21 April 2017
EMA/359350/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Celsentri

International non-proprietary name: maraviroc

Procedure No. EMEA/H/C/000811/X/0046/G

Note

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

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List of abbreviations

AE	Adverse event
AIDS	Acquired immune deficiency (HIV) syndrome
ARV	Antiretroviral drug(s)
ART	ARV therapy
AUC	Area under the time-concentration curve
AUC24	24 hour AUC
BID	Twice daily
BSA	Body surface area
Cavg	Average concentration
CCR5	C-C chemokine receptor 5
CCR5	tropic Using C C chemokine receptor 5
CD4+	Cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
CXCR4	C-X-C chemokine receptor 4
CYP, P450	Cytochrome P450
CYP3A, P4503A	Cytochrome P4503A
EC	European Commission
EMA;	EMEA European Medicines Agency
Emax	Maximal effect
FDA	US Food and Drug Administration
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IC50	Concentration producing 50% maximal inhibition
IC90	Concentration producing 90% maximal inhibition
Ka	Absorption rate constant
LDPE	Low Density Polyethylene
LOCF	Last observation carried forward

LPV/r	Lopinavir/ritonavir
m2	Square meter(s)
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
MD=F	Missing, discontinuation =failure
mg	Milligrams
Min	Minimum
Min-max	Minimum-maximum
mL	Milliliters
MVC	Maraviroc
NCA	Non compartmental analysis
NDA	New Drug Application (US)
ng	Nanogram(s)
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OBT	Optimized background therapy
P450, CYP	Cytochrome P450
P4503A CYP3A	Cytochrome P4503A
PDCO	Paediatric committee of the EMA
PD	Pharmacodynamic
PDVF	Protocol defined virologic failure
P-gp	P-glycoprotein efflux transporter
PI	Protease inhibitor
PIP	Paediatric investigation plan
PK	Pharmacokinetics
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
QWP	Quality Working Party
RH	Relative Humidity
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Standard deviation
SOC	System-order-class categories of MedDRA
TE	Treatment experienced

TEAE	Treatment emergent adverse events
Tmax	Time at which Cmax is reached
UNAIDS	Joint United Nations Program on HIV/AIDS
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
V2	Volume of central compartment
V3	Volume of peripheral compartment
VL	Virus load (HIV-1 RNA copies/mL plasma)

VPC Visual predictive check, a model evaluation technique that uses simulation based on a population model fit to compare data-derived statistics from the observed and simulated data files

1. Background information on the procedure

1.1. Submission of the dossier

ViiV Healthcare UK Limited submitted on 24 May 2016 a group of variations consisting of extensions of the marketing authorisation and the following variation:

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

The MAH applied for the addition of a new pharmaceutical form (20mg/ml oral solution), and 2 new strengths for film coated tablets (25 mg, 75 mg).

In addition, the MAH proposed to extend the indication for Celsentri, in combination with other antiretroviral medicinal products for treatment experienced adolescents and children of 2 years of age and older infected with only CCR5-tropic HIV-1 detectable (see section 4.2 and 5.1). As a consequence, sections 4.2 and 4.8, 5.1 and 5.2 of the SmPC are updated to detail posology in paediatric patients and to update the safety, efficacy and pharmacokinetic information, respectively. SmPC is also updated regarding existing information on adult patients in section 4.5 and the new strengths/pharmaceutical form in sections 6.3 and 6.5.

Annex II, Package Leaflet and Labelling are updated in accordance.

Furthermore, the PI is brought in line with the latest QRD template version 10.

The MAH applied for the following indication for new pharmaceutical form (20mg/ml oral solution), and 2 new strengths for film coated tablets (25 mg, 75 mg):

CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment experienced adults, adolescents and children of 2 years of age and older infected with only CCR5-tropic HIV-1 detectable (see section 4.2 and 5.1).

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0237/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0237/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0237/2015.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan

medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Bruno Sepodes

- The application was received by the EMA on 24 May 2016.
- The procedure started on 16 June 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2016.
- During the meeting on 29 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 13 October 2016, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 14 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 26 January 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 17 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 10 April 2017.
- During the meeting on 21 April 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for the group of extensions of the marketing authorisation and variation for Celsentri on 21 April 2017.

2. Scientific discussion

2.1. Problem statement

The Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that in 2014 more than 36 million people globally were living with HIV/Acquired Immune Deficiency Syndrome (AIDS) and that since 2000, 25.3 million people have died of AIDS-related illnesses. Globally, there were 2.6 million children living with HIV at the end of 2014, of whom 2.3 million live in sub-Saharan Africa.

The vast majority of HIV+ children are infected at time of birth (>90%). Although significant progress has been made, universal access to treatment to prevent mother to child transmission has not yet been achieved in many developing countries and a significant number of perinatal transmissions still occur. During 2014, 220,000 children (190,000 in sub-Saharan Africa) were newly infected. The majority of children with HIV/AIDS living outside sub-Saharan Africa are in Asia and the Pacific, with smaller numbers living in the United States of America (US), Europe and Latin America.

Actual access to therapy is lower in children than in adults in the high epidemic regions, and treatment outcomes are poor. There is still a gap between the numbers of agents that are available for children as compared to adults, in particular for the very young. Of note, antiretroviral treatment are nowadays recommended for all HIV-infected children, regardless of clinical symptoms, viral load or CD4 count according to HIV treatment guidelines, including that of WHO.

About the product

Celsentri (maraviroc) was first approved in the US in August 2007 (accelerated approval, followed by full approval in November 2008), and in the EU in September 2007. In addition to the US and EU, maraviroc is currently approved in more than 30 other countries. Maraviroc is presently available as 150 mg or 300 mg oral tablets. The present EU indication concerns Celsentri in combination with other antiretroviral medicinal products for the treatment of treatment-experienced adults infected with only CCR5-tropic HIV-1 detectable.

Maraviroc is a CCR5-inhibitor, and as such blocks the host cell co-receptor CCR5 that is utilized by CCR5-tropic viral strains, in addition to the CD4-receptor, in the process of viral entry. Maraviroc is presently the only antiretroviral agent that binds to the host and not to the virus.

Type of Application and aspects on development

Paediatric post marketing studies were required in the US and EU in association with approval of maraviroc. The scope of the approved Paediatric Investigation Plan in EU (PIP, October 17, 2008 Opinion), was similar to the US Pediatric Research Equity Act (PREA) requirements of the FDA.

Following interactions with the EMA and FDA, the Sponsor initiated Study A4001031 (main study of the present application, concerning children from age of 2-18 years), where recruitment started in 2009. Clinical investigation of paediatric subjects <2 years of age was planned to be started following the completion of Study A4001031. To enable adequate dosing in the younger ones two new tablet strengths were developed, and also an oral solution. The oral solution has, outside study A4001031, also been studied in an oral bioavailability study in adults (study A4001034).

Despite all efforts by the sponsor, the rate of enrolment in Study A4001031 declined to less than 1 subject per month by the year 2013 and no subject was enrolled 1Q/2Q 2014. The decline in recruitment was predominantly attributed to advances in availability and effectiveness of HIV treatment options for children and

a reduction in mother to child transmissions, since the planning of study 1031 in 2008. The sponsor's proposal to consequently stop enrolment was addressed in a PIP modification agreed upon after discussions with PDCO and the Modelling and Simulation Working Group (Opinion 18 July 2014). PIP Modification 5 was submitted on 18 June 2015 to request a waiver of the study in subjects ≤2 years (EMEA-000020-PIP01-07-M05; agreed 21 September 2015). In summary, the application is considered adequate to fulfil the requirements of the PIP in the EU. These plans, including the waiver for the youngest, were also agreed upon by the FDA.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 25 mg or 75 mg maraviroc as active substance and as an oral solution containing 20 mg/ml maraviroc as active substance.

Other ingredients are:

- For the film coated tablets:

Tablet core : microcrystalline cellulose, calcium hydrogen phosphate, anhydrous, sodium starch glycollate, magnesium stearate;

Film-coat: poly vinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, soya lecithin, indigo carmine aluminium lake (E132);

- For the oral solution: anhydrous citric acid, sodium citrate dihydrate, sucralose, sodium benzoate, strawberry flavouring, purified water.

The tablets are available in HDPE bottles with polypropylene child resistant closures and an aluminium foil/polyethylene heat induction seal as described in section 6.5 of the SmPC.

The oral solution is available in HDPE bottles, with a child resistant closure. The pack also includes a polyethylene applicator-adapter, and a 10 ml oral applicator comprised of a polypropylene barrel (with ml graduations) and a polyethylene plunger as described in section 6.5 of the SmPC.

2.2.2. Active substance

The active substance is the same as the one used in the currently marketed product with the following two exceptions: a lower specification limit for palladium was implemented. Revised specifications and method description and validation were provided. In addition, only one source of active substance is now used.

2.2.3. Finished medicinal product

Film coated tablets 25 mg and 75 mg

Description of the product and Pharmaceutical development

Both strengths (25 mg and 75 mg) are oval and biconvex in shape with a blue film-coat, to match the existing commercial tablets. The tablets dimensions are provided in the table below:

Table 1 Dimensions and debossing of the Celsentri tablet strengths

Tablet Strength	Dimensions	Debossing
25 mg	4.6 mm x 8.0 mm	MVC 25
75 mg	6.74 mm x 12.2 mm	MVC 75
150 mg	8.56 mm x 15.5 mm	MVC 150
300 mg	10.5 mm x 19.0 mm	MVC 300

Celsentri is approved in the EU (EMEA/H/C/000811), and is available as 150 mg and 300 mg immediate release film-coated tablets. A 75 mg tablet was developed and data generated on this strength were then presented as supporting data. However, the 75 mg tablet was not registered, as this strength was not required for treatment of adults. To fulfil the regulatory commitment for paediatric-appropriate maraviroc formulations, two lower tablet strengths, i.e., the previously developed 75 mg tablet and a new 25 mg tablet, as well as an oral solution (20 mg/ml) are now proposed for registration and commercialisation. The 25 mg and 75 mg film-coated tablets are manufactured using the same common blend and film-coating system as the registered for the 150 mg and 300 mg film-coated tablet. The different tablet strengths will be differentiated by tablet size, weight and debossing.

The physicochemical properties of the active substance relevant for product performance were identified and assessed. Maraviroc presents 3 polymorphic forms. The tablets are manufactured using the same solid form as the registered 150 mg and 300 mg tablets. According to the Biopharmaceutical Classification System (BCS) maraviroc is a high solubility, low permeability molecule (BCS Class III).

The effect of active substance particle size on tablet content uniformity and dissolution was addressed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the film-coating material Opadry II blue which is tested according to an in-house specification. In addition, the colorant indigo carmine aluminium lake (E132) complies with EC regulation. The CHMP raised a question on the use of this specific colorant in a paediatric preparation. The applicant justified the use of the colorant by the need to distinguish this medication from others that are very likely to be being taken concomitantly in this patient population, and thus reduce the risk of medication errors and by the fact that the colourant amount per tablet is low and significantly less than the Acceptable Daily Intake (ADI) of 5 mg/kg recommended by the European Commission. The justification provided was considered acceptable by CHMP. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The new 25 mg tablet formulation has undergone the same optimisation process as the higher strengths. Minor modifications were made to the clinical formulation. Taking into consideration these minor changes, a bioequivalence study has not been conducted between the clinical and commercial 25 mg and 75 mg formulations. This is further supported by comparative dissolution studies and the bioequivalence study conducted with the 300 mg strength during the adult tablet development program.

The dissolution method used for quality control (QC) during release and stability is the same as the one used for the approved strengths and is considered suitable for the 25 mg and 75 mg strengths.

A risk assessment of the proposed manufacturing process was performed by reviewing the risk assessment performed previously for 150 and 300 mg tablets considering process knowledge achieved and also considering quality attributes most likely to be impacted by a decrease in tablet weight. From this review, it was determined

that the critical quality attributes and associated critical process parameters for the 25 mg and 75 mg tablets are identical to those for the 150 mg and 300 mg tablets. Based on knowledge and experience of manufacturing the 150 and 300 mg tablets, the existing control strategy will be used also for the new maraviroc 25 mg and 75 mg tablet strengths.

The primary packaging is a high density polyethylene bottle (HDPE) with polypropylene child resistant (CR) closure and an aluminium foil/polyethylene heat induction seal. The material complies with Ph.Eur. and EC requirements. Compliance with the International Standard (EN ISO 8317) Child-resistant packaging – Requirements and testing procedures for reclosable packages was provided for the closure. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The process is the same as approved for the 150 mg and 300 mg tablets. The manufacturing process consists of nine main steps which includes blending, screening, dry granulating, milling, compression, film-coating and packaging steps. The process is considered to be a standard manufacturing process.

The manufacturing process was validated for the 25 mg tablets and a validation protocol is provided for the 75 mg tablets. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls (tablet core weight and tablet core hardness) are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product specifications include the following appropriate tests for this kind of dosage form: appearance, identity (HPLC, UV), assay (HPLC), impurities (HPLC), dissolution (HPLC), content uniformity (HPLC, Ph.Eur.), microbial limits (Ph. Eur.), colorant identification (colorimetric test, UV).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch data are provided for 10 pilot scale batches of the 25mg strength and for 11 pilot scale batches of the 75 mg strength. All batches comply with the specifications. Batch results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for 3 production scale batches of finished product of each strength stored for up to 60 months (75 mg tablet) or 12 month (25 mg tablet) at 25 ºC / 60% RH and at 30°C/65% RH (75 mg strength) or 30°C/75% RH (25 mg strength) according to the ICH guidelines. In addition those batches were stored for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The only difference between the 75 mg tablets used in the stability program and the proposed commercial image is the debossing, which has no impact on stability. The batches were packed in the primary packaging proposed for marketing.

A supporting stability program consisting of one batch of 25 mg white tablets (as used in the clinical studies) packaged in HDPE bottles has been completed through 60 months at the long term storage condition of 30°C/65% RH, at the intermediate storage condition of 30°C/75%RH for 24 months, and 6 months at the accelerated storage condition of 40°C/75% RH. The supporting stability batch was manufactured and packaged

at a different manufacturing site, with some minor differences (film coat and tablet shape) to the commercial product. These minor differences are not expected to have any impact on finished product performance or stability.

The stability samples were evaluated for appearance, assay, degradation products and dissolution. The 75 mg stability samples were also assessed for microbiological quality. The analytical methods are the same as those used for release. The methods used were validated and are stability indicating.

No significant changes have been observed in any of the measured parameters.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed in any of the measured parameters, and it is concluded that the 25 mg and 75 mg tablets are stable to light and no precautionary packaging or labelling is required.

Based on available stability data, the proposed shelf-life of 60 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

Oral solution, 20mg/ml

Description of the product and Pharmaceutical development

The oral solution is a clear, colourless solution containing 20 mg/ml of active substance. The solution is packaged in white, 250 ml high-density polyethylene (HDPE) bottles containing 230 ml of solution and capped with a white, low density polyethylene (LDPE) lined closure lined polypropylene (PP) closure. In addition, the oral solution is co-packaged with a press-in bottle adapter, which is incorporated into the finished product container at first use, and an oral dosing syringe. The oral syringe is a Class I device with measuring function and is CE marked.

The oral solution has been developed for patients unable to swallow tablets. The formulation concentration was selected at 20 mg/ml to provide appropriate dose flexibility in the target population, 2-12 years old. Appropriate volumes of maraviroc oral solution can be administered for both the lowest and highest proposed doses in acceptable administration volumes.

The level of sodium benzoate included in the finished product has been optimised to retain antimicrobial effectiveness throughout shelf life and intended use whilst minimising patient exposure. The formulation is buffered to a pH of 4.0 ± 0.2 which ensures API is fully dissolved and maintains antimicrobial effectiveness over the shelf life of the product by maintaining benzoic acid in its non-ionised form. The proposed commercial formulation has been designed to mask the bitter taste of maraviroc. Sucralose is a non-nutritional sweetening agent that is non-cariogenic, and suitable for prolonged use in a paediatric population. The strawberry flavour has been shown to have appropriate taste masking properties.

All of the excipients used are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards with the exception of the strawberry flavour. It is composed of propylene glycol, artificial flavours and acetic acid. It has been confirmed that the flavour does not contain any excipients requiring declaration in the labelling. The rationale for choice of the strawberry flavour has been justified in line with the guideline

EMA/CHMP/QWP/805880/2012 Rev 2. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

During pharmaceutical development three different formulations were developed: one for Phase I, one for Phase II and the formulation proposed for commercial use. A detailed account of the development of the formulation is presented with clear explanations provided for the adjustments made at each point. A bioequivalence study between the Phase II and the proposed commercial formulation was not conducted due to the minor differences between the formulations and the high solubility of maraviroc across the physiological pH range, in line with EMA guidance CPMP/EWP/QWP/1401/98.

During development of the oral solution some particulate matter was observed, on a single occasion, in the compounding tank, prior to filtration of the drug product. The particulates were identified. Active substance specifications were modified to prevent the issue.

The primary packaging is a high density polyethylene (HDPE) bottle, with a child resistant closure, containing 230 ml maraviroc 20 mg/ml solution. Compliance with the International Standard (EN ISO 8317) Child-resistant packaging – Requirements and testing procedures for reclosable packages was provided for the closure. The pack also includes a thermoplastic elastomeric press in bottle adapter, and a 10 ml oral dosing syringe comprised of a polypropylene barrel (with ml graduations) and a polyethylene plunger. The material of the primary packaging complies with Ph.Eur. and EC requirements. During development the suitability of the container closure system and dosing device selected for use with the oral solution was determined in terms of choice of materials, moisture permeability, compatibility, safety (of materials of construction) and performance. The oral syringe is considered a Class I device with a measuring function. The oral dosing syringe bears the CE marking as required by the Medical Device Directive, EC Directive 93/42/EC and its associated amendments. The oral dosing syringe bears volume calibration marks that have been demonstrated to be accurate for delivering the intended volumes of the maraviroc oral solution in line with Ph.Eur. 2.9.27 criteria. The compatibility of maraviroc oral solution with the oral syringe has been demonstrated where solution was withdrawn from the bottle and held in the syringe for 24 hours at 30°C. Following storage in contact with the syringe for 24 hours, no changes in the appearance, preservative content or potency of the solution were observed. In addition, results for impurities met the acceptance criteria of the specification. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 3 main steps: compounding, filtration and packaging. The process is considered to be a standard manufacturing process.

Adequate justification for holding times of bulk intermediates has been provided.

Formal validation will be performed post-approval on the first three consecutive commercial batches, prior to launching the product. An acceptable validation plan has been provided.

Product specification

The finished product specifications described below include the following appropriate tests for this kind of dosage form: appearance, identity (HPLC, UV), assay (HPLC), impurities (HPLC), sodium benzoate content (HPLC), pH, microbial Limits (Ph. Eur.).

An elemental impurities risk assessment was performed on maraviroc oral solution. The product was analysed for individual elemental impurities according to ICH Q3D. The justification not to test elemental impurities in the specification is considered acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and preservative content has been presented.

Batch analysis results are provided for five production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Supportive batch analysis results are provided for batches with previous phase I and phase II formulations.

Stability of the product

Stability data were provided for 4 production scale batches of finished product stored under long term conditions for up to 18 months at 30 ºC / 35% RH and for up to 6 months under accelerated conditions at 40 ºC / 20% RH. Low humidity conditions were selected to support use of semi-permeable HDPE bottles. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The batches were analysed for appearance, assay, and degradation products as well as preservative efficacy (pH, sodium benzoate assay) and microbiological quality in accordance with the release specification. In addition tests for antimicrobial effectiveness and weight loss were studied.

All data meet the specification limits at all time points, in all storage conditions.

In-use stability studies have been performed. Samples were analyzed at initial and after 10 months.

The batches were analyzed for appearance, assay, and degradation products as well as preservative efficacy (pH, sodium benzoate assay) and microbiological quality in accordance with the release specification. In addition tests for antimicrobial effectiveness were studied.

There were no significant changes observed in any of the parameters tested and it was concluded that the data support a 60 day in-use shelf-life.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The samples were analysed for appearance, assay, degradants, sodium benzoate content and pH. There was little or no change observed in any test attributes tested indicating that the oral solution is not sensitive to light.

One batch was cycled through -20°C for two days and 30°C for two days, three times in upright orientation and then tested. The samples were analysed for appearance, assay, degradants, sodium benzoate content and pH. There was little or no change observed in any test attributes indicating that the oral solution is stable to freeze thaw conditions and no precautionary packaging or labelling is required.

Based on available stability data, the proposed shelf-life of 2 years when stored below 30°C as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Pharmacology

The pharmacology of maraviroc was thoroughly evaluated during the original approval procedure for Celsentri. No new non-clinical pharmacology studies were submitted in support of the present application.
Pharmacokinetics

The non-clinical pharmacokinetic aspects of maraviroc were thoroughly evaluated during the original approval procedure for Celsentri. No new non-clinical pharmacokinetic studies were submitted in support of the present application.

2.3.2. Toxicology

The toxicological profile of maraviroc was investigated during the original procedure for the approval of Celsentri. Repeat-dose toxicity studies were conducted in mice, rats, dogs and monkeys. Liver toxicity was observed in rats. Additional findings in rats comprised increased TSH and T4, thyroid follicular cell hypertrophy, vacuolation of adrenal glands and dilation of the cecum, the former likely a result of liver enzyme induction. In dogs and monkeys, gastrointestinal effects and QTc interval increase were the main findings.

No new non-clinical toxicology studies have been conducted in support of the present indication. The Applicant refers to the original MAA for Celsentri, which is acceptable. In response to a question the Applicant provided a discussion regarding organ systems undergoing postnatal growth and development. It is agreed that the results of non-clinical toxicology studies in adult animals do not give any cause of concern for developing organ systems and thus there is no need for juvenile toxicity studies.

2.3.3. Ecotoxicity / environmental risk assessment

An ERA was submitted by the Applicant during the original MAA for Celsentri (in 2006), having been concluded in 2008 after two follow-up measures. The Applicant was asked to submit a revised ERA, taking into account the subset of the population represented in the present indication. Recent prevalence data demonstrates a worst case figure of 1.13% for the adult EU population. This is conservative enough to cover children 0-14 years of

age. Furthermore, a paediatric study submitted in this application showed that pharmacokinetics in adults and children is similar. Calculations of PEC/PNEC ratios by the Applicant, using market penetration factors of 0.01 or 1.29 (based on the actual sales for all indications in the EU in 2015) showed that a risk to the environment is unlikely.

2.3.4. Discussion on non-clinical aspects

The Applicant has provided satisfactory responses to a question raised over potential safety concerns for the paediatric population. The absence of a juvenile toxicity study is considered acceptable. Furthermore, a revised ERA has been submitted, taking into account the presently sought indication.

2.3.5. Conclusion on the non-clinical aspects

There is no objection to an approval of Celsentri from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

Both studies (main study A4001031 and oral bioavailability study A4001034) were performed in accordance with Good Clinical Practice as claimed by the MAH.

The MAH 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.

In support of this application, data are provided from a single uncontrolled study conducted in paediatric patients, study **A4001031**, for which safety, efficacy and pharmacokinetics were evaluated. In addition, the absorption characteristics of the new formulations were evaluated in adult healthy volunteers in study **A4001034**. Further, a population pharmacokinetic analysis was carried out using the paediatric PK data from study A4001031 pooled with adult PK data obtained in patients and healthy volunteers.

2.4.2. Pharmacokinetics

As the main interest of paediatric studies is to verify that a similar drug exposure as compared to that seen in adults is achieved, the pharmacokinetic data are considered crucial in this application for a paediatric indication for maraviroc. The pharmacokinetic package consisted of a relative bioavailability and effect of food study (A4001034) and an efficacy, safety and pharmacokinetic study in HIV-1 infected children 2 to < 18 years of age (A4001031).

Bioanalysis

The bioanalytical method used for determination of maraviroc in studies A4001031 and A4001034 was well validated and showed acceptable in-study validation.

Population pharmacokinetic analysis

The population pharmacokinetic analysis (PMAR-EQDD-A400b-DP4-195) included data for maraviroc with selected potent CYP3A inhibitors (with or without potent CYP3A inducers) and included paediatric data from study A4001031 (intensive and sparse sampling) with adult healthy volunteer data from five drug interaction studies (intensive sampling) combined with adult HIV-1 infected subjects' PK data from Phase 2b/3/4 studies (sparse sampling). The adult studies included were A4001013, A4001021, A4001025, A4001026, A4001027, A4001028, A4001029, A4001031, A4001041 and A4001052.

Among the objectives were "To develop an empirical population PK model for MVC with adult and paediatric concentration- time data (restricted to patients receiving concomitant treatment with potent CYP3A inhibitors) that adequately describes the data and allows comparison of PK in paediatric and adult subjects."

The analysis was carried out according to common practice using non-linear effects modeling in the NONMEM software. A base model was developed followed by covariate selection. The model with covariates included was further refined and the final model evaluated in a qualification step.

Covariate modeling was performed in NONMEM using forward inclusion/backward deletion. No significant effect on relative bioavailability was found for: food, formulation, age or sex.

The final covariate model was further evaluated by running diagnostic, sensitivity testing for previously fixed parameters, simplification tests and VPCs in the development of a final model. A two-compartment, first order absorption model with allometric scaling of disposition parameters (clearance and volume scaled by weight to the power of 0.75 and 1, respectively) was selected as the final model. The parameter estimates of the final model are shown in the table below. The point estimates and standard error (%) associated with model parameter estimates were assessed by the bootstrap technique. The estimates were found to be adequate.

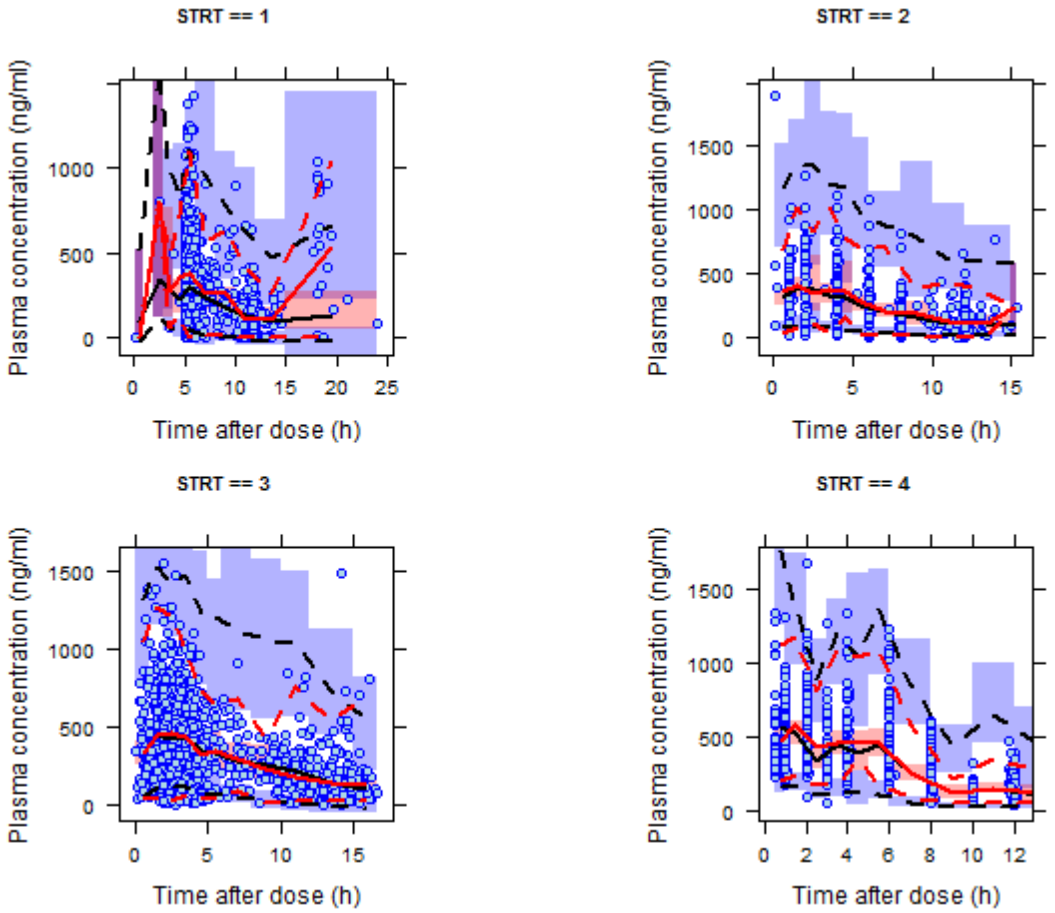
Table 7. NONMEM Results for Final Model (Adult and Paediatric Data, Run 19)

Parameter (units)	Typical Value	Standard Error (%)	Shrinkage (%)[a]
Physiological			
Absorption Rate Constant KA (/h) (θ_1)	0.674	20.0	
Central Volume V2 (L for 70 kg WT) (θ_2)	237	16.5	
Clearance CL (L/h for 70 kg WT) (θ_3)	36.4	6.48	
Inter-compartmental Clearance Q (L/h for 70 kg WT) (θ_4)	29.4	16.8	
Peripheral Volume V3 (L for 70 kg WT) (θ_5)	1840 FIX	-	
Absorption Lag Time for 1013 and 1052 (h) (θ_8)	0.864	3.85	
Absorption Lag Time for 1021, 1025 and 1041 (h) (θ_9)	0.357	6.86	
Absorption Lag Time for 1098 (h) (θ_{10})	0.631	77.7	
Absorption Lag Time for 1027, 1028, 1029 and 1031 (h) (θ_{11})	0.393	15.1	
WT Power Scaling:			
Central Volume V2 (θ_{12})	1 FIX	-	
Clearance CL (θ_{13})	0.75 FIX	-	
Inter-compartmental Clearance Q (θ_{14})	1.59 FIX	-	
Peripheral Volume V3 (θ_{15})	1.9 FIX	-	
Covariates			
Dose power on F1 (θ_{16})	0.546	24.9	
Fractional reduction in CL inhibition of PIs ATV alone, ATV/r, FPV/r and DRV/r vs reference LPV/r (θ_{19})	0.463	44.3	
Fractional increase in CL for BECCL greater than 120 mL/min vs reference 120 mL/min (L/h per mL/min) (θ_{23})	0.00367	48.5	
Fractional increase in CL of NNRTIs EFV, ETR and other CYP3A inducers vs reference no inducers (θ_{22})	0.267	35.4	
Fractional increase in V2 for Black patients vs reference Caucasians (θ_{20})	0.329	63.9	
Fractional increase in V2 for Asian and Other patients vs reference Caucasians (θ_{21})	-0.305	48.9	
Inter-Individual Variability			
Clearance CL (ω_3) (%CV)	42.2	7.72	14.1
Absorption Rate Constant KA (ω_4) (%CV)	73.2	16.5	41.7
Inter-Occasion Variability			
Absorption Rate Constant KA ($\omega_{5\text{-}9}$) (%CV)	37.7	28.3	40.6-73.3
Fraction Absorbed F1 ($\omega_{10\text{-}31}$) (%CV)	61.7	6.12	0.0-57.0
Fractional IOV on F1 for Phase 1 Subjects vs Patients Reference IOV (θ_{24}) (%)	52.0[b]	14.7	
Residual Variability			
Additive Error Profile Data (ng/mL) (θ_6) (SD)	0 FIX	-	15.8
Proportional Error Profile Data (θ_7) (%CV)	26.7	6.33	
Additive Error Sparse Data (ng/mL) (θ_{17}) (SD)	37.9	18.0	43.9
Proportional Error Sparse Data (θ_{18}) (%CV)	15.5	14.6	

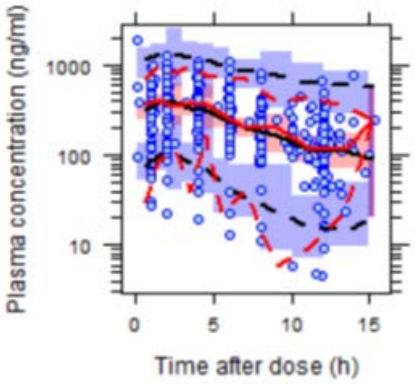
Model qualification

The pcVPCs below shows the median (solid line) and 5th and 95th percentiles (dashed lines) of simulated (black lines) and observed data (red lines). The first four plots show the final Model Prediction Corrected VPC (Linear Plot with 95% CIs) where STRT=1 is Pediatric Sparse; STRT=2 is Pediatric Profiles; STRT=3 is Adult Phase 2/3 Sparse and STRT=4 is Adult Phase 1 Profiles, respectively.

Final Model Prediction Corrected VPC (Linear Plot with 95% CIs) (STRT=1 is Paediatric Sparse; STRT=2 is Paediatric Profiles; STRT=3 is Adult Phase 2/3 Sparse; STRT=4 is Adult Phase 1 Profiles)



A pc-VPC of rich sampling PK data (profiles) in children is plotted on the log scale below.



Study A4001034

The pharmacokinetic bridge between the commercial adult formulation of Celsentri and the paediatric formulations is dependent of a number of steps.

Firstly, the applicant has shown that the commercial approved adult 300 mg tablet formulation and the 150 mg tablet research formulation is bioequivalent in an earlier assessed study (A4001040). Secondly, given the composition and dissolution a strength waiver is considered acceptable between the 150 mg tablet research

formulation and the 75/25 mg tablet formulations. Lastly, even though no absolute bioavailability was shown between the paediatric oral solution and 75 mg tablet the formulations are considered comparable.

The effect of food observed for the maraviroc oral solution was much more pronounced (a 73% decrease after a high fat meal as compared to the food effect observed for the commercially available 300 mg tablet (a 33% decrease after a high fat meal). However, the similar PK profiles and similar doses per m2 for the paediatric oral solution and tablets in study A4001031 indicate that that no large exposure differences were evident between the oral solution and tablets in a clinical setting. Therefore, even though this food effect is substantial in adult healthy subjects it does not seem to affect the PK to a large extent in children with HIV in study A4001031 and thus Celsentri can be dosed irrespective of food also for paediatric patients.

Study A4001031

Rich and sparse pharmacokinetic sampling was included during the pivotal study A4001031 in HIV-1 infected children 2 to < 18 years of age. It was fairly complex and included dose adaptation based on concentration measurements and sparse sampling on different occasions. *Stage 1* was the dose finding intensive PK portion of the study where each subject's individual dose was adjusted over the course of a few weeks according to target criteria based on PK measurements (Cavg ≥100 ng/mL). *Stage 2* was the 48-week safety and efficacy portion of the study with subjects participating in Stage 1 could continue into Stage 2 once target PK was achieved and an additional minimum of 58 subjects were enrolled directly in Stage 2. Rich PK sampling was obtained at week 2 and 2 weeks following dose adjustment in stage 1 and at the 48 week visit in all Stage 1 subjects rolled over into Stage 2. Sparse sampling was obtained from all subjects at all treatment visits up to and including Week 48 in stage 2.

Treatment and dosing strategy

The initial doses of maraviroc used in A4001031 were scaled from adult doses to paediatric body size based on BSA bands and adjusted for OBT and/or concomitant medications category. Initial paediatric doses were therefore approximately 173 mg/m2 in the absence of potent CYP3A inhibitors or potent CYP3A inducers (neutral agents), 87 mg/m2 in the presence of potent CYP3A inhibitors, and 347 mg/m2 in the presence of potent CYP3A inducers (in the absence of potent CYP3A inhibitors).

For the intensive PK evaluations of maraviroc, the primary PK parameter was Cavg. Cavg was calculated as area under the curve from time 0 to 12 hours (AUC0-12)/12.

The following dose adjustments were applied:

- If Cavg <75 ng/mL the dose was doubled, not to exceed a unit dose maximum of 600 mg.
- If Cavg >75 ng/mL and <100 ng/mL the dose was increased by 50%, not to exceed a unit dose maximum of 600 mg.
- No upper limit of concentration (or Cavg) had been identified. Consideration could be given to reducing the dose if Cavg ≥300 ng/mL. Such cases were to be discussed on an individual basis taking into consideration both safety and efficacy parameters in relation to the PK profile of the subject.

The first 6 subjects enrolled in each cohort of Stage 2 (who did not also participate in Stage 1) had their first 3 PK samples analyzed in real time, to confirm dosing selection. The dose selection was provisionally confirmed if the median of maraviroc Cavg fell within the range 50 ng/mL to 200 ng/mL, provided that there were no values below the limit of quantification (BLQ).

Population pharmacokinetic analysis was used to integrate all the data (sparse and rich) from both stages of the study into a model to explore relation between drug disposition and body weight and the extent and sources of variability in exposure. Further, it was used to explore other dosing regimens and evaluate the change from BSA based to body weight based dosing.

Maraviroc clearance was found to be related to body weight which supports body weight based dosing. However, further model qualification is required to draw final conclusions. A high inter- and intra-individual variability was estimated for absorption parameters leading to variable exposure.

Results

In total, 285 subjects were screened for the study and 103 subjects received at least one dose of study drug (maraviroc). The disposition of study subjects is shown in the tables below.

Number (%) of Subjects	**Cohort 1 (N=16)**	**Cohort 2 (N=31)**	**Cohort 3 (N=13)**	**Cohort 4 (N=43)**	**Total (N=103)**
Screened 285					
Assigned to Study Drug	16	31	13	43	103
Treated	16	31	13	43	103
Treated in Stage 1	13 (81.3)	11 (35.5)	11 (84.6)	21 (48.8)	56 (54.4)
Treated in Stage 2	15 (93.8)	31 (100.0)	12 (92.3)	39 (90.7)	97 (94.2)
Rolled over from Stage 1	12 (75.0)	11 (35.5)	10 (76.9)	17 (39.5)	50 (48.5)
Entered directly into Stage 2	3 (18.8)	20 (64.5)	2 (15.4)	22 (51.2)	47 (45.6)
Completed Week 24[a]	14 (87.5)	30 (96.8)	12 (92.3)	30 (69.8)	86 (83.5)
Completed Week 48[b]	12 (75.0)	26 (83.9)	9 (69.2)	27 (62.8)	74 (71.8)

Table 8. Demographic Characteristics, Full Analysis Set

Analysis Set	Cohort 1 (N=16)	Cohort 2 (N=31)	Cohort 3 (N=13)	Cohort 4 (N=43)	Total (N=103)
Age (years)					
≥2 - <6, n (%)	16 (100.0)	0	1 (7.7)[a]	0	17 (16.5)
≥6 - <12, n (%)	0	31 (100.0)	12 (92.3)	1 (2.3)[b]	44 (42.7)
≥12 - <18, n (%)	0	0	0	42 (97.7)	42 (40.8)
Mean (SD)	3.4 (0.9)	9.1 (1.7)	8.9 (2.0)	14.0 (1.6)	10.3 (4.1)
Range (min-max)	2.0-5.0	6.0-11.0	5.0-11.0	11.0-17.0	2.0-17.0
Race					
White	1 (6.3)	5 (16.1)	1 (7.7)	9 (20.9)	16 (15.5)
Black	11 (68.8)	21 (67.7)	12 (92.3)	27 (62.8)	71 (68.9)
Asian	2 (12.5)	3 (9.7)	0	6 (14.0)	11 (10.7)
Other	2 (12.5)	2 (6.5)	0	1 (2.3)	5 (4.9)
Weight (kg)					
Mean (SD)	15.0 (2.3)	27.4 (8.0)	26.8 (11.2)	40.2 (10.3)	30.8 (12.7)
Range (min-max)	10.0-17.6	13.6-46.9	13.9-57.6	24.0-67.5	10.0-67.5
Height (cm)					
Mean (SD)	97.6 (6.4)	130.9 (14.0)	126.6 (14.2)	150.2 (10.1)	133.2 (21.4)
Range (min-max)	82.0-108.0	103.5-158.0	103.0-157.5	131.0-174.0	82.0-174.0
BSA (m^2)[c]					
Median (SD)	0.6 (0.0)	0.9 (0.1)	0.8 (0.2)	1.2 (0.2)	1.0 (0.3)
Range (min-max)	0.48-0.71	0.69-1.45	0.63-1.60	0.93-1.83	0.48-1.83

Abbreviations: BSA=body surface area; CRF=case report form; Max=maximum; Min=minimum; N=number of subjects in cohort; n=number of subjects with observations; SD=standard deviation.

a One subject was 5 years at screening but was 6 years at the time of first dose and hence was included in Cohort 3.

b One subject was 11 years at screening but 12 years at the time of first dose and hence was included in Cohort 4.

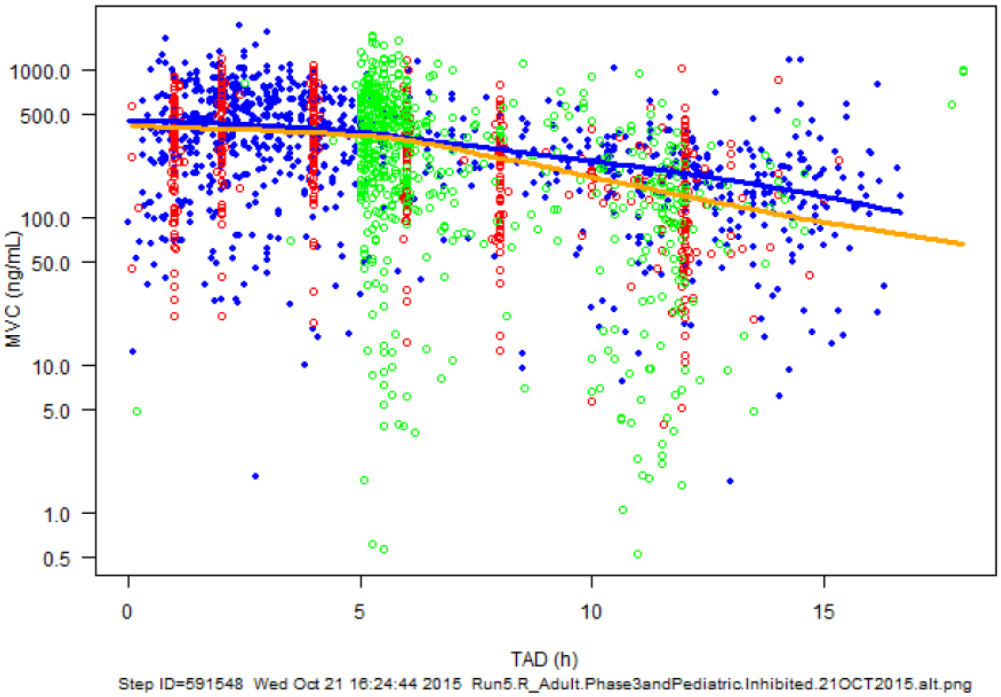
c BSA: Value from CRF.

Stage 1 PK results

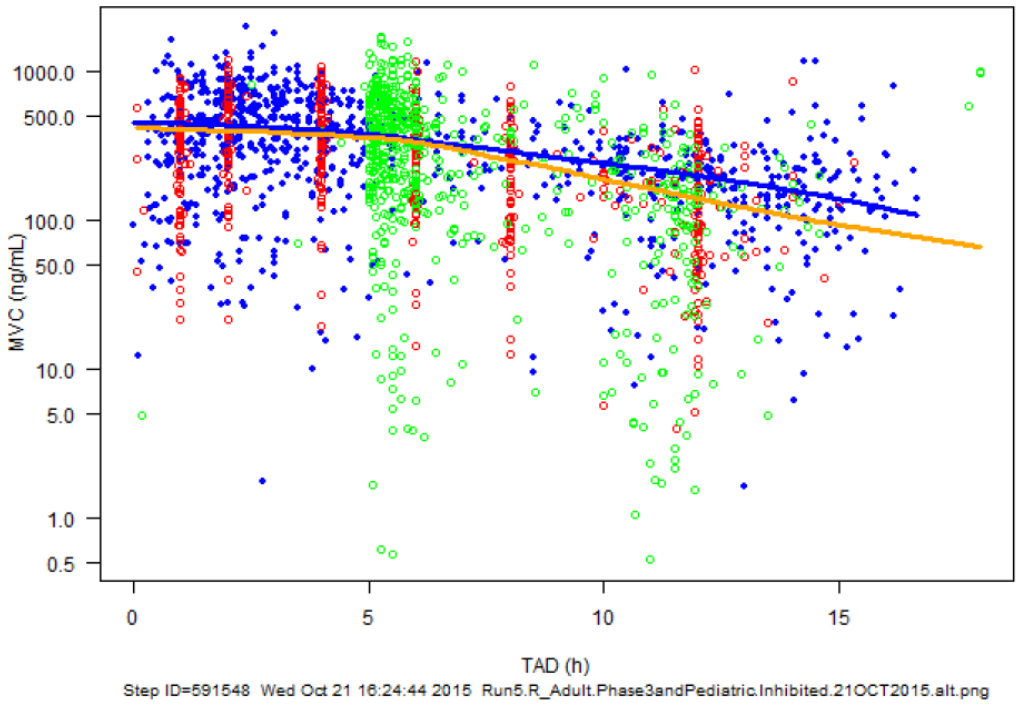
Of the 56 subjects enrolled and treated in Stage 1, 49 subjects reached the exposure target (Cavg ≥100 ng/mL) on their initial or adjusted MVC dose at Week 2 and were subsequently rolled over into Stage 2.

Stage 2 PK results

MVC concentration versus time after dose data, for HIV-1 infected subjects taking MVC in combination with neutral concomitant medication (non-interacting ARVs e.g. NRTIs, raltegravir and tipranavir/ritonavir (TPV/r) are shown below. The sparse data obtained in children during stage 2 is shown below in green, however overlaid with the data from adult studies that were included in the analysis set.



MVC concentration versus time after dose data are shown for subjects taking MVC with potent CYP3A inhibitors (with or without CYP3A inducers) in the plot below.



There is little data (n=3) for subjects taking maraviroc with potent CYP3A inducers.

2.4.3. Discussion on clinical pharmacology

As stated, population pharmacokinetic analysis was used to integrate all the data into a model to explore relation between drug disposition and body weight and the extent and sources of variability in exposure. Further, it was used to explore other dosing regimens and evaluate the change from BSA based to body weight based dosing. Maraviroc clearance was found to be related to body weight which supports body weight based dosing. A high inter- and intra-individual variability was estimated for absorption parameters leading to variable exposure. The model is important as support for the posology of Celsentri in children down to 2 years of age.

Study A4001031 was fairly complex and included dose adaptation based on concentration measurements and sparse sampling on different occasions. Stage 1 was the dose finding intensive PK portion of the study while Stage 2 was the 48-week safety and efficacy portion of the study. Rich PK profiles as well as sparse PK samples were obtained in the paediatric study. It is difficult to get an overview of PK results from sparse samples obtained in stage 2 as compared to the rich data. Interpretation of sparse PK data is facilitated by population PK analysis and the stage 2 sparse PK data were therefore modelled. Essentially, the proposed model assumes that the primary PK parameters are identical regardless of study stage. The difference between sparse and rich PK in terms of uncertainty is taken into account in the residual error model. The model may be less capable of describing sparse PK data for subjects that entered stage 2 directly. However, the overall conclusions from the model are regarded valid.

The Applicant has provided an overview of how the individual average concentration is anticipated to change with a switch from BSA-based to body weight-based dosing and reduction of the number of weight bands from 5 to 4. Body surface area (BSA) and body weight are both descriptors of body size. The relation between the two variables is well defined and translation is possible. This means that the study data and the model can support dosing by body weight instead of BSA.

The modelling identified that drug disposition is influenced by body size and that concomitant administration of inhibitors of CYP3A4 has a similar impact on clearance as seen in adult patients. Due to the relative paucity of data in children that took maraviroc in absence of interacting drugs the proposed dosing regimen in this group is not well supported. Further, the dose levels suggested by the Applicant for children <30 kg in this group seem too high considering the dependency of drug disposition on body size.

It is agreed that children >30 kg taking maraviroc with a "neutral regimen" (no interacting drugs) may use a dose of 300 mg twice daily. However, for children with lower body weight a specific dosing recommendation should not be made.

For children taking maraviroc with inhibitors the Population PK model is supportive of the suggested simplified dosing regimen. However, children with a body weight just above 40 kg may achieve higher plasma concentrations compared to the studied mg/kg dosing regimen (see further discussion in the section about Clinical Safety).

2.4.4. Conclusions on clinical pharmacology

It can be concluded that the behaviour of the new paediatric tablet formulations and the currently approved commercial tablets are similar and the PK bridge is acceptable.

The proposed posology in children aged 2 years and above and weighing at least 10kg, taking potent CYP3A4 inhibitors, is justified by observed data in combination with PK modelling and simulation. The use of maraviroc in children < 30 kg neither taking potent CYP3A4 inhibitors nor inducers is not recommended due to limited data. For the same reason, maraviroc is not recommended for children taking only potent inducers of CYP3A4.

2.5. Clinical efficacy

2.5.1. Dose response studies

In line with the CHMP Guidance, no dose response studies were undertaken in children.

2.5.2. Main study

Study A4001031:

"An Open-Label, Multicenter, Multiple-Dose Pharmacokinetic (PK), Safety, and Efficacy Trial of Maraviroc in Combination with Optimized Background Therapy for the Treatment of Antiretroviral (ARV)-Experienced CCR5-Tropic HIV-1 Infected Children 2 to < 18 Years of Age".

Date of First Enrolment: 22 Apr 2009; Last Subject Completed (Week 48 analysis): 14 Apr 2015

Centers: 24 sites across 8 countries: South Africa (n=62), US (n=12), Thailand (n=11), Brazil (n=6), Spain (n=6), Portugal (n=4), Italy (n=1), and Puerto Rico (n=1)

Previously treated children and adolescents with a treatment failure (HIV-1 RNA ≥1000) on their current ARV therapy, or on their most recent ARV regimen could enter the study, provided that only CCR5-tropic virus was seen at screening. Participants needed to have had experience (or intolerance) of at least two ARV drug classes for ≥6 months. Other inclusion and exclusion criteria were those commonly used.

The overall screen-failure rate for the study exceeded 60%. To a great extent this was due to the presence of dual mixed (DM) or CXCR4 virus in the screening sample (28%) or that the tropism test did not generate a result

(15%). Considering all screened patients with successfully obtained tropism test, the proportion of non-R5 virus (DM or CXCR4) was around 40%, (30% in the 2- <6 year-olds, 38% in the 6- <12 year-olds and 45% in the 12- <18 year-olds).

The objectives of the study were primarily to determine the PK and safety profile of maraviroc in this study population. A target maraviroc C_{avg} of 100 ng/mL was chosen based on previous data generated in the pivotal studies in treatment experienced adults (MOTIVATE 1 + 2).

Secondary objectives included efficacy endpoints including viral response at weeks 24 and 48, CD4 counts, and resistance development in those failing therapy.

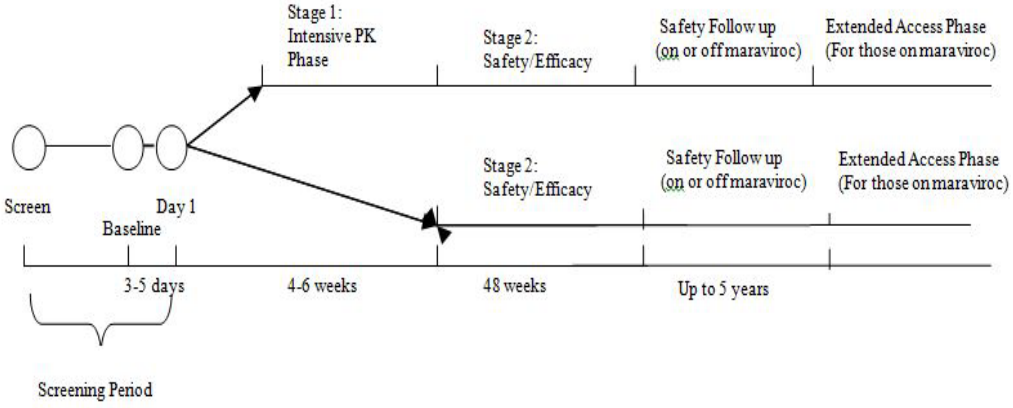
Design

The study contained 2 stages and 4 different cohorts. In stage 1 intensive maraviroc PK data were obtained for dose optimisation at Week 2 of maraviroc + OBT. Each stage 1 subject was to be enrolled into Stage 2 once it was determined that they were receiving appropriate maraviroc doses (maraviroc $C_{avg} \geq 100$ ng/mL).

Once appropriate doses were determined for a particular cohort in Stage 1, screening began directly into Stage 2 using the determined dose for that cohort. Across the 4 cohorts, 56 subjects were enrolled to stage 1 and another 47 directly into stage 2.

Subjects were stratified at Day 1 by age and formulation into one of the following cohorts:

1. Cohort 1: ≥2 to <6 years of age, maraviroc oral solution;
2. Cohort 2: ≥6 to <12 years of age, maraviroc tablet formulation;
3. Cohort 3: ≥6 to <12 years of age, maraviroc oral solution;
4. Cohort 4: ≥12 to <18 years of age, maraviroc tablet formulation.



Maraviroc was administered as 25 mg, 75 mg or 150 mg research tablets in Cohorts 2 and 4, or 20 mg/mL oral solution in Cohorts 1 and 3, in combination with other ARVs.

For details on initial dose adjustments please refer to the pharmacokinetic section.

Results

Efficacy and safety over 48 weeks were provided for all subjects. Additional tables containing data up to 5 years for subjects who completed more than 48 weeks of treatment were also provided.

Baseline characteristics

The route of HIV exposure was stated to be perinatal for 102/103 patients (unknown for one). Resistance associated mutations (RAMs; NRTI, NNRTI and PI) found at screening were not presented by cohort. Overall, the majority of subjects had NRTI and NNRTI RAMs, but 80% had no major PI RAMs and only 10% had >3 major PI RAMs. Since boosted PIs (such as lopinavir/ritonavir as Aluvia with activity to such viruses) were widely available during the time of this study, the high viral loads at baseline may indicate that a large proportion of subjects were in fact likely OFF therapy when entering the study.

Table 9. Main baseline characteristics, Study A4001031

Parameter	Cohort 1 (N=16)	Cohort 2 (N=31)	Cohort 3 (N=13)	Cohort 4 (N=43)	Total (N=103)
Male gender, n (%)	11 (69)	15 (48)	7 (54)	16 (37)	49 (48)
White race, n (%)	1 (6.3)	5 (16.1)	1 (7.7)	9 (20.9)	16 (15.5)
Black	11 (68.8)	21 (67.7)	12 (92.3)	27 (62.8)	71 (68.9)
Asian	2 (12.5)	3 (9.7)	0	6 (14.0)	11 (10.7)
Other	2 (12.5)	2 (6.5)	0	1 (2.3)	5 (4.9)
Mean weight, kg	15 (10-18)	27 (14-47)	27 (14-58)	40 (24-68)	31 (10-68)
Median BSA, m^3	0.6 (0.5-0.7)	0.9 (0.7-1.5)	0.8 (0.6-1.6)	1.2 (0.9-1.8)	1.0 (0.5-1.8)
HIV-RNA (log_{10}), mean	5.1 (3.9-6.2)	4.2 (3.1-5.4)	4.5 (3.3-5.3)	4.3 (2.4-6.1)	4.4 (2.4-6.2)
CD4 count, cells/µL	966 (1-1654)	503 (5-991)	592 (186-1440)	419 (24-912)	551 (1-1654)
CD4 %, mean	23 (7-37)	23 (0-42)	23 (8-38)	19 (5-40)	21 (0-42)

For weight, BSA, HIV-RNA, CD4 counts (range) is provided.

Optimized background treatment (OBT)

The OBT (started at baseline), consisting of 3 to 5 commercially available ARV agents, was selected by the investigator and approved by Pfizer, on the basis of resistance testing and treatment history. The OBTs included a boosted PI for the majority of patients (around 90/103). In the vast majority of cases as Kaletra (all cohorts), followed by a few patients receiving darunavir/r and atazanavir/r and with single exceptions given fosamprenavir and tipranavir/r. In the cases where the OBT did not include a PI/r, the backbone consisted of raltegravir or an NNRTI.

Rescue therapy

If a subject met the criteria for virologic failure or discontinued study drug for another reason (eg, pregnancy, AE) and required an alternative regimen, they were followed in study off drug (ISOD). The new regimen, selected by the investigator based on the results of resistance testing at the time of failure, had to be recorded in the CRF.

Virological outcome

The Outcome table below summarizes disposition as well as response (Snap shot algorithm). The table includes frequencies of protocol-defined virologic failure (PDVF), defined below. Of note, maraviroc was stopped (permanently) in case of PDVF, according to the protocol.

Protocol-defined virological failure (PDVF)

<1.0 log10 HIV-RNA reduction and VL >400 copies/mL starting at Week 12, confirmed at Week 16;
<2.0 log10 reduction and VL >400 copies/mL at Week 24 OR plasma HIV-1 RNA >10,000 copies/mL at Week 24, and confirmed 14–21 days later;
VL increase ≥1 log10 from nadir at any time, confirmed 14–21 days later.

A substantial proportion of subjects stopped therapy prior to week 48, in particular the adolescents. Of the 31 who stopped maraviroc therapy prior to week 48; 20 remained in the study (ISOD) and 11 left the study. The main reason for stopping therapy was "insufficient response" (i.e. PDVF), likely linked to adherence issues. Very few stopped for reasons of AEs.

Table 10. Disposition and outcomes (response by snap shot), Study A4001031 (FAS)

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Screened, N					286
Treated	16	31	13	43	103
Completed 24 weeks of therapy	14 (88)	30 (97)	12 (92)	30 (70)	86 (84)
Completed 48 weeks of therapy	12 (75)	26 (84)	9 (69)	25 (58)	74 (72)
Discontinued MVC prior to week 48	4 (25)	5 (16)	4 (31)	18 (42)	31 (30)
Insufficient clinical response	3 (19)	4 (13)	3 (23)	13 (30)	23 (22)
No longer willing to participate	0	1 (3)	0	1 (2)	2 (2)
Non-compliance	1 (6)	0	0	2 (5)	3 (3)
Other	0	0	0	1 (2)	1 (1)
Adverse event	0	0	1 (8)	1 (2)	2 (2)
Response					
week 24, <48 cps/ml	4 (25)	20 (65)	8 (62)	21 (49)	53 (52)
week 48, <48 cps/ml	8 (50)	17 (55)	7 (54)	17 (40)	49 (48)
week 48, <400 copies/mL	12 (75)	24 (77)	9 (69)	22 (51)	67 (65)
PDVF (week 48)	3 (19)	4 (13)	3 (23)	13 (30)	23 (22)
Other Failure (week 48, remainder)	5 (31)	10 (32)	3 (23)	13 (30)	31 (30)

PDVF: protocol defined virological failure (definition previous page).

There was no difference in degree in baseline resistance in responders and non-responders, next table.

Table 11. Outcome by screening RTI and PI RAMs (IAS USA, 2014)

Screening Resistance associated mutations	Response (n=49)	PDVF (n=23)	Other Failure (n=31)
NRTI			
None	8 (16.3)	5 (21.7)	5 (16.1)
Any	41 (83.7)	18 (78.3)	26 (83.9)
>3 RAMs	14 (28.6)	5 (21.7)	4 (12.9)
NNRTI			
None	10 (20.4)	3 (13.0)	10 (32.3)
Any	39 (79.6)	20 (87.0)	21 (67.7)
>3 RAMs	8 (16.3)	2 (8.7)	4 (12.9)
Major (primary) PI			
None	34 (69.4)	20 (87.0)	27 (87.1)
Any	15 (30.6)	3 (13.0)	4 (12.9)
>3 RAMs	5 (10.2)	1 (4.3)	1 (3.2)

Change in viral tropism, and change in genotypic resistance in RT and PI sequencies

De novo resistance was, when possible, analyzed for the group that had PDFV (N=23). De novo CXCR4 tropic-virus was detected in 5/23 (22%) subjects at virologic failure. One additional subject had CCR5 tropic-virus with reduced susceptibility to maraviroc at virologic failure, although this was not retained at the end of treatment.

Table 12. Viral tropism through week 48 in PDVF population

Tropism result	Cohort 1	Cohort 2	Cohort 3	Cohort 4	TOTAL
Number of PDVF	3	4	3	13	23
R5	2	3	2	9	16
DM	0	1	1	2	4
NR	1	0	0	1	2
ND	0	0	0	12	1

R5=CCR5-tropic virus; DM=dual or mixed tropic virus; NR=not reportable; ND=on-treatment analysis not performed

Emergence of RAMs in the RT or protease sequence was seen in 8 cases. In 5/8 cases this concerned minor PI mutations (minor significance for PI activity), and in 3/8 cases emergence of NNRTI mutations (n=2) and lamivudine resistance (n=1) was seen. Of the latter 3 cases, a true de novo resistance was only seen in one case (NNRTI RAMs); in the other two cases it most likely concerned resistance archived from prior treatment failures.

2.5.3. Discussion on clinical efficacy

The efficacy outcomes of this study are of limited interest for the application. It is quite obvious that the poor outcome (around 50% response over 48 week of therapy) is linked to adherence issues. With a proper adherence higher response rates may indeed have been expected with the use of the optimized regimens *per se*.

The main interest of paediatric studies is to verify that a similar drug exposure is achieved, as compared to that seen in adults. Having in mind that maraviroc targets the host and not the virus, it is in a way not self-evident that the same PK/PD relation would be seen in the very young as in adults. Or with other words, that the target exposure is necessarily the same in children as in adults; an issue not discussed by the MAH. There are some publications where the CCR5 expression in children has been compared to that seen in adults (Review by Tobon and Aldrovendi 2013; Shalekoff et al 2004). In summary CCR5-expression is lower in the young than in adults, and the dose needed to saturate the CCR5-receptors would rather be lower, definitely not higher. From an efficacy perspective this is therefore not considered an issue. Therefore, there are reasons to believe that maraviroc exposure similar to that seen in adults would yield the same effects in children as in adults. As seen in this section, and further discussed in the PK section, the vast majority of children received maraviroc in combination with a boosted protease inhibitor (CYP3a inhibitor). Very few were co-treated with a “neutral regimen” and next to none received an inducing co-treatment. The data (including modelling and simulation) support a dosing schedule across the proposed age and weight span, when maraviroc is taken in combination with an inhibitor, but available data can only support dosing from 30 kg and upwards when maraviroc is given with a neutral regimen (300 mg bid) and no recommendation for children can be given when maraviroc is given in combination with an inducer. In practice, this is in line with the way maraviroc would be used in the EU, also in adults.

The proportion of patients with a screening failure due to the presence of dual-mixed or CXCR4 virus was high also in these young patients. When looking at all screened patients with a successfully assessed tropism test (enhanced Trofile assay), the proportion of non-R5 virus (DM or CXCR4) was around 40%, (30% in the 2- <6 year-olds, 38% in the 6- <12 year-olds and 45% in the 12- <18 year-olds), that is to say similar figures as reported in adults. In addition, the test failed in around 15% of cases. This underscores the need for a successfully analysed tropism test prior to the use of maraviroc in all treatment populations, children included, in line with what is now stated in the SmPC.

2.5.4. Conclusions on the clinical efficacy

The efficacy outcomes observed in study A4001031 were low, evidently for reasons of suboptimal adherence to therapy and a high rate of treatment discontinuations/dropouts. The study included patients who had failed prior therapy, a population selected for suboptimal adherence and other problems related to non-virological failure. The efficacy contribution of maraviroc in children and adolescents must therefore rely on data obtained in adults.

2.6. Clinical safety

The primary focus of the safety analysis for this application is the safety information through Week 48 in Study A4001031. Additional supporting cumulative data through 5 years, using the same cut-off date of 14 April 2015 as 48 weeks data have also been presented.

The study is single-armed and of limited size. The focus of the safety assessment is therefore a descriptive comparison of safety in children versus safety data generated in adults, mainly with focus on severe AEs and AEs of interest.

Patient exposure

Up to a cut-off date of 14 April 2015, 74 out of 103 subjects (72%) completed 48 weeks of study and 64 subjects (62%) the week 96 visit, table below.

Table 13.

Study Category	Cohort 1 (N=16)	Cohort 2 (N=31)	Cohort 3 (N=13)	Cohort 4 (N=43)	Total (N=103)
Assigned Treatment	**16**	**31**	**13**	**43**	**103**
Treated	16	3. 31	4. 13	5. 43	6. 103
Completed Week 24	14 (87.5)	7. 30 (96.8)	8. 12 (92.3)	9. 30 (69.8)	10. 86 (83.5)
Completed Week 48	12 (75.0)	11. 26 (83.9)	12. 9 (69.2)	13. 27 (62.8)	14. 74 (71.8)
Completed Week 96	10 (62.5)	15. 23 (74.2)	16. 8 (61.5)	17. 23 (53.5)	18. 64 (62.1)
Completed 5 years	1 (6.3)	19. 6 (19.4)	20. 4 (30.8)	21. 3 (7.0)	22. 14 (13.6)
Duration of treatment[a]					
Mean Duration (days)	863.2	1080.9	1026.4	737.0	896.6
Median Duration (days)	957.5	1093.0	969.0	714.0	914.0
Range (days)	66-2120	140-2115	2-2123	14-1839	2-2123
Person-Years	37.8	91.7	36.5	86.8	252.8

Disposition

Prior to looking at AEs it may be of interest to view all available data on the disposition of subjects up to and including 5 years. The upper half of the table concerns proportions of patients who left the study. The lower half

show reasons for discontinuing maraviroc therapy; some of these patients still stayed in the study (in study off drug, ISOD).

Table 14. Disposition, data up to and including 5 Years (cut off 14 Apr 2015)

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
N =	16	31	13	43	103
Subject Discontinuations from Study [FAS]					
Completed	1	4	4	3	12
Ongoing	9	19	6	15	49
Discontinued	4	6	3	16	29
Insufficient response	1	-	-	1	2
AE	-	1	1	-	2
Non-compliance	-	2	-	2	4
No longer willing to participate	-	-	-	6	6
Pregnancy	-	-	-	1	1
Other	-	-	-	-	-
Death				1 (ISOD)	1
LTFU	3	3	2	5	13
Subject discontinuations from treatment phase [FAS]					
All, n (%)	5 (36)	11 (35)	5 (38)	27 (63)	48 (47)
Insufficient response (PDVF)	4	7	4	16	31
AE		1 [A]	1 [B]	1 [C]	3
Non-compliance	1	1		3	5
No longer willing to participate		1		3	4
Pregnancy				1	1
Other				2	2
Death	-	-	-	-	-
LTFU		1		1	2

A AE unspecified, Day 847; B Vomiting grade 2, Day 2; C Pelvic inflammatory disease, Day 29

The problems of managing HIV therapy in children (and particularly adolescents) with a history of failing therapy, is evident. Around half of the patients stopped maraviroc therapy (two thirds of the adolescents), with a median follow-up of around 2.5 years. As clarified in the efficacy section, “insufficient response” was most likely an effect of low adherence rather than advanced resistance in the vast majority of cases. Of note, numbers stopping for reasons of AEs were low.

Adverse events

Reported AEs were generally mild to modest, next table. Grade 3/4 AEs were reported for 6 subjects, none of which considered related to maraviroc treatment by the investigator, next table.

Table 15. All Causality, Treatment-Emergent AEs Through Week 48 (Study A4001031)

Category	Cohort 1 (N=16)	Cohort 2 (N=31)	Cohort 3 (N=13)	Cohort 4 (N=43)	Total (N=103)
Number (%) of subjects:	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects evaluable for adverse events	16	31	13	43	103
Number of adverse events	57	72	32	124	285
Subjects with adverse events	11 (68.8)	20 (64.5)	9 (69.2)	34 (79.1)	74 (71.8)
Subjects with serious adverse events	2 (12.5)	2 (6.5)	2 (15.4)	6 (14.0)	12 (11.7)
Subjects with Grade 3 or 4 adverse events	2 (12.5)	1 (3.2)	1 (7.7)	2 (4.7)	6 (5.8)
Deaths	0	0	0	0	0
Numbers who discontinued due to AEs	0	0	1 (7.7)	1 (2.3)	2 (1.9)
Dose reduced due to adverse events	0	0	0	0	0
Temporary discontinuations due to AEs	0	0	2 (15.4)	1 (2.3)	3 (2.9)

Treatment emergent, treatment-related AEs showed the expected pattern, in line with that reported in adult patients, next table. SOC terms that would link to the safety concerns of maraviroc were reported infrequently.

Vomiting was numerically more frequent in the youngest children (cohort 1, receiving maravirioc mixture), but not more common in 6-12 years old taking the mixture as compared to those taking the tablet (cohort 3 versus 2). One child (cohort 3) stopped maraviroc therapy due to vomiting (day 2, grade 2).

Table 16. Treatment-Emergent, Treatment-Related AEs through week 48

System Organ Class	Cohort 1 (N=16)	Cohort 2 (N=31)	Cohort 3 (N=13)	Cohort 4 (N=43)	Total (N=103)
Preferred Term					
Any AEs	54 (12.9)	5 (38.5)	14 (32.6)	28 (27.2)	51 (49.5)
Gastrointestinal disorders	43 (9.7)	2 (15.4)	9 (20.9)	18 (17.5)	
Abdominal pain	0	0	0	2 (4.7)	2 (1.9)
Abdominal pain upper	0	0	0	1 (2.3)	1 (1.0)
Constipation	0	0	0	1 (2.3)	1 (1.0)
Diarrhoea	0	0	1 (7.7)	3 (7.0)	4 (3.9)
Nausea	0	0	0	3 (7.0)	3 (2.9)
Vomiting	4 (25.0)	3 (9.7)	1 (7.7)	3 (7.0)	11 (10.7)
General disorders and administration site conditions	0	0	0	1 (2.3)	1 (1.0)
Fatigue	0	0	0	1 (2.3)	1 (1.0)
Malaise	0	0	0	1 (2.3)	1 (1.0)
Hepatobiliary disorders	0	0	0	2 (4.7)	2 (1.9)
Hyperbilirubinaemia	0	0	0	2 (4.7)	2 (1.9)
Injury, poisoning and procedural complications	0	0	0	1 (2.3)	1 (1.0)
Overdose	0	0	0	1 (2.3)	1 (1.0)
Investigations	1(6.3)	0	1 (7.7)	0	2 (1.9)
Blood HIV RNA increased	1 (6.3)	0	0	0	1 (1.0)
Hepatic enzyme increased	0	0	1 (7.7)	0	1 (1.0)
Metabolism and nutrition disorders	0	1(3.2)	0	1 (2.3)	2 (1.9)
Decreased appetite	0	0	0	1 (2.3)	1 (1.0)
Hypertriglyceridaemia	0	1 (3.2)	0	0	1 (1.0)
Insulin resistance	0	1 (3.2)	0	0	1 (1.0)
Musculoskeletal and connective	0	0	1 (7.7)	0	1 (1.0)
Pain in extremity	0	0	1 (7.7)	0	1 (1.0)
Nervous system disorders	0	0	1 (7.7)	5 (11.6)	6 (5.8)
Dizziness	0	0	0	3 (7.0)	3 (2.9)
Headache	0	0	0	2 (4.7)	2 (1.9)
Lethargy	0	0	1 (7.7)	0	1 (1.0)
Somnolence	0	0	0	1 (2.3)	1 (1.0)
Psychiatric disorders	0	0	1 (7.7)	1 (2.3)	2 (1.9)
Depression	0	0	0	1 (2.3)	1 (1.0)
Nightmare	0	0	1 (7.7)	0	1 (1.0)
Reproductive system and breast	0	1(3.2)	0	1 (2.3)	2 (1.9)
Breast enlargement	0	0	0	1 (2.3)	1 (1.0)
Skin and subcutaneous tissue	0	1 (3.2)	0	2 (4.7)	3 (2.9)
Lipodystrophy acquired	0	1 (3.2)	0	0	1 (1.0)
Rash	0	0	0	1 (.3)	1 (1.0)

Serious adverse event

Treatment-emergent SAEs (n=15) were reported for 12 (11.7%) subjects up to Week 48, 2 subjects each in Cohorts 1, 2, and 3; and 6 subjects in Cohort 4. It mainly concerned infections (oral abcess 1, pneumonia 4, influenza 1, pulmonary TB 1). Other SAEs were vomiting (1, resolving without stopping therapy), cellulitis (1), prurigo (2), pelvic inflammatory disease (1). None of the events were considered related to maraviroc therapy.

Discontinuation due to adverse events

Overall, 2 (1.9%) subjects (1 each in Cohort 3 and 4) permanently discontinued maraviroc due to AEs. One subject in cohort 3 stopped maraviroc at day 2 (Grade 2 vomiting, related); 1 subject in cohort 4 at day 29 (pelvic inflammatory disease, unrelated).

Adverse events of special interest

Adverse events of special interest (AESI), identified on the basis of hypothetical concerns, or as a result of signals during clinical development program or post-marketing experience concern: hepatotoxicity, malignancy, infections, autoimmune diseases, delayed-type hypersensitivity reactions, ischaemic cardiovascular events, rhabdomyolysis/muscle toxicity, and postural hypotension.

- The incidence of elevated LFTs from baseline was low and mainly of grade 1-2, in line with results in adults. Two cases of grade 3 and 4 ALT/AST, neither considered related to maraviroc therapy (concomitant TB therapy in one case, and a negative re-challenge in the other case). Shift tables on transaminases are presented in Day80 clinical report.

- Infections were reported in >50% of the subjects, which would be awaited in this setting. Infections reported as serious AEs were described in the previous page (not considered related). Although a decreased neutrophil count (at any time during treatment) was a common lab abnormality, this mainly concerned grade 1 reactions (overall around 15%) or grade 2 (around 10%). Shift tables with on-treatment values, presented in detail in the day80 clinical report, were not indicate of trends of decreasing neutrophil counts over time, and no apparent temporal association between worsening or improvement of the neutropenia with the use or discontinuation of MVC (ISOD). The 8 subjects who had a neutropenia of grade 3-4 (2004 DAIDS criteria) had other concomitant medications associated with a risk of neutropenia. Of note, benign neutropenia (or rather a value below the European normal range) is a well-known finding in people (including children) of African descent (issue reviewed by e.g. Thobakgale and Ndung'u, 2014). Lymphocyte counts were without remarks.

- Potential treatment emergent skin or hypersensitivity reactions were seen in 9 subjects (excluding those with clearly localized non-serious adverse events). The time to onset of the events was variable, ranging from 2 to 169 days, and all but one was grade 1 (the ninth case not serious).

- Postural hypotension was not reported, but on the other hand not searched for (standing BP measurements not routinely taken). Three subjects (2.9%), all in Cohort 4, were reported to have nonserious, unrelated Grade 1 or 2 TEAEs of dizziness (in one case possibly related to concomitant nausea and diarrhea). In summary no signal was seen for problems with postural hypotension (a dose limiting event of maraviroc). No cases of autoimmune disease or rhabdomyolysis/muscle toxicity were reported. Through 48 weeks there were no malignancies. There was one case of Hodgkin lymphoma (13-yearl-old female) with onset around 1.5 years after stopping maraviroc therapy. Hodgkin´s lymphoma is overrepresented in HIV-infected patients.).

In summary no signal was seen for problems with postural hypotension. To simplify dosing, the company decided to go from BSA-based dosing (5 bands) used in the clinical study, to weight based dosing (4 bands) in

the SmPC recommendation (see pharmacokinetic section). For children weighing 40 kilos and co-treated with a boosted regimen (which in practice would be the expected co-treatment) this may, according to modelling, yield Cmax values in the range that caused postural hypotension in adult studies exploring higher doses. However, the risk for postural hypotension may be smaller in children than in adults, and this side effect (not considered a serious side effect) is described in the SmPC.

Deaths

There was one death in the study when using the full data set (up to and including 5 years). This 18 year-old female had stopped maraviroc therapy after some 4.5 months, but remained in study. She died around 1.4 years after stopping maraviroc; on the basis of an interview in a severe pneumonia. The event was not considered related to maraviroc therapy.

2.6.1. Discussion on clinical safety

The safety data obtained in a single armed study of limited size is only descriptive. The majority of patients remained in study up to week 24 (86/103), 14 of whom were in the youngest age group (2-6 years). From week 24 and onwards large numbers stopped therapy/and or left the study. However, reasons for stopping therapy were not attributed to safety problems in the vast majority of cases. In fact, using all data up to and including 5 years of therapy (median follow-up of around 2.5 years), only 3 patients topped maraviroc for reasons of AEs (2 non-related, 1 related non-serious).

Reported AEs were of a similar pattern as normally reported in HIV studies (in adults as well as in paediatric patients). Overall, there is no signal for a different safety profile of maraviroc in children and adolescents as compared to in adult patients.

Laboratory wise, a neutrophil count below the normal range, mostly of grade 1-2, was a common finding. However, there were no trends of decreasing neutrophil counts over time, and no apparent temporal association between worsening or improvement of the neutropenia with the use or discontinuation of MVC, and lymphocytes were without remarks. It is well established that low grade neutropenia is frequent in people of African descent; the majority of subjects were recruited in South Africa.

In the study BSA-based dosing with 5 bands was used. On the basis of modelling, a weight based dosing schedule (4 bands) is recommended in the SmPC. As a consequence, children weighing 40 kg, and taking maraviroc in combination with a boosted PI (CYP3A inhibitor), may, according to modelling, yield Cmax values in the range that caused postural hypotension in adult studies exploring higher doses. However, the risk for postural hypotension may be smaller in children than in adults, and this side effect (not considered a serious side effect) is described in the SmPC.

No concerns on clinical safety are raised.

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

2.6.2. Conclusions on the clinical safety

The data suggest a comparable safety profile in children, adolescents and adults. No new safety concerns are raised.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

2.7. Risk Management Plan

Safety concerns

Table 17. Summary of the Safety Concerns

Important identified risks	Hepatotoxicity Postural hypotension
Important potential risks	Potential to alter immune function: Infections Malignancies Autoimmune Disease Delayed-type hypersensitivity reactions Ischaemic cardiac disorders Muscular toxicity (rhabdomyolysis, myositis) Change in the observed HIV tropism Drug resistance - HIV mutations impacting CCR5 interactions Potential for QT prolongation **Potential for medication error (dosing) in children due to drug drug interactions**
Missing information	Use in pregnant or lactating women **Long term safety in children and adolescents** ~~Use in paediatric and adolescent population~~

Considering the data in the safety specification, a slight amendment of missing information based on the new data has been proposed, a change to “Long term safety in children and adolescents” instead of “Use in paediatric and adolescent population”, which is endorsed. Since dosing of children (by weight and also interactive concomitant drugs) is likely particularly prone for medication error, having in mind the substantial interaction potential of maraviroc, the company was requested to add “Potential for medication error (dosing) in children due to drug drug interactions” as an important potential risk. That proposal was accepted.

Pharmacovigilance plan

Table 18. On-going and planned studies in the post-authorisation pharmacovigilance development plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
A4001067 (POEM): Prospective Observational Study of the Safety of Maraviroc (Category 3)	To assess the safety of MVC in TE HIV subjects in a real world setting. To estimate the incidence rates of specific safety endpoints (all cause mortality, liver related death, hepatic failure, CDC category C AIDS-defining OIs, viral encephalitis, rhabdomyolysis, MI or ischaemia and all malignancies) in HIV-infected TE patients treated with MVC plus OBT, and to compare with the rates in concurrently enrolled HIV-infected patients unexposed to MVC (ie receiving only OBT).	Hepatotoxicity Potential to alter immune function – infections and malignancies Muscle toxicity (rhabdomyolysis) Ischaemic cardiac disorders Will also provide information on long term safety and will collect SAEs	Ongoing	Final study report planned Q1 2020 with 5 year data

Table 19. Summary of post-authorisation efficacy development plan

Study(type and study number), title and category	**Objectives**	**Efficacy uncertainties addressed**	**Status (planned, started)**	**Date for submission of interim or final reports**
A4001031 (Paediatrics 2-<18 years)	To select MVC doses for children and adolescents, and to evaluate safety, tolerability, and PK of MVC in combination with other ARTs	Efficacy in paediatric patients	Ongoing	48 week report submitted in October 2015 under EMEA/H/C/000811/P46/041. Opinion received 1 April 2016 Final 5 year CSR due in October 2019

The final clinical study report from the ongoing study (Study A4001067, POEM) will be available Q1 2020. The MAH has included a separate heading for the summary of post authorisation efficacy plan and has incorporated study A4001031 (Paediatrics 2-<18 years) under the heading. The final CSR is expected in October 2019.

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

Risk minimisation measures

Table 20. Summary of the changes in the table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Potential for medication error (dosing) in children, due to drug-drug interactions.	**Boxed warning regarding the potential for drug-drug interactions to occur, and the need for careful selection of the appropriate dose for children and adolescents is included in the Posology**	**None**
Missing information		
~~Use in paediatric and adolescent population~~ **Long term safety in children and adolescents**	~~Indication only in adults is described in Section 4.1 of the SmPC; Section 4.2 and 5.2 of the SmPC indicate that there are no data to support use in children.~~ ~~PIL includes warning not to be used in children and adolescents~~ **None**	None

This application concerns a paediatric indication and the proposed amendment for missing information is acceptable.

“Potential for medication error (dosing) in children, due to drug drug interactions” has been added for reasons outlined in the previous section. The PRAC does not see a need for additional risk minimization activities for that issue (such as studies or education material).

Overall, the PRAC is of the opinion that the proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indication(s).

Conclusion

The CHMP and PRAC considered that the risk management plan version V11.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.10. Product information

2.10.1. 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 Celsentri 150 mg and 300 mg film-coated tablets (maraviroc). The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

Beneficial effects

Maraviroc has been shown to be effective in adults. Provided similar exposure, by suitable dose regimens, maraviroc would be expected to yield a similar contribution to antiretroviral efficacy in children and adolescents. Available data indicate that the doses proposed may give reasonably similar exposures as seen in the adult population.

The efficacy outcomes observed in study A4001031 were low, evidently for reasons of suboptimal adherence to therapy and a high rate of treatment discontinuations/dropouts. The safety profile was in line with that seen in adults, and numbers stopping therapy for reasons of AEs low (around 1%).

Uncertainty in the knowledge about the beneficial effects

In line with other paediatric studies on antiretroviral therapy in children and adolescents, study A4001031 was a single armed study of limited size, and efficacy as well as safety should be viewed as descriptive. The study included patients who had failed prior therapy, a population selected for suboptimal adherence and other

problems related to non-virological failure. The efficacy contribution of maraviroc in children and adolescents must therefore rely on data obtained in adults.

The current bridging of efficacy and safety from adults is based on pharmacokinetic data from study A4001031. Therefore, the quality of pharmacokinetic data and the interpretation of the data through population PK modelling is crucial to this application. The applicant's proposed doses are likely to roughly yield similar exposure as in adults. However, the data set in practice concern children who were treated with maraviroc as part of a regimen with a boosted protease inhibitor (CYP3A inhibition). A very limited number of children (across weight spans) had a "neutral" co-treatment, and very few a net inducing regimen. Consequently, for reasons of residual uncertainty about the exposure in the latter groups, dosing recommendations can only be made for children weighing >30 kg receiving a neutral co-treatment, and no recommendation can be made for those with an inducing co-treatment.

Risks

Unfavourable effects

The data suggest a comparable safety profile in children, adolescents and adults. No new safety concerns are raised.

Uncertainty in the knowledge about the unfavourable effects

The numbers of adolescents and children exposed to maraviroc are limited, and particularly longer term since therapy was stopped/subjects left the study to a great extent already after the first 24 weeks of therapy. Since maraviroc is a CCR5 inhibitor (i.e. targeting host cell and not the virus), long term safety, in particular issues potentially associated with CCR5 inhibition, is closely followed in the adult population since the approval of maraviroc in 2007. That safety follow-up is so far re-assuring.

Maraviroc is a very prone victim of interactions (CYP3A substrate). Dosing in children, by interactive drugs typically part of HIV regimens and weight, may therefore be considered more complicated than for most drugs. While HIV physicians are used to handle interactions, paediatricians, who would be the main prescribers, may be less trained. There may therefore be a risk for medication error (incorrect dosing) and issue was therefore added to the list of important potential risks in the RMP, however, without a need for specific safety measures outside an optimized SmPC.

To simplify dosing, the company decided to go from BSA-based dosing (5 bands) used in the clinical study, to weight based dosing (4 bands) in the SmPC. For children weighing 40 kilos (around 12 years of age) this will, according to modelling, may cause a higher exposure than that seen in adults, according to modelling. For these children, the increased Cmax could increase the risk of the dose (Cmax) dependent side effect of maraviroc, postural hypotension. However, the risk for postural hypotension may be smaller in children than in adults, and this side effect (not considered a serious side effect) is described in the SmPC.

Importance of benefits and risks

In EU maraviroc is only approved for use in treatment experienced (presently adult) patients. In practice it is mainly considered an add-on drug for usage in patients with advanced background resistance, where it is hard to achieve a complete viral suppression, that is to say in patients with a long treatment history including times when resistance accumulated due to lack of agents or the use of less optimal regimens available at that time. Following the approval of a number of very effective antiretrovirals during recent years (i.e. from the time

around the maraviroc approval and onwards), the number of such patients is quite limited. When looking at the most recent maraviroc PSUR, the total number of adult patients treated with maraviroc in the EU (>1 million persons living with HIV) may be estimated to be around 3000 at the most. The number of children with HIV-infection in the EU is low, and those failing HIV therapy (virus not suppressed) would seldom have advanced resistance, but rather fail as a consequence of low adherence, but with remaining treatment options. The role of maraviroc as part HIV treatment in children is therefore projected to be very limited.

When the study was initiated a 5 year follow-up on safety was decided for. From a regulatory perspective the need and relevance of further data is not obvious. Firstly, there are no safety concerns of maraviroc that seem to be specific for children, and long terms safety is being followed in larger adult cohorts. Secondly, any findings in the present one-armed study of limited size would only be considered as descriptive. Thirdly, the children that were recruited to this study are highly selected for non-adherence (including treatment failure and high drop-out rates), which further questions the relevance of collecting such data. At the time of this procedure around 20 children had passed the 5-year time point, and another 38 children were still in study (some of whom no longer treated with maraviroc). The MAH was therefore invited to discuss whether the study could in fact be halted. The MAH will continue with the original plan, in order to fulfil the obligations with the study informed consents, for which study related examinations, tests and treatments were guaranteed for this time span.

Benefit-risk balance

Overall, despite the expected very limited use in children, the pharmacokinetic and clinical data may support a favourable benefit-risk balance for treatment-experienced children aged 2 years (with a minimum weight of 10 kilograms) and above.

Conclusions

The overall B/R of Celsentri (comprising new tablet strengths of 25 and 75 mg, and an oral solution of 20 mg/ml, in addition to existing tablet strengths of 150 and 300 mg) in patients aged from 2 years (minimum weight 10 kilograms) and above is considered to be favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of, Celsentri is favourable in the following indication:

“CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adults, adolescents and children of 2 years of age and older and weighing at least 10 kg infected with only CCR5-tropic HIV-1 detectable (see sections 4.2 and 5.1)”.

The CHMP therefore recommends the extensions of the marketing authorisation for Celsentri subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0237/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change:

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

To extend the indication for Celsentri, in combination with other antiretroviral medicinal products for treatment-experienced adolescents and children of 2 years of age and older and weighing at least 10 kg infected with only CCR5-tropic HIV-1 detectable. As a consequence, sections 4.2 and 4.8, 5.1 and 5.2 of the SmPC are updated to detail posology in paediatric patients and to update the safety, efficacy and pharmacokinetic information, respectively. SmPC is also updated regarding existing information on adult patients in section 4.5 and the new strengths/pharmaceutical form in sections 6.3 and 6.5. In addition sections 4.6 and 4.7 of the

SmPC were updated according to relevant guidelines.

Annex II, Package Leaflet and Labelling are updated in accordance.

Furthermore, the PI is brought in line with the latest QRD template version 10.