log_{10}$ decrease in plasma VL versus Baseline, calculated according to the TLOVR algorithm.

Overall, these 48 weeks data speak in favour of a sustainability of the virologic suppression. While mostly receiving the adult dose (i.e. maximum dose), adolescents had lower virologic suppression as compared to adults and children. This might be related to adherence; however the data collected cannot allow drawing formal conclusion.

The change in log10 plasma VL from Baseline was calculated using the NC=F imputation method. A mean decrease in log10 plasma VL from Baseline was observed at all time points. At Week 48, the mean (SE) change in log10 plasma VL from Baseline was -1.53 (0.132) log10 copies/mL for all subjects.

An increase in absolute CD4 cell count was observed at all time points. The beneficial effect of ETR on restoration of the immune function was shown by a clear immunologic response versus Baseline at Week 24 and this was still observed at Week 48. At Week 48, the mean change in absolute CD4 cell count from Baseline was +156 x 10^6 cells/L overall.

In conclusion, it appears from the study C213 that paediatric patients achieved similar virologic suppression as compared to that observed in adults from the pivotal DUET studies.

1.5.3. Conclusions on the clinical efficacy

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

Study C213 has been designed accordingly and therefore efficacy wasn't a primary endpoint. However, overall, the 48 weeks data are in favour of a sustainability of the virologic suppression over time in the paediatric population.

1.6. Clinical safety

Patient exposure

Study TMC125-C126

This phase I multi-centre study was conducted from 29 September 200 to 27 February 2008. Thirty-five treatment-experienced HIV-1 infected subjects participated in this study. Twenty-one subjects started treatment in Stage 1 of the study, testing the 4 mg/kg b.i.d. dose regimen; 10 children aged 6 to < 12 years and 11 adolescents aged 12 to < 18 years. One adolescent prematurely discontinued Stage 1 after 1 ETR intake due to a grade 3 creatinine elevation in the pre dose sample. All other subjects completed the 8-day treatment period of Stage 1. Twenty-one subjects (12 children and 9

adolescents) started treatment in Stage 2 of the study, in which ETR was dosed at 5.2 mg/kg b.i.d. up to a maximum of 200 mg b.i.d. All subjects completed the 8-day treatment period of Stage 2. Seven subjects (3 children and 4 adolescents) participated in both Stage 1 and 2 of this study.

Study TMC125-C213

The median duration of ETR treatment from first intake up to the time of the cut-off date for the Week 24 analysis was 48.1 weeks, with a maximum individual duration of 97 weeks. The total patient-years of ETR exposure was 91.4 at the time of the cut-off date. The most frequently used dose of ETR in this study is the adult dose of 200 mg b.i.d. (69.3%). Most adolescents started on this dose (93.3%). In children, 34.1% started on 200 mg b.i.d., 29.3% on 150 mg b.i.d. and 26.8% on 125 mg b.i.d. Most of the patients received the adult formulation. Indeed, 69.3% of the overall paediatric population received the adult formulation (34.1% of the children between 6 and 12 year-old and 93.3 % of the adolescents). Only 65.9% of the 41 children received the paediatric formulation.

Adverse events

Study TMC125-C126

Overall, 14 subjects (66.7%) and 9 subjects (42.9%) reported at least 1 AE in Stage 1 and 2, respectively. The most common AEs were headache (14.3% in both Stages); and rhinitis (9.5% in both Stages). Five subjects (28.3%) in Stage 1 and 6 subjects (28.6%) in Stage 2 had an AE that was considered at least possibly related to ETR by the investigator.

There were no treatment-emergent SAEs in either stage of the study; one SAE (grade 1 influenza considered by the investigator to be not related to ETR) was reported in a child during follow-up of Stage 1. One adolescent reported a grade 3 AE (increased creatinine on Day 1 predose) which led to permanent discontinuation and another patient reported a grade 4 AE (increased triglycerides considered probably related to ETR and possibly related to the background regimen). Apart from these grade 3 and grade 4 AE, all other AEs were grade 1 or 2. Three subjects (2 children [9.5%] during stage 1 and one child [4.8%] during stage 2) reported skin events during the administration of ETR.

Treatment-emergent neuropsychiatric events of interest were reported in 3 subjects (14.3%) in stage 1 and in 4 subjects (19.0%) in stage 2. Headache was the most frequently reported AE in this SOC. No hepatic, pancreatic or cardiac events of interest were described in this phase I open-label study.

Study TMC125-C213

Table 10. Adverse Drug Reactions – TMC125-C213 Week 48 Analysis

System Organ Class Grouped Preferred term[a], n (%)	All subjects N = 101			
	Any ADR	At least Grade 2 ADRs	Serious ADRs	ADRs leading to permanent stop
At least 1 ADR	**67 (66.3)**	**42 (41.6)**	**0**	**5 (5.0)**
Gastrointestinal disorders	**36 (35.6)**	**11 (10.9)**	**0**	**0**
Diarrhea	16 (15.8)	6 (5.9)	0	0
Vomiting	11 (10.9)	4 (4.0)	0	0
Nausea	10 (9.9)	1 (1.0)	0	0
Abdominal pain	7 (6.9)	1 (1.0)	0	0
Constipation	4 (4.0)	0	0	0
Abdominal distension	1 (1.0)	0	0	0
Blood amylase increased	1 (1.0)	1 (1.0)	0	0
Gastroesophageal reflux disease	1 (1.0)	0	0	0
Lipase increased	1 (1.0)	1 (1.0)	0	0
Skin and subcutaneous tissue disorders	**27 (26.7)**	**16 (15.8)**	**0**	**4 (4.0)**
Rash	24 (23.8)[b]	15 (14.9)	0	4 (4.0)
Dry skin	1 (1.0)	0	0	0
Erythema multiforme	1 (1.0)	1 (1.0)	0	0
Prurigo	1 (1.0)	0	0	0
Nervous system disorders	**10 (9.9)**	**4 (4.0)**	**0**	**0**
Headache	9 (8.9)	4 (4.0)	0	0
Somnolence	1 (1.0)	0	0	0
Metabolism and nutrition disorders	**8 (7.9)**	**5 (5.0)**	**0**	**0**
Hypertriglyceridemia	4 (4.0)	2 (2.0)	0	0
Hypercholesterolemia	3 (3.0)	3 (3.0)	0	0
Anorexia	1 (1.0)	1 (1.0)	0	0
Hyperglycemia	1 (1.0)	0	0	0
Blood and lymphatic system disorders	**5 (5.0)**	**4 (4.0)**	**0**	**0**
Anemia	2 (2.0)	1 (1.0)	0	0
Thrombocytopenia	2 (2.0)	2 (2.0)	0	0
Neutropenia	1 (1.0)	1 (1.0)	0	0
Respiratory, thoracic and mediastinal disorders	**3 (3.0)**	**3 (3.0)**	**0**	**0**
Bronchospasm	3 (3.0)	3 (3.0)	0	0
Eye disorders	**2 (2.0)**	**1 (1.0)**	**0**	**0**
Vision blurred	2 (2.0)	1 (1.0)	0	0
Psychiatric disorders	**2 (2.0)**	**0**	**0**	**0**
Anxiety	1 (1.0)	0	0	0
Nightmare	1 (1.0)	**0**	0	0
General disorders and administration site conditions	**1 (1.0)**	**1 (1.0)**	**0**	**0**
Fatigue	1 (1.0)	1 (1.0)	0	0
Immune system disorders	**1 (1.0)**	**1 (1.0)**	**0**	**1 (1.0)**
Drug hypersensitivity	1 (1.0)	1 (1.0)	0	1 (1.0)

N = number of subjects, n = number of subjects with ADR

AE of special interest: Skin events

During the treatment period, 22.0% of children and 36.7% of adolescents were reported with skin events of interest. “Rash Cases” was the most common category.

Table 11. Treatment-Emergent Skin Events of Interest (Regardless of Severity or Causality)

Skin Events of Interest During Treatment Period Category Preferred Term, n (%)	Children ≥ 6 to < 12 years N = 41	Adolescents ≥ 12 to < 18 years N = 60	All subjects N = 101
Any Skin Event of Interest	**9 (22.0)**	**22 (36.7)**	**31 (30.7)**
Rash Cases	**6 (14.6)**	**17 (28.3)**	**23 (22.8)**
Rash	2 (4.9)	9 (15.0)	11 (10.9)
Rash Maculo-papular	3 (7.3)	6 (10.0)	9 (8.9)
Rash Papular	2 (4.9)	1 (1.7)	3 (3.0)
Rash Erythematous	0	1 (1.7)	1 (1.0)
Rash Generalized	0	1 (1.7)	1 (1.0)
Rash Macular	1 (2.4)	0	1 (1.0)
Rash Pruritic	0	1 (1.7)	1 (1.0)
Severe Cutaneous Reactions	**3 (7.3)**	**4 (6.7)**	**7 (6.9)**
Conjunctivitis	2 (4.9)	4 (6.7)	6 (5.9)
Erythema Multiforme	1 (2.4)	0	1 (1.0)
Angioedema	**1 (2.4)**	**3 (5.0)**	**4 (4.0)**
Choking	0	1 (1.7)	1 (1.0)
Hypersensitivity	1 (2.4)	0	1 (1.0)
Urticaria Papular	0	1 (1.7)	1 (1.0)
Wheezing	0	1 (1.7)	1 (1.0)

N = number of subjects, n = number of subjects with observations

Rash Cases

Rash cases were reported in 23 (22.8%) subjects, 6 (14.6%) children and 17 (28.3%) adolescents. Of the 23 rashes reported during treatment with ETR, 18 (78.3%) were considered at least possibly related to ETR by the investigator. In both age groups, rashes during treatment with ETR occurred early. The median time to first onset was 10 days (range 5 to 119 days) and the median duration was 7 days (range 2 to 29 days). Rashes during treatment with ETR were usually grade 1 or 2 in severity. One subject in each age group developed a grade 3 rash, and 4 subjects (1 child and 3 adolescents) discontinued treatment because of rash. No grade 4 rashes or rash-related SAEs were reported. By sex, 17 (26.6%) females and 6 (16.2%) males were reported with rash cases. In the pooled DUET studies, rash occurred in 28.3% of females and 15.8% of males in adults. Skin adverse events occurred almost in a third of patients (30.7%) and, as already mentioned, the frequency is more important in adolescents than in children. Additionally, females seemed more at risk of rashes than males. The distribution of rashes by sex was similarly reported in adults' study (DUETs) (see below).

Comparison of incidence of adverse drug reactions in study TMC125-C213 with other studies with ETR

Data of the Week 48 analysis of the pooled Phase III DUET studies in ETR-treated adults (N = 599) are tabulated side-by-side with the data of the Week 48 analysis of TMC125-C213 (N = 101) in table 12 below. Overall, the incidence of ADRs was similar in both age groups.

Table 12. Incidence of Adverse Drug Reactions in the Pooled DUET Studies Week 48 Analysis and in Study TMC125-C213 Week 48 Analysis.

Study Age at Screening Treatment AE Summary, n (%)	Pooled DUET Week 48 Adults ETR N = 599	TMC125-C213 6 to < 18 years ETR N = 101
Median exposure, weeks (range)	52.3 (2 – 85)	48.9 (1 – 97)
At least one ADR	**475 (79.3)**	**67 (66.3)**
At least one Serious ADR	41 (6.8)	0
At least one grade 2 or more ADR	330 (55.1)	42 (41.6)
At least one grade 3 or 4 ADR	133 (22.2)	11 (10.9)
At least one ADR leading to permanent discontinuation	31 (5.2)	5 (5.0)

N = number of subjects with data; n = number of observations

The incidence of individual ADRs in paediatric subjects was not different from the incidence in adults. The ADR rash was reported slightly less frequently in the DUET studies (19.2%) than in paediatric subjects (23.8%) (Table 13); this difference of 4.6% is not considered significant since the confidence interval encompasses zero (95% CI of -4.3% to 13.4% [ad hoc analysis]). In addition, there were a lower proportion of female subjects in the DUET studies: 10.0% female ETR-treated subjects compared to 63.4% in the paediatric study. In the Week 48 safety analysis of the DUET studies, rash was reported as an ADR with ETR in 30.0% of females and in 18.0% of males. In the Week 48 safety analysis of study TMC125-C213, the ADR rash was recorded in 26.6% of females and in 18.9% of males. ADR rash with severity 2 or greater was recorded in 20.3% females and in 5.4% of males in study TMC125-C213. These data suggest that the incidences of ADRs in study TMC125-C213 are not different from those seen in the DUET studies, and that female sex seems to be a risk factor for developing rash in paediatric subjects.

The type and natural evolution of the rash in children and adolescents was similar to the rash reported in adults: most often, rash was mild to moderate, of macular/papular type, occurred mostly in the second week of therapy, was self-limiting, resolved within 1 week on continued therapy and lead to treatment discontinuation in 4.0% of the paediatric study population.

Table 13. Incidence of all ADRs in Study TMC123-C213 Week 48 Analysis, and Incidence of these ADRs in the Pooled DUET Studies Week 48 Analysis

System Organ Class Grouped Preferred term, n (%)	Pooled DUET Week 48[a] Adults N = 599	TMC125-C213 6 to < 18 years N = 101
Median exposure, weeks (range)	*52.3 (2 – 85)*	*48.1 (2 – 97)*
Any ADRs	**475 (79.3)**	***67 (66.3)***
Gastrointestinal disorders	**257 (42.9)**	**36 (35.6)**
Diarrhea	108 (18.0)	16 (15.8)
Vomiting	49 (8.2)	11 (10.9)
Nausea	89 (14.9)	10 (9.9)
Abdominal pain	50 (8.3)	7 (6.9)
Constipation	13 (2.2)	4 (4.0)
Abdominal distention	15 (2.5)	1 (1.0)
Blood amylase increased	18 (3.0)	1 (1.0)
Gastroesophageal reflux disease	14 (2.3)	1 (1.0)
Lipase increased	12 (2.0)	1 (1.0)
Skin and subcutaneous tissue disorders	**161 (26.9)**	**27 (26.7)** [b]
Rash (grouped term)	115 (19.2)	24 (23.8) [b]
Dry skin	10 (1.7)	1 (1.0)
Erythema multiforme	0	1 (1.0)
Prurigo	9 (1.5)	1 (1.0)
Nervous system disorders	**136 (22.7)**	**10 (9.9)**
Headache	65 (10.9)	9 (8.9)
Somnolence	11 (1.8)	1 (1.0)
Metabolism and nutrition disorders	**110 (18.4)**	**8 (7.9)**
Hypertriglyceridemia	41 (6.8)	4 (4.0)
Hypercholesterolemia	31 (5.2)	3 (3.0)
Anorexia	14 (2.3)	1 (1.0)
Hyperglycemia	11 (1.8)	1 (1.0)
Blood and lymphatic system disorders	**43 (7.2)**	**5 (5.0)**
Anemia	36 (6.0)	2 (2.0)
Thrombocytopenia	10 (1.7)	2 (2.0)
Neutropenia	15 (2.5)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	**8 (1.3)**	**3 (3.0)**
Bronchospasm	7 (1.2)	3 (3.0)
Eye disorders	**12 (2.0)**	**2 (2.0)**
Vision blurred	12 (2.0)	2 (2.0)
Psychiatric disorders	**70 (11.7)**	**2 (2.0)**
Anxiety	23 (3.8)	1 (1.0)
Nightmare	2 (0.3)	1 (1.0)
General disorders and administration site conditions	**56 (9.3)**	**1 (1.0)**
Fatigue	48 (8.0)	1 (1.0)
Immune system disorders	**10 (1.7)**	**1 (1.0)**
Drug hypersensitivity	9 (1.5)	1 (1.0)

[a] ADRs identified in the pooled DUET studies but not in study TMC125-C213 are not recorded in this table.
[b] Since the AE papular urticaria was not grouped under 'rash' but under 'angioedema' in the AE of interest analysis, and under 'rash' in the ADR analysis, the incidence of the AE of interest rash (n = 23) is lower than the incidence of the ADR rash (n = 24).
N = number of subjects with data; n = number of observations

Serious adverse event / deaths / other significant events

Severity and relatedness

Overall, the incidence of grade 3 or grade 4 AEs (13.9%), regardless of causality, was low. All grade 3 or 4 AE preferred terms were reported in no more than 2 subjects. Only 2 subjects (both children) were reported with a grade 4 AE (both thrombocytopenia). Both grade 4 AEs were considered not related to ETR. The percentage of subjects with at least 1 AE assessed as at least possibly related to

ETR was 22.0% for children and 40.0% for adolescents. By SOC, most AEs considered at least possibly related to ETR occurred in the SOCs skin and subcutaneous tissue disorders (12.2% in children and 23.3% in adolescents) and gastrointestinal disorders (4.9% and 20.0%). By preferred term, the most common individual events considered at least possibly related to ETR were rash (4.9% and 11.7%), rash maculo-papular (7.3% and 10.0%), and diarrhea (2.4% and 10.0%). All other preferred terms at least possibly related occurred in no more than 3 subjects. AEs that were considered very likely related to ETR included abdominal pain upper (1 child), rash maculo-papular (1 adolescent) and overdose (1 adolescent). The most frequently reported AE preferred terms with at least grade 2 severity and at least possibly related to ETR included rash maculo-papular (7.3% in children and 8.3% in adolescents), rash (2.4% and 5.0%), and diarrhea (none and 5.0%). All other AE preferred terms with at least grade 2 severity and at least possibly related to ETR occurred in no more than 1 subject. The most frequently reported AE preferred terms with at least grade 3 severity and at least possibly related to ETR included diarrhea (1 adolescent), hypersensitivity (1 child) and rash maculo-papular (1 child).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths were reported in this study. Overall, 5 adolescents were reported with at least 1 SAE during the treatment period. There were no SAEs reported during treatment in children. No new issue emerged from these data. One adolescent experienced a SAE (overdose with ETR) considered very likely related to treatment with ETR; all other SAEs were considered not related to ETR. One adolescent permanently discontinued treatment because of an SAE (drug resistance).

Pregnancies

Two pregnancies were reported during the study. As per protocol, both subjects were withdrawn from the study.

Laboratory findings

Study TMC125-C126

Most of the laboratory abnormalities were Grade 1 or 2, except for the Grade 3 increase in pancreatic amylase, Grade 4 increase in triglycerides and also Grade 3 blood creatinine in the pre dose sample day 1 adolescent which led to permanent discontinuation.

Study TMC125-C213

The most common treatment-emergent graded laboratory abnormalities were lipid-related, and mainly included increases in total cholesterol (50.0% in children and 38.8% in adolescents) and LDL calculated (31.6% and 25.0%). The incidence of other treatment-emergent graded laboratory abnormalities was low in both age groups. The majority of graded laboratory abnormalities were grade 1 or 2. Grade 3 laboratory abnormalities were uncommon and included increases in LDL calculated fasting (1 adolescent), bilirubin (2 adolescents) and plasma prothrombin time (1 child and 2 adolescents), and decreases in neutrophils (1 child and 2 adolescents). One child was reported with a grade 4 abnormality (platelet count decreased). The most common graded laboratory abnormalities were lipid-related, mainly increases in total cholesterol fasting (40.2%) and LDL fasting (24.4%). All abnormalities in total cholesterol and LDL were grade 1 or 2 except for 1 adolescent who had a grade 3 increase in LDL cholesterol.

Cardiovascular safety

Vital signs

The within-group comparison for the changes from Baseline in vital signs parameters at Week 48 revealed a statistically significant difference at the 0.05 level (Wilcoxon signed-rank test) for pulse (p = 0.0177) in all subjects. No statistically significant changes from Baseline were observed for blood pressure. Among newly available data from the 48 week report of TMC213, the within-group comparison for the changes from baseline in vital signs parameters at Week 48 revealed a statistically significant increase for pulse (mean increase: 3.39 (SE: 1.5); p = 0.0177) in all subjects. Although this small mean increase might not be of clinical relevance, the risk of tachycardia should be monitored and any relevant case should be reported as part of the PSUR.

Individual abnormalities in vital signs

Grade 3 increased DBP and SBP occurred in 15.8% and 25.7% of subjects, respectively. Three children and 6 adolescents had pyrexia reported as a grade 1 or 2 AE, considered not or doubtfully related to ETR. No treatment-emergent AEs related to a vital signs abnormality were reported in this study.

Safety in special populations

Pubertal development – Tanner Scale

The assessment of pubertal development was performed by a modified Tanner assessment, consisting of a discrete visual inspection and comparison to the illustrated Tanner scales provided in the electronic case report file. Since puberty starts at 8 years of age in girls, and at 10 years in boys, pubertal maturity using the Tanner scales is performed from 8 years onwards. A total of 96 subjects were included in the Tanner stage assessment at Baseline, 83 subjects had Week 24 data and 75 subjects had Week 48 data. Overall, there were no findings suggestive of delayed sexual maturation.

With respect to the development of genitalia and breasts in adolescents, at Baseline, 2 (3.3%) subjects were classified as stage I (pre-pubertal stage) and 19 (31.7%) subjects were classified as stage V (puberty completed). By Week 48, all subjects had started puberty and the proportion of subjects who completed puberty had increased to 40.9%. A similar evolution was seen with regard to the development of pubic hair in adolescents. At Baseline, 7 (11.7%) subjects were at pre-pubertal stage (stage I) and 19 (31.7%) subjects were classified as stage V. By Week 48, 19 (43.2%) subjects had completed puberty (stage V) and there were no subjects in stage I anymore.

Growth and development

At Baseline, the mean age-adjusted z-scores indicated that children were below the normal population median with respect to height (-1.21), weight (-0.97) and BMI (-0.30). The mean age-adjusted z-scores for height (-1.05) and weight (-0.46) in adolescents were also below the normal population median, but the BMI (0.07) was normal. The mean age-adjusted z-scores remained stable over time during ETR treatment. The within-group comparison for the changes from Baseline for the age-adjusted z-scores at Week 48 showed no significant changes for height (+0.02 in children and +0.03 in adolescents), weight (+0.02 and +0) and BMI (-0.03 in both children and adolescents).

Relationship between pharmacokinetics and safety in TMC125-C213 week 48 primary analysis

The categories 'Rash' (grouped term, skin events of interest), neuropsychiatric events of interest, as well as the preferred terms headache, diarrhea, nausea, dizziness, somnolence, insomnia, depression and anxiety were included in the pharmacokinetic/safety analyses. A higher incidence of rash in the highest AUC_{12h} quartile (AUC > 6454 ng.h/mL) was observed. It should be noted that these subjects were more likely to have a different PI in their OBR than LPV/rtv or DRV/rtv. This is consistent with the findings of the multivariate logistic regression model, which identified, among others, ETR AUC_{12h} and the PI in the OBR as a potential independent prognostic factor for the development of rash. The median ETR AUC_{12h} for subjects using LPV/rtv (n = 39), DRV/rtv (n = 52) or another boosted PI (n = 10) in the OBR was 3156 ng.h/mL, 4518 ng.h/mL and 6885 ng.h/mL, respectively (ad hoc analysis). No firm conclusions can be drawn from these exploratory analyses due to the small sizes of the subgroups and potential confounding factors. There was no apparent relationship between ETR AUC_{12h} and the other selected categories of AEs of interest.

Discontinuation due to adverse events

In study C213, 2 (4.9%) children and 6 (10.0%) adolescents permanently discontinued ETR due to (S)AEs. The number of subjects with at least 1 AE for which treatment with ETR was temporarily interrupted was 3 (7.3%) for children and 5 (8.3%) for adolescents. Four subjects discontinued treatment with ETR due to a rash-related event. One case of rash and both cases of rash maculo-papular were considered at least possibly related to ETR. Other events, leading to treatment discontinuation included pregnancy, drug resistance and hypersensitivity. The case of hypersensitivity was considered at least possibly related to ETR. Treatment was more interrupted for adverse event reasons in adolescents than in children.

Post marketing experience

In the last PSUR evaluation, there are only limited post-marketing data available in children/adolescents. According to the Article 9 of the Commission Regulation (EC) No 507/2006, the periodic safety update reports provided for in Article 24(3) of Regulation (EC) No 726/2004 shall be submitted to the Agency and Member States immediately upon request or at least every six months following the granting or renewal of a conditional marketing authorisation.

1.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

In the study C126, the reported events are compatible with the safety profile of ETR. Most of the skin events occurred within the 1st week of treatment and resolved with corrective treatment. No new safety signal emerged from these data.

Overall, 82.9% of children and 91.7% of adolescents experienced at least 1 AE in study C213. Grade 3 or 4 AEs occurred only in 6 (14.6%) children and 8 (13.3%) adolescents. A possible causal relationship was reported for 9 (22.0%) children and 24 (40.0%) adolescents by the investigator, and very likely related to ETR in one (2.4%) child and 2 (3.3%) adolescents. No death occurred up to the cut-off for the Week 48 analysis. Six adolescents reported serious adverse events whereas none were reported in children. Treatment with ETR was permanently discontinued because of an AE for 2 (4.9%) children

and 6 (10.0%) adolescents, and was temporarily interrupted in 3 (7.3%) children and 5 (8.3%) adolescents.

Severe rashes are the main safety issue of ETR and were firstly identified in adults. In September 2009, hypersensitivity reactions including TEN, SJS and DRESS were added in the EU SPC and a DHCP was adopted and distributed within the EU to inform prescribers (EMEA/H/C/900/II/06). These events occurred in the adolescents and the children exposed to ETR as part of studies C213 and C126. A comparison between the paediatric and the adult safety data showed that the overall frequencies of "skin events of interest" were similar (27.9% in adults vs 30.7% in paediatric).

An ad hoc multivariate logistic regression model was used to identify potential prognostic factors for the development of rash. This analysis was performed for exploratory purposes only. Results should be interpreted with caution as sample sizes within the subgroups were small.

Gender was identified as an important risk factor (female being more at risk than men). At the CHMP request, the applicant performed a review of the literature that highlight a relationship between rash and female gender for some drugs, notably ARV. This review did not lead to definite explanation on this issue. As mentioned in the RMP, this risk will be monitored. In addition, this risk is adequately reflected in section 4.4 and 4.8 of the SmPC.

The specific PI used in the OBR was identified as a potential independent predictor of rash ($p < 0.05$) by the final multivariate model. Indeed, rash appeared to occur less frequently in subjects using LPV/rtv in the OBR (3 out of 39 subjects or 7.8%) compared to subjects using DRV/rtv (15 out of 52 or 28.9%) or another boosted PI (5 out of 10 or 50%). DRV has been associated with severe skin reactions such as SJS and TEN. Therefore, its association with ETR could potentiate the occurrence of these skin events.

Other factors that appeared to be weaker predictors of rash were race and region (both $p < 0.05$), with the incidence of rash increasing in White subjects and those living in North America. In addition, a higher incidence of rash cases with higher exposure (AUC_{12h}) to ETR was observed ($p < 0.05$). No firm conclusions can be drawn from these exploratory analyses due to the small sizes of the subgroups and potential confounding factors. There was no apparent relationship between ETR AUC_{12h} and the other selected categories of AEs of interest.

Although age was not identified as a risk factor in the above mentioned multivariate analysis, AE occurred more frequently in adolescents than in children.

In the study C213, there were no signals that rash, or other skin events of interest, presented any consistent biological pattern of associated signs or symptoms suggestive of a hypersensitivity syndrome. Similarly, no biological feature compatible with hypsensitivity syndrome was observed.

In the study C213, there were no noteworthy changes versus baseline with respect to the development of genitalia/breasts and pubic hair. ETR does not seem to have a major impact on growth. However, it is reminded that the length of exposure is quite short (48 weeks).

1.6.2. Conclusions on the clinical safety

Severe rashes are the main safety issue of ETR and were firstly identified in adults. These events occurred in the adolescents and the children exposed to ETR as part of studies C213 and C126. A comparison between the paediatric and the adult safety data showed that the overall frequencies of "skin events of interest" were similar. An ad hoc multivariate logistic regression model was used to identify potential prognostic factors for the development of rash and gender was identified as an important risk factor with female being more at risk than men.

This is adequately reflected in section 4.4 and 4.8 of the SmPC.

Overall, the safety data in the claimed paediatric indication do not give rise to new safety concerns in the paediatric population in comparison to the adult population and the CHMP concludes that the safety profile of ETR in the proposed indication is acceptable.

1.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk Management Plan

The applicant submitted a risk management plan (RMP). Overall, the RMP submitted by the applicant is in accordance with the "Guideline on Risk management systems for medicinal products for human use" (EMEA/CHMP/96268/2005) and with the Risk Management plan template (EMEA/192632/2006, published on October 2006).

Further to the issues covered by the RMP, the applicant should consider and discuss the following additional safety concerns: the risk of medical errors also for paediatric population, the age-dependant risk of overdosing/underdosing and the acceptability of the dispersed form of ETR as potential risks. Moreover, off-label use of Etravirine without a boosted PI should be considered.

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

- antiretroviral pregnancy registry,
- participation in the ongoing European RegiSCAR trial to monitor and characterise severe skin reactions in patients receiving etravirine,
- monitoring long term safety through HAART Oversight Committee.

The following studies in paediatric population are currently ongoing or planned:

- Trial TMC125-C213: An ongoing Phase II, open-label trial to to collect long-term safety data up to 48 weeks of ETR treatment in children aged 6 to less than 18 years of age,
- Trial TMC125-C239: An ongoing trial to provide continued access to ETR for paediatric subjects completing 48 weeks of treatment in trial TMC125-C213 and collect safety information beyond 48 weeks of ETR treatment in children aged 6 to less than 18 years of age,
- Trial IMPAACT P1090: A planned phase I/II, open-label trial to determine the appropriate dose of ETR in combination of an OBR and to determine the safety and tolerability of etavirine in combination with an OBR through 48 weeks of therapy in children aged ≥2 months to <6 years.

The applicant considers that no specific risk minimization measures beyond SmPC labelling are necessary which is endorsed.

Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important identified risks:		
1. Rash	**Routine pharmacovigilance** Including close monitoring and appropriate documentation of spontaneously reported cases of severe cutaneous reactions, through enhanced and standardised follow-up activities. Including a discussion on severe cutaneous reactions in each PSUR, with particular attention to patients with a history of rash to NNRTIs.**Additional Activities** The Company participates in the ongoing European RegiSCAR trial with the aim of further monitoring and characterising severe cutaneous reactions in patients receiving INTELENCE. Individual case reports will be forwarded by the MAH to RegiSCAR for review and assessment. Individual case assessment reports and bi-annual reports will be prepared and provided to the MAH	Listed in the Special warnings and precautions section of the SmPC (section 4.4), including advice for caution. Rash, Erythema multiforme, Stevens-Johnson syndrome, TEN and DRESS are listed as an ADR in Section 4.8.
2. Hepatotoxicity	**Routine pharmacovigilance** Monitoring of hepatic events in co-infected subjects in ongoing and planned trials, monitoring long-term safety through HAART Oversight Committee and routine PV monitoring.	Hepatic steathosis, increased ALT/AST, cytolytic hepatitis, hepatic steatosis, hepatitis and hepatomegaly are listed as ADRs in Section 4.8.
3. Pancreatitis	**Routine pharmacovigilance**	Pancreatitis, increase in amylase and lipase are listed as an ADR in Section 4.8.
4. Hyperlipidaemia	**Routine pharmacovigilance** **Additional Activities** **Monitoring long-term safety through HAART Oversight Committee.**	Hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia and dyslipidaemia are listed as ADRs in Section 4.8.
5. Coronary artery disorders	**Routine pharmacovigilance** **Additional Activities** **Monitoring long-term safety through HAART Oversight Committee.**	Myocardial infarction and angina pectoris are listed as an ADR in Section 4.8.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
4. Elderly (over 65 years of age)	**Routine pharmacovigilance**	Listed in Section 4.2. Listed in the Special warnings and precautions section of the SmPC (section 4.4).

1.8. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

ETR is a non nucleoside analogue that can retain some level of activity against strains harbouring NNRTI resistance. The conditional MA for Intelence relies on the two pivotal DUET studies, the design of which has been built on the principle to avoid functional monotherapy. Therefore, a boosted PI (i.e. DRV/RTV) was used as part of the OBT in the DUET studies. Data from these studies have established that ETR adds to the level of virologic suppression achieved by the OBT containing DRV/RTV and the conditional MA has been granted for use of ETR in combination with a boosted Protease inhibitor.

Study TMC125-C213 was designed as an open-label, single arm study to evaluate the safety, tolerability, pharmacokinetics and antiretroviral activity of ETR in a treatment-experienced paediatric population. The study design is in line with current recommendations in the Guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02. Revision 2, 20 November 2008) which stipulate that extrapolation to children from efficacy data obtained in adults is acceptable if reliable pharmacokinetic data allow for proper dose recommendations. Given the similarity of the disease in adults and children, the CHMP acknowledged that there is no need to duplicate the level of efficacy demonstration obtained in adults since the dose has been adequately selected on the basis of the adult exposure.

The pharmacokinetics of ETR in 101 treatment experienced HIV 1 infected paediatric patients, 6 years to less than 18 years of age and weighing at least 16 kg, showed that the administered weight based dosages resulted in ETR exposure comparable to that in adults receiving ETR 200 mg b.i.d. when administered at a dose corresponding to 5.2 mg/kg b.i.d. Therefore the CHMP considered that the 5.2 mg/kg dose was satisfactory.

The virologic suppression achieved in paediatric patients is similar to that achieved in adults from the DUET studies.

Uncertainty in the knowledge about the beneficial effects.

Despite the PK/PD data and the overall good virological and immunological response rates, the sample size was too small to draw definite conclusions.

Due to the open label design of study C213, the efficacy evaluation was addressed only to a limited extent.

While the adolescents were receiving the adult dose, the exposure in this age group was lower than the one in adults. In addition, adolescents had a trend for lower virologic response. More challenging adherence in adolescents could have driven this finding. Given the limitations of the adherence data collected, this possible relationship could not be established.

Risks

Unfavourable effects

The main safety concern for ETR is related to cutaneous disorders, sometimes severe such as hypersensitivity including DRESS, TEN and SJS. These issues have already been identified in adults and are confirmed in adolescents and children. As for the adult population, gender is a risk factor (female at higher risk) for cutaneous reaction.

Uncertainty in the knowledge about the unfavourable effects

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

As derived from the adult, gender is a risk factor (female at higher risk) for cutaneous reaction. The mechanisms behind this difference are not clear.

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 C126 and C213 lead to recommendation to use the dose of 5.2mg/kg in paediatric patients aged 6 years to less than 18 years of age and weighing at least 16 kg. The exposure in the paediatric population with the 5.2 mg/kg b.i.d dose was comparable to the exposure observed in the adult studies. Therefore, this dose was considered adequate by the CHMP and the CHMP concluded that extrapolation from adult to the paediatric population covered by the proposed indication is acceptable.

This is supported by the overall satisfactory virological and immunological response rates in Study C213.

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

As a consequence, the CHMP concluded that the benefit /risk balance is favourable for use of ETR in combination with a boosted PI and other ARV medicinal products for the treatment of HIV-1 infection in ARV treatment experienced paediatric patients aged 6 years to less than 18 years of age and weighing at least 16 kg.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Intelence in combination with a boosted PI and other ARV medicinal products for the treatment of HIV-1 infection in ARV treatment experienced paediatric patients from 6 years of age is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the conditions below.

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

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

Update the section 4.1 of the SmPC for the existing 100mg and 200mg tablet with the new paediatric indication (children from the age of 6 years) and introduce consequential changes to the Annexes I, II.C, IIIa and IIIb.

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

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

Risk Management plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

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

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities.

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached.

- At the request of the European Medicines Agency.

PSURs

The PSUR cycle for the product will follow the a half-yearly cycle until otherwise agreed by the CHMP.

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
TMC125IFD0000003 is a retrospective observational study which will be conducted to describe the antiretroviral activity of and resistance to etravirine in combination with background regimens containing boosted PI other than darunavir/ritonavir, using clinical cohort data of HIV-1 infected patients. Following agreement with the CHMP on the protocol, the final results for the study should be provided to the CHMP no later than 2Q 2013.	2Q 2013

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/273/2011) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.