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ASSESSMENT REPORT FOR PREZISTA

International Nonproprietary Name:
darunavir

Procedure No. EMEA/H/C/707/X/20&21

Marketing Authorisation Holder/Applicant: Janssen-Cilag International NV

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

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1. Introduction

As of the end of 2007, an estimated 33.2 million people worldwide – 30.8 million adults and 2.5 million children younger than 15 years – were living with human immunodeficiency virus (HIV)/AIDS. An estimated 370,000 children under age 15 became infected with HIV in 2007 (Source: UNAIDS). In western and central Europe, an estimated 740,000 persons were living with HIV in 2006. In 2005, 27,555 new HIV diagnoses were reported by 26 European countries, of which 1% (275) were children < 15 years of age and 10% (2,755) were young people aged between 15 and 24 years.

HIV-related mortality and opportunistic and other related infections have significantly decreased in HIV-infected children in the era of Highly Active AntiRetroviral Treatment (HAART). More specifically, since the introduction of Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)- or protease inhibitor (PI)-containing combinations, HIV mortality in children in resource-rich countries has decreased by 70%. However, along with the wider use of antiretroviral therapy (ART) in HIV-1 infected children and adolescents, treatment failure (virologic or associated with tolerance) and the emergence of resistance have become of growing concern. Treatment-experienced HIV-1 infected paediatric patients not adequately controlled on currently available antiretroviral (ARV) drugs represent a population with high medical need. Off-label use of ARV drugs approved for treatment of HIV-1 infection in adults, in the absence of appropriate paediatric formulations and dose recommendations, is not uncommon. Consequently, there continues to be a need for effective and tolerable therapeutic agents for use in the paediatric population.

The use of PIs has been a major breakthrough in the therapy for HIV-1 infection, substantially reducing morbidity and mortality in infected individuals. However, the long-term use of the currently licensed PIs is often hampered by different factors such as poor compliance due to a high pill burden and food restrictions, side effects with impact on the quality of life and the emergence of resistant virus that is no longer inhibited by the medicine used.

Preclinical data supported clinical trials of a darunavir/ritonavir-containing regimen in HIV-1 infected paediatric patients aged 3 years and older. The paediatric clinical development program of darunavir/ritonavir first focused on treatment-experienced HIV-1 infected children and adolescents from 6 to < 18 years of age, given the medical need in this population due to virologic failure, resistant virus strains and/or tolerability issues.

In order to accommodate posologies in children and adolescents, the Applicant developed two lower strength tablets, 75 mg and 150 mg, for which a Marketing Authorisation (MA) is sought within this line extension procedure. In order to support the indication in treatment experienced paediatric patients above the age of 6, a Phase II trial, investigating the pharmacokinetics, safety, tolerability and efficacy of darunavir/ritonavir in the target population (TMC114-212, DELPHI), was initiated during the third quarter of 2006.

The primary Week-24 analyses were performed (as requested during the assessment of the initial Marketing Authorisation Application (MAA) for the 300 mg strength) and were submitted within the initial application for this procedure. With the submission of the 24 Week analysis of study C212, the Applicant has consequently fulfilled follow-up measure (FUM) 025. Furthermore, the Week-48 data were submitted by the Applicant in the framework of the responses to the D120 CHMP List of Question of this extension application.

In parallel, a type II variation (EMEA/H/C/707/II/25) was submitted on 21 January 2009, in order to extend the existing indication for the 300 mg and 600 mg film-coated tablets, to also include ARV treatment experienced children and adolescents aged 6 years or older.

The PI darunavir (TMC114) is a close analogue of amprenavir. The binding of darunavir to the wild-type protease was 87-fold greater than that of amprenavir versus 33-fold more tightly than amprenavir in the case of multi-drug resistant protease. Darunavir binds also more tightly to HIV-1 proteases than the PIs indinavir, ritonavir, nelfinavir, saquinavir, amprenavir, lopinavir, and atazanavir.

Darunavir 300 & 600 mg film coated tablets are currently licensed for use in treatment-experienced patients at a dose of 600 mg twice daily (b.i.d.), with ritonavir 100 mg b.i.d.; the indication for the 300 mg and 600 mg was extended to included 'treatment experienced adults' (variation EMEA/H/C/707/II/14: Commission Decision dated 25-11-2008). The outcome thereof was also taken into account during the procedure. The 400 mg film coated tablet is currently authorised in the treatment of ART naïve patients at a dose of 800 mg once daily (q.d.), with ritonavir 100 mg q.d., both in combination with other ARV medicinal products. For the added new strengths - 75 mg and 150 mg film coated tablet – the following new indication was initially proposed by the Applicant (of note, following the submission of the line extensions at issue, the indication for the 300 mg and 600 mg strengths was extended to include 'treatment experienced adults'):

PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI) ***and for the treatment of HIV-1 infection in antiretroviral treatment-experienced adolescents and children of 6 years and above.***

The proposed posology for children and adolescents was:

Antiretroviral treatment-experienced paediatric patients (6 to 17 years of age) (see section 5.1)
The recommended dose of PREZISTA with low dose ritonavir for paediatric patients (6 to 17 years of age and weighing at least 20 kg) is based on body weight (see table below) and should not exceed the recommended adult dose (600/100 mg b.i.d.). PREZISTA tablets should be taken with ritonavir twice daily and with food. The type of food does not affect exposure to darunavir.
Recommended dose for treatment-experienced paediatric patients (6 to 17 years of age) for PREZISTA tablets and ritonavir:

Body weight (kg)	**Dose**
≥ 20 kg–< 30 kg	375 mg PREZISTA/50 mg ritonavir b.i.d.
≥ 30 kg–< 40 kg	450 mg PREZISTA/60 mg ritonavir b.i.d.
≥ 40 kg	600 mg PREZISTA/100 mg ritonavir b.i.d.

The proposed indication and posology were supported by the 24-Week and 48-Week data from study TMC114-C212.

A Paediatric Investigation Plan (EMEA-000038-PIP01-07) was submitted on 20 September 2007 and an opinion was adopted on 4 June 2008 by the Paediatric Committee, in which a waiver was granted for children below the age of three. A PIP modification request was submitted on 30 October 2008 and an opinion on the modification was adopted on 12 December 2008 by the Paediatric Committee.

No Scientific Advice from any European regulatory authority including the EMEA was requested by the Applicant within the framework of the current submission. The Paediatric European Network for Treatment of AIDS (PENTA) group provided advice on study protocols, which the Applicant took on board.

The following guidelines in particular are applicable for the current application:
- Guideline on the clinical development of medicinal products for treatment of HIV infection (CPMP/EWP/633/02, Rev. 1)
- Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)
- Clinical trials in small populations (CHMP/EWP/83561/2005)
- Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (EMEA/CHMP/PhVWP/235910/2005)

The Applicant has declared that all studies were performed in accordance with ICH requirements for GCP.

2. Quality aspects

Introduction

The medicinal product Prezista 75 mg is presented as white caplet-shaped film-coated tablets, debossed with "75" on one side and "TMC" on the other side and containing 81.31 mg darunavir ethanolate, corresponding to 75 mg darunavir. The medicinal product Prezista 150 mg is presented as white oval-shaped film-coated tablets, debossed with "150" on one side and "TMC" on the other side and containing 162.62 mg darunavir ethanolate, corresponding to 150 mg darunavir.

The other ingredients include microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, polyvinyl alcohol – partially hydrolyzed, macrogol 3350, titanium dioxide (E171) and talc. The tablets are packed in a high-density polyethylene (HDPE) plastic bottle closed with a polypropylene (PP) child resistant closure.

Active Substance

The active substance is darunavir. It is manufactured in solvated form as darunavir ethanolate, an established substance not described in any pharmacopoeia. Darunavir ethanolate is a hygroscopic substance, which is very slightly soluble in aqueous solutions. The active substance possesses 5 chiral centres [1S,2R,3aS,4S,6aR] and stereochemical purity is controlled by adequate specifications on stereochemical purity of the starting materials.

Full documentation on the active substance has already been assessed within the original Prezista application (300 mg strength), including all post-marketing authorisations, and within the Prezista 400 mg and 600 mg line extension applications. For the 75 and 150 mg strength application, no new data on the active substance has been submitted as the data is identical to the data submitted and assessed for the 400 mg and 600 mg strength line extensions.

- Manufacture

The purified active substance is produced by a 4 step process, out of two starting materials. For the manufacturing process reference is made to the already marketed 300 mg Prezista and the 400 mg and 600 mg strength line extensions. For the manufacturing of the 75mg, 150 mg, 400 mg and 600 mg strength, an additional active substance manufacturer has been introduced. This manufacturer applies a different method of drying, resulting in a different particle size distribution of the active substance. Due to this change, the formulation of the finished product needed to be modified, compared to the original 300 mg strength, in order to keep flow characteristics of the blend at an acceptable level. Bioequivalence/Bioavailability studies have been performed with modified formulations.

- Specification

The active substance specification has been established in-house by the Applicant. The Applicant has justified the acceptance criteria for the particle size of the active substance by submission of laser diffraction patterns of the active substance batches used in clinical studies. For both the approved and the proposed additional manufacturing site, batch analytical data demonstrating compliance with the active substance specification have been provided for at least 3 full scale batches. The data demonstrate consistency in the manufacturing process and compliance with the proposed active substance specifications.

- Stability

Active substance stability data from one active substance manufacturer has already been assessed in the original MAA for the 300 mg strength. Satisfactory stability data covering 24 months stability results at 25°C/60% RH and 30°C/65% RH and satisfactory 6 months results at 40°C/75% RH have been provided. For the 75 mg, 150 mg, 400 mg and 600 mg line extension applications, the Applicant

has submitted stability data from 3 full scale batches manufactured at the additional production site. The results cover 3 months at 30°C/65%RH and 40°C/75%RH.

The manufacturing of the active substance at the new manufacturing sites does neither lead to changes in the impurity profile of the substance nor to the container closure system. It is thus not expected to affect the stability of the active substance. The particle size distribution is not expected to affect the stability of the active substance either. The currently approved active substance retest period for the 300 mg is therefore approvable for both manufacturing sites. No special storage conditions are necessary.

Medicinal Product

The currently approved commercial dosage forms for darunavir are the 300 mg, 400 mg and 600 mg film-coated tablets. To address clinical needs, the additional 75 mg and 150 mg strengths have been developed. The 75 mg and 150 mg film-coated tablets are prepared from a formulation that is qualitatively the same as that used for the approved commercial 300 mg film-coated tablets, incorporating all the same ingredients, with a minor decrease in the percentage of microcrystalline cellulose, and a corresponding minor increase in the percentages of colloidal anhydrous silica and magnesium stearate, to provide better powder flow properties for compression of the tablets (i.e. modified formulation). Multiple strengths (the 400 mg, 600 mg, 75 mg and 150 mg) of the modified formulation can be compressed from a common powder blend.

- Pharmaceutical Development

The development of the 75 mg and 150 mg tablets is based on the 300 mg tablets. However, the Applicant has slightly amended the formulation for the 75 mg and 150 mg strengths. The changes were considered necessary due to the change in particle size of the active substance.

In total, 14 different formulations were evaluated. The test formulations varied slightly from the current 300 mg tablet formulation and were manufactured with mechanically dried active substance lots having a small particle size and reduced flow properties. For each formulation, the physical properties of the final blend (particle size, flowability, volume) and the tablet cores (appearance, weight, hardness, disintegration time, friability) were measured. Results from the current formulation manufactured with a statically dried (i.e., good flowing) active substance lot were used as the baseline. The currently proposed formulation was identified as having improved manufacturability: improved flow properties and/or a reduced tendency for sticking without risk of blend flow obstruction or tablet sticking on scale-up.

The qualitative composition of the 75 mg and 150 mg strengths is identical to the already approved 300 mg tablets. Only a minor change in quantitative composition has taken place. The pharmaceutical development of the product has been adequately performed.

- Adventitious Agents

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

- Manufacture of the Product

The manufacturing process for the 75 mg, 150 mg, 400 mg and 600 mg strengths of the darunavir modified formulation tablets consists of typical pharmaceutical delumping, blending of the tablet core components, direct compression of the tablets and coating of the tablet cores. The manufacturing process can be considered as standard. Adequate in-process controls are proposed and the critical aspects of the manufacturing process (e.g. particle size, manufacturability, active substance content of 52%) are adequately dealt with.

Batch analysis results data support the view that drug dosage, uniformity of content, degradation products and chromatographic purity, dissolution, and microbiological purity are adequately controlled. The Process Validation Scheme proposed by the Applicant is appropriate.

- Product Specification

Appropriate medicinal product specifications have been set. The specifications for the finished product at release and shelf life are classical for this pharmaceutical form and include tests for appearance, identity, assay, degradation, dissolution, microbiological purity and uniformity of dosage units. The excipients used in the medicinal product comply with pharmacopoeial requirements or national standards where applicable. The proposed test parameters and acceptance criteria are acceptable. The analytical methods have been adequately described and validated. Satisfactory batch analysis data from the proposed production site have been provided for the 75 mg and 150 mg strengths, demonstrating compliance with the release specification.

- Stability of the Product

The stability studies include long term and accelerated studies, bulk tablet studies, in-use studies, photostability studies and some auxiliary studies. The performed stability studies follow a bracketing design that incorporates the high (600 mg) and the low (75 mg) strengths of the modified formulation tablets, the various package sizes and counts, and the tablet colours under development. The bracketing approach has been adequately justified.

Stability data have been provided for 3 pilot scaled batches of 75 mg tablets and 6 pilot scaled batches of 600 mg tablets filled in two sizes of containers. The batches have been stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) in the proposed container. The conditions used in the stability studies are according to the ICH stability guideline; several additional conditions have also been tested.

Several supportive studies have been performed. Data covering 24 months have been provided for 2 batches of modified 300 mg tablets and 9 month data of modified 400 mg tablets stored at ICH long term and accelerated conditions.

During all of the above studies, the test parameters were shown to be stable at all test conditions. In view of the stability results, the proposed shelf-life, with no special storage condition, can be approved.

Furthermore, in-use stability data has been provided demonstrating that the modified formulation is stable after opening the container (75 mg, 3 months and 600 mg, 1 month). Photostability studies show that the product is not sensitive to light. In view of the observed stability during the in-use trials with the modified formulation, no additional in-use storage conditions nor a separate in-use shelf-life are considered necessary for the 75 mg, 150 mg, 400 mg and 600 mg film-coated tablets. The stability data are considered adequate and support the proposed shelf life for the 75 mg, 150 mg, 400 mg and 600 mg strength.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterized and documented. The pharmaceutical form selected is adequate taking into account the properties and the stability of the active substance. The excipients are commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process enhances to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life. At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the benefit-risk balance of the product. The Applicant committed to resolve this as a follow up measure after the opinion, within an agreed timeframe.

3. Non clinical aspects

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

With respect to the earlier submitted FUM 15 (regarding possible juvenile toxicity studies), two studies in juvenile rats had been submitted. The results then suggested that the exposure in rats aged 5-11 days is higher than in adult rats. After 23 days of age, it was comparable to adult rats.

It was concluded that the high exposure at young age and the subsequent decrease in exposure from postnatal day 8 onwards is probably related to the maturation of the liver metabolising enzymes and the blood brain barrier. Data further showed that it cannot be excluded that toxicity was higher in animals aged 5-11 days than in adult animals. In animals aged 23-50 days, toxicity was not higher than in adult animals.

These results suggested that in rats, roughly after 3 Weeks, the exposure in juvenile animals is comparable to that in adults. The results suggested that in very young children, who do not have mature drug-metabolising enzymes yet, it may be expected that comparable doses cause a higher exposure as compared to adults. The activity of drug metabolising enzymes increases from birth and approaches adult values by 1-3 years of age.

In the current application, an extension of the indication to include also children from 6 years of age and above is applied for. From a non-clinical point of view, based on the data as given above, no increased exposure levels are expected in children of 6 years and older. Also, clinical pharmacokinetic data in children of 6 years and older indicate a comparable exposure compared to adults at the indicated dose (see clinical part of this report). From a non-clinical point of view, no additional toxicity is expected in children from 6 years of age and above.

Ecotoxicity/environmental risk assessment

The Applicant has provided an overview with the available information regarding environmental risk. No new information was provided. Since FUM 13 and FU2 013.1 sequel to FUM 13 already have been fulfilled, no new information regarding the environmental risk is needed. During the registration procedure and the subsequent follow-up measures, an environmental risk assessment has been performed which was based on the standard penetration factor (F_{pen}) of 1%. It is not expected that the use of darunavir will be extended beyond that indicated by the default penetration factor because of this proposed line extension and new indication.

4. Clinical aspects

The Applicant submitted one clinical (phase II) study in support of the current application. This study, TMC114-C212, included treatment-experienced HIV-1 infected paediatric patients. Darunavir was administered orally either as the commercial 300 mg tablet formulation (F016) and/or as a dose proportional 75 mg tablet formulation (F027), together with low dose ritonavir (80 mg/ml oral solution, or capsule 100 mg). TMC114-C212 consisted of two parts. Part I was the dose finding part of the study, in which the short-term safety, tolerability, antiviral activity, and pharmacokinetics of lower (dose Group A) and higher (dose Group B) weight-based dose levels of darunavir/ritonavir were evaluated. The respective dose groups were further divided into weight bands. In Part II, the long-term safety, tolerability, efficacy, and pharmacokinetics of the darunavir/ritonavir dose selected from Part I (dose Group B) were evaluated. In both parts of the study, darunavir/ritonavir was administered in combination with other ARV medications.

Pharmacokinetics

Dose selection (Part I)
The selected doses in Part I of this study were based upon the adult 600/100 mg dose and extrapolated using allometric scaling. This was applied as children have a faster metabolism than adults, and linear scaling may have resulted in an inadequate darunavir exposure. However, while this may be true for darunavir, as indicated by the non-clinical data as discussed above, it could be questioned for ritonavir. Ritonavir is used as booster in this study. As such, ritonavir plasma levels should be high enough to ensure (complete) inhibition of CYP3A4. CYP3A4 levels in paediatrics/adolescents are comparable to those in adults, and especially in young children, metabolism by CYP3A4 is higher.

The ratio of darunavir:ritonavir ranged from 4.5:1 to 7.5:1 in this study. For adult treatment-experienced patients, the ratio of darunavir:ritonavir is 6:1. Therefore, the ritonavir doses used in this trial are in line with the ratio of darunavir:ritonavir in treatment-experienced adults. A comparison of the use of 100 and 200 mg ritonavir as pharmacokinetic enhancer for darunavir in a previous Phase I trial showed that higher dose of ritonavir increased its exposure, but not relevantly to darunavir. Additionally, in a drug-drug interaction trial between darunavir/ritonavir and carbamazepine, the mean exposure to ritonavir was decreased by 49% in the co-administration. However, this lower ritonavir exposure did not influence the exposure to darunavir. These results suggest that ritonavir doses of 50 to 200 mg as pharmacokinetic enhancer result in therapeutic and comparable darunavir exposure in adults. In addition, the results in Part I showed that the dosing in both groups (except for two non-compliers) resulted in trough concentrations above the target *in vitro* EC_{50}, further justifying the chosen ritonavir doses.

The following 2 dose schemes for darunavir/ritonavir were administered under fed conditions for 14 days as follows:

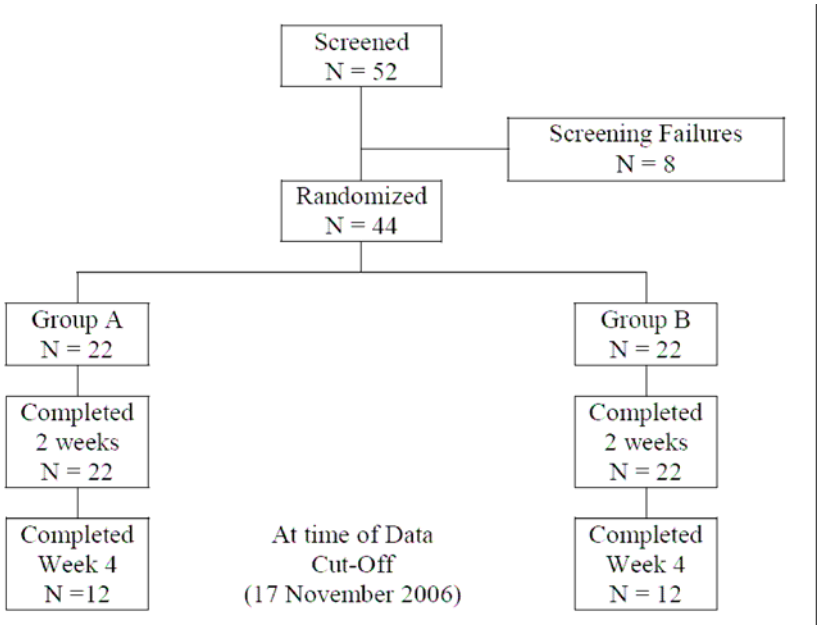
Dose Group A (<u>9-15</u> mg/kg darunavir and 1.5-2.5 mg/kg ritonavir):

≥20 to <30 kg:	300/50 mg	darunavir/ritonavir b.i.d.
≥30 to <40 kg:	375/60 mg	darunavir/ritonavir b.i.d.
≥40 to <50 kg:	450/100 mg	darunavir/ritonavir b.i.d.

Dose Group B (<u>11-19</u> mg/kg darunavir and 1.5-2.5 mg/kg ritonavir):

≥20 to <30 kg:	375/50 mg	darunavir/ritonavir b.i.d.
≥30 to <40 kg:	450/60 mg	darunavir/ritonavir b.i.d.
≥40 to <50 kg:	600/100 mg	darunavir/ritonavir b.i.d.

In total, 52 patients were screened, of which 44 patients were randomised and treated, 22 patients in each group:



The results showed that in general ritonavir plasma levels were comparable to those obtained in adults; however, data indicate also that in several cases lower ritonavir plasma levels were observed compared to adults (this is further discussed in Part II).

Both dosing schemes (higher and lower dose groups) resulted in adequate darunavir plasma levels compared to those observed in adults. Both groups fell inside the specified criteria, i.e. mean values of the pharmacokinetic parameters in this paediatric population should fall within 80 to 130% of the corresponding treatment-experienced adult pharmacokinetic plasma parameters.

When all results of groups A and B were pooled, the mean data indicated a higher exposure for group B, in line with the higher administered dose. There was a considerable overlap in C0h, AUC and C_{max} values of Groups A and B. Data for each weight band showed that all the children in groups A and B in the 20-< 30 and 40-< 50 weight bands had actual trough concentrations above the target *in vitro* EC_{50} value of 550 ng/ml, but in the 30-< 40 kg band this was not the case for either group A or group B (the range was 181-6060 ng/ml for Group A and 147-5070 for group B). Here, all patients achieved plasma darunavir concentrations above 550 ng/ml, except for 2 patients (1 each in Group A and B, respectively), by whom the criteria for compliance were not met. They had low darunavir trough values, and ritonavir trough levels were low as well or even not quantifiable.

The individual observed concentration - time curves compared with adult exposure, separated for all dose groups (weight bands) for part A and B did not indicate that any of the two groups were at risk of underexposure. The dose scheme applied in group B was used for further evaluation in part II of this study. This was, as indicated by the Applicant, based upon favourable efficacy, safety and tolerability profile in this group (see also below).

Main clinical study (Part II)

Following selection of the dose at Week 2, all patients not already receiving this dose were switched to the selected dose, and the 44 patients enrolled in Part I continued the overall schedule of assessments up to Week 48 as per the protocol. An additional 24 patients equally distributed in the above weight bands were recruited directly into Part II as well as a cohort of 12 patients ≥ 50 kg who received the adult dose of darunavir/ritonavir 600/100 mg b.i.d. The 68 patients weighing between 20 and 50 kg received the selected dose of group B in Part I:

Of the 74 patients with sparse sampling data, a total of 19 patients were included in the 20-29 kg weight band, 23 patients in the 30-39 kg weight band, 20 patients in the 40-49 kg weight band and 12 patients in the ≥ 50 kg weight band at screening.

Based upon the sparse sampling data and using population pharmacokinetic analysis, the selected dose for Part II for children resulted in mean C0h and AUCtau values comparable to those observed in adults. This was in line with findings in Part I. Furthermore, race, sex, region and effects of co-administered efavirenz or tenofovir showed no clinically relevant effect of these covariates on darunavir exposure, consistent with findings in adults.

The population PK analysis showed darunavir AUC and trough concentrations comparable to those observed in adults for all weight bands. Although for the 30-< 40 kg weight band had some lower values compared to the other weight bands, the estimated troughs exceeded clearly the target of 550 ng/ml.

In adults, linear pharmacokinetics is observed after single dose administration over the 300 – 1200 mg darunavir dose range with 100 mg ritonavir, thus for a wide range of the darunavir:ritonavir ratios, which still is sufficient to inhibit darunavir metabolism by ritonavir (see above). As such the comparable exposure observed in children and adults support the applied darunavir/ritonavir ratios in children and that ritonavir sufficiently inhibits the metabolism of darunavir.

Addition of the 75 and 150 mg tablet formulations

A biowaiver was considered acceptable, as for the 75 and 150 mg tablet formulations dissolution studies comparing the tablets with the 300 and 600 mg tablets showed comparable results. Moreover, the tablets are dose-proportional, and darunavir with ritonavir shows linear pharmacokinetics after single dose administration.

Clinical efficacy

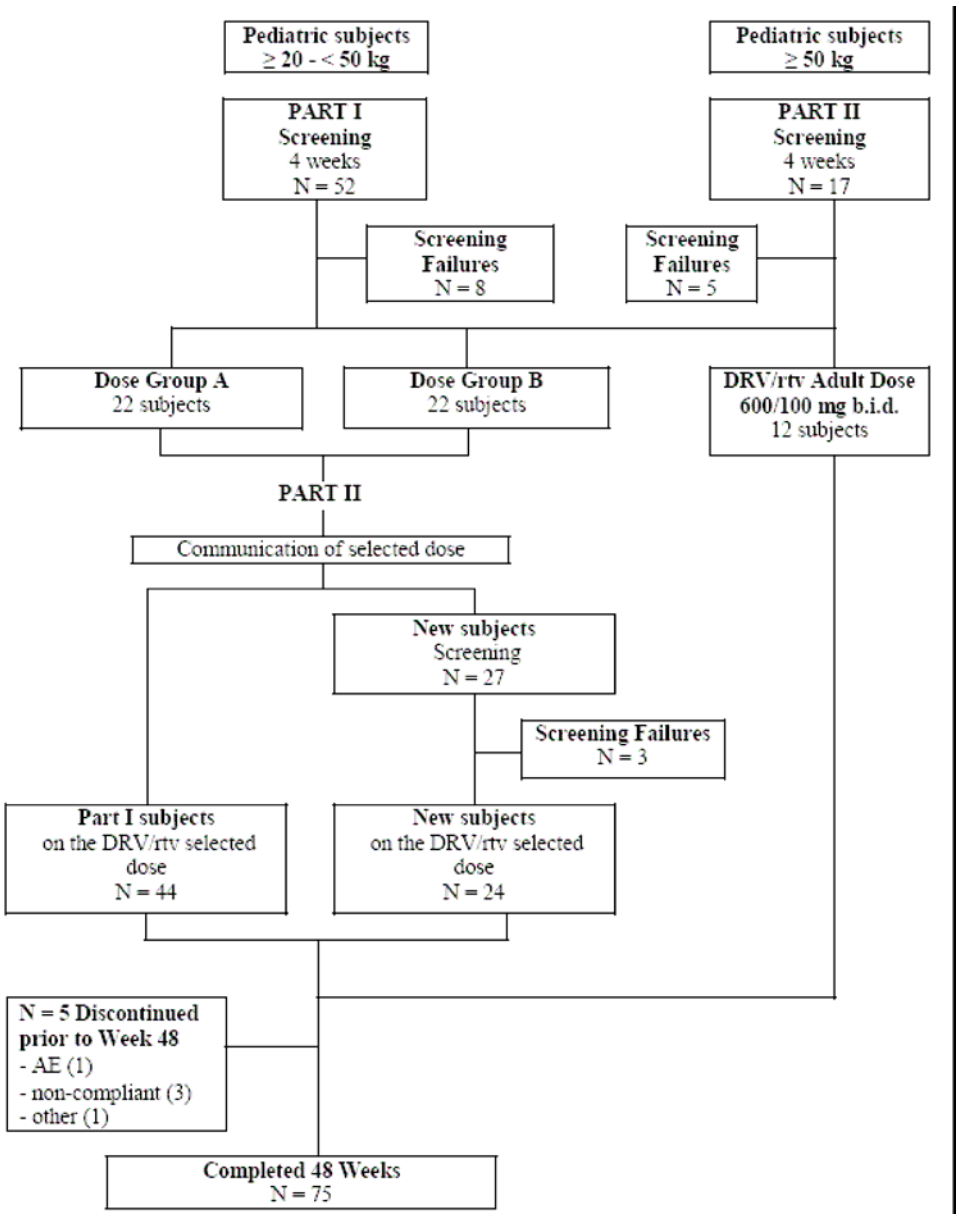
Dose selection (Part I)
Part I of study TMC114-C212 was designed to provide dose recommendations of darunavir/ritonavir in HIV-1 infected treatment-experienced children and adolescents weighing between 20 and 50 kg (see above). The recommended dose was selected based on short-term safety, tolerability, antiviral activity and pharmacokinetics on Day 14. As discussed above, the dose scheme applied in group B was used for further evaluation in part II of this study.

Dose Group B (<u>11-19</u> mg/kg darunavir and 1.5-2.5 mg/kg ritonavir):

≥ 20 to < 30 kg:	375/50 mg	darunavir/ritonavir b.i.d.
≥ 30 to < 40 kg:	450/60 mg	darunavir/ritonavir b.i.d.
≥ 40 to < 50 kg:	600/100 mg	darunavir/ritonavir b.i.d.

There was no indication that the virologic response in Group B was better than in Group A, thus that the higher dose showed favourable efficacy as claimed by the Applicant. There were no consistent differences in virological response (including the < 50 copies/ml level efficacy parameter) between the different weight bands during the short-term (4 Weeks) evaluation. The virological responses in both dose groups per kg body weight seemed to be similar in the very small number of evaluated patients. However, for more explanation see below clinical efficacy Week 24 and 48 data in support of the chosen higher dose level.

Main clinical study (Part II)
Part II was designed as an observational study looking at the efficacy and safety of darunavir/ritonavir b.i.d. in treatment experienced, HIV-1 infected children and adolescents between 6 and < 18 years of age. In total, 80 patients were included in this part, of who 44 were included in part I (see above) and 36 newly recruited into Part II.



The primary efficacy endpoint was the decrease in viral load (copies/ml) ≥ 1.0 log10 at Week 24. Secondary endpoints included: decrease in viral load (copies/ml) ≥ 1.0 log10 at all other time points; decrease in viral load (copies/ml) ≥ 0.5 log10; change in log10 plasma viral load (copies/ml); change in CD4+ and CD8+ (absolute and %), and CD4+/CD8+ ratio.

All patients were ARV treatment-experienced. The majority had previously used at least 1 NNRTI, at least 3 NRTIs, or at least 2 PIs. Only few had previously used a fusion inhibitor (FI). Sixty-five percent of patients had previously used ARV drugs from 3 classes (PI + NRTI + NNRTI). Ninety-two percent of patients had previously received ritonavir, most likely as part of a boosted PI regimen. Seventy percent of patients had previously received lopinavir/ ritonavir; nelfinavir (NFV) had been used previously by 58% of patients.

Overall, the baseline characteristics, including resistance associated mutations (RAMs), of these patients were reflective of advanced HIV infection. Most patients (66.3%) used a NRTI-based regimen consisting of NRTIs only (in addition to trial treatment). Based on the Antivirogram, in 48% of the cases the HIV was not susceptible to any or only to one ARV drug in the initial ART in addition to trial treatment. Initial baseline susceptibility data imply that a more effective optimised background therapy (OBT) could have been constructed.

Week-24 analyses showed that a small group of patients who used no sensitive ARVs in their OBT showed quite a high virological response, most likely mainly due to darunavir. In the other subgroups a higher number of sensitive ARVs used in patients' OBT was associated with better virological response in the adolescents group, as expected.

However, such a trend was not seen in the small subgroups of younger children. Response rates in adolescents remained lower compared to the younger age group. This was also the case for viral load < 50 copies/ml parameter in the overwhelming majority of the patients with darunavir sensitive virus (darunavir FC < 10). The data should be interpreted with caution as the subgroups especially in the young age category are too small to draw robust conclusions.

At Week 24, 73.8% of all patients had a decrease in viral load ≥ 1 $\log_{10}$ and at Week 48, 65.0%. The highest response was seen in Week 4 and 8. (See the following table. Sensitivity analysis demonstrated that results for virologic response were robust and consistent across the different imputation methods used).

Table 1 Confirmed Virologic Response (≥ 1 log10 decrease in Viral Load) (ITT, TLOVR)

	darunavir/ritonavir **N = 80** **Number of Responders n (%)**
≥ 1$\log_{10}$ Decrease from Baseline	
Week2	63 (78.8)
Week 4	66 (82.5)
Week 8	66 (82.5)
Week 12	65 (81.3)
Week 16	62 (77.5)
Week 20	61 (76.3)
Week 24	59 (73.8)
Week 32	54 (67.5)
Week 40	53 (66.3)
Week 48	52 (65.0)
n = number of observations; N = number of patients; ITT = Intent-to-Treat; TLOVR = Time to loss of virological response	

The virologic response at 24 Weeks was reasonably high and in line with the relatively high virologic response found in (highly) treatment experienced adults. Direct comparisons to efficacy of other PIs in the paediatric patient population cannot be made, as different studies mostly include different populations with different treatment history or different baseline characteristics and studies in paediatric patients are mostly open labelled, uncontrolled and not randomised. However, the virologic response detected in this trial seems to be on the high end of what is found with other PI based regimens in treatment experienced paediatric patients. In addition, there was a clear immunological response with an overall shift towards higher CD4 count.

Overviews of the virologic response parameters plasma viral load < 50 copies/ml and a decrease in plasma viral load ≥ 1.0 log (TLOVR) at Weeks 24 and 48 are provided by weight (Table 2). Table 3 gives an overview of the virologic response parameters plasma viral load < 50 copies/ml and a decrease in plasma viral load ≥ 1.0 log (TLOVR) at Weeks 24 and 48 by dose per kg body weight and age.

Table 2 Virologic Response (Viral Load < 50 Copies/ml, ≥ 1.0 log10 Decrease in Viral Load) (ITT -TLOVR) at Weeks 24 and 48 by Weight Band – Trial TMC114- C212 – Week-48 Analysis

Virologic Response, n (%) Time Point	**20 - 29 kg N = 20**	**30 - 39 kg N = 24**	**40 - 49 kg N = 24**	**≥ 50 kg N = 12**
Confirmed Plasma Viral Load < 50 Copies/ml				
Week 24	12 (60.0)	15 (62.5)	8 (33.3)	5 (41.7)
Week 48	14 (70.0)	12 (50.0)	7 (29.2)	5 (41.7)
Confirmed Decrease in Plasma Viral Load ≥ 1.0 log10 Copies/ml				
Week 24	16 (80.0)	18 (75.0)	17 (70.8)	8 (66.7)
Week 48	16 (80.0)	16 (66.7)	14 (58.3)	6 (50.0)
n = number of responders; N = number of patients				

Table 3 Virologic Response (Viral Load < 50 copies/ml, ≥ 1.0 log10 Decrease in Viral Load) (ITT -TLOVR) at Weeks 24 and 48 by Age and Dose per kg Body Weight – Trial TMC114-C212 – Week-48 Analysis

	≤ 13.1 mg/kg		**> 13.1 mg/kg**	
Virologic Response, n (%) Time Point	**6 - 11 Years N = 7**	**12 - 17 Years N = 33**	**6 - 11 Years N = 7**	**12 - 17 Years N = 33**
Confirmed Plasma Viral Load < 50 Copies/ml				
Week 24	5 (71.4)	16 (48.5)	13 (76.5)	6 (26.1)
Week 48	4 (57.1)	16 (48.5)	13 (76.5)	5 (21.7)
Confirmed Decrease in Plasma Viral Load ≥ 1.0 log10 Copies/ml				
Week 24	4 (57.1)	24 (72.7)	16 (94.1)	15 (65.2)
Week 48	4 (57.1)	20 (60.6)	16 (94.1)	12 (52.2)
n = number of responders; N = number of patients				

The virological response data with respect to < 50 copies/ml level for week 24 and 48 showed a remarkable difference between adolescents and the younger children across both dose levels in favour of the younger children, probably due to the fact that the younger patients were less experienced compared to the adolescents (see also below the response in relation to compliance). The higher dose level trended to give better results in the younger group (6-11 years of age). In contrast, the lower dose level gave better results in the adolescents group (12-17 years of age).

These trends in better response to the higher dose level were also reflected in plasma viral load ≥ 1.0 log (TLOVR) measurements for the younger age group, whereas the difference between doses became less obvious for the adolescents group for this parameter. The response at week 48 became similar for both age groups at the lower dose level whereas the difference in favour of the younger group was maintained at the higher dose level.

For both virological response parameters results trended clearly to show decreasing response by weight band with increasing weight category especially at week 48 evaluation; the lowest response seemed to be associated with the 40-49 kg weight band. The results for the > 50 kg weight band were better than those for the 40-49 kg weight band for the < 50 copies/ml level parameter but not for the plasma viral load ≥ 1.0 log (TLOVR) measurements; the number of involved patients in the former group was too small to allow a good comparison.

Overall, the virological response data favoured the choice of the higher dose level especially in the younger age group, whereas based on the plasma viral load ≥ 1.0 log (TLOVR) measurements the difference between doses became less obvious for the adolescents group. The latter group was more pre-treated and the lower response in this group could be explained at least partly by resistance to darunavir which was only seen in adolescents. The observed trend showing decreasing response with increasing weight band category especially at Week 48 evaluation reflects the age related observations associated with increased weight category. Thus the data in favour of the higher dose are not fully conclusive; however, it is a plausible choice and can be expected to offer better coverage to contain the risk of resistance development in this already pre-treated group of patients.

Of the 80 patients included in the study at week 24, 22 experienced virologic failure (15 were classified as "rebounders", 7 were "non-responders"). Of the "rebounders", baseline and endpoint genotypic profiles were available for 13. Protease mutations emerging in over 10% of "rebounders" were V32I (n = 4), I54L (n = 4) and L89M (n = 2). V32I and I54L have been described as darunavir RAMs. It was unclear what proportion of the rebounders developed darunavir mutations, and whether issues related to adherence or possibly the adequacy of the dosage could have played a role in these cases. As requested, the Applicant provided additional analyses. The Week 48 data showed that out of 17 rebounders, 9 (53%) developed darunavir RAMs. I54L developed in 5 patients, V32I in 4 patients, I50V in 3 patients, and V11I, L33F and I84V in 1 patient. As mentioned before, plasma drug concentration < 550 ng/ml was used to monitor compliance. There seemed to be no connection between the development of darunavir RAMs and measurements of compliance by darunavir plasma concentration measurements < 550 ng/ml. The data should be interpreted with caution because the groups are too small to draw robust conclusions.

Conclusions on Efficacy

Week 24 and 48 data on virologic and immunologic response of trial TMC114-C212 demonstrated that darunavir/ritonavir offers an effective treatment option in treatment-experienced HIV infected paediatric patients from 6 to 18 years of age at the recommended dose regimen:

≥20 to <30 kg:	375/50 mg	darunavir/ritonavir b.i.d.
≥30 to <40 kg:	450/60 mg	darunavir/ritonavir b.i.d.
≥40 to <50 kg:	600/100 mg	darunavir/ritonavir b.i.d.

The virologic response defined as decrease from baseline of at least 1.0 $\log_{10}$ in plasma viral load was achieved by 65.0% of the patients, and 47.5% of patients achieved an undetectable plasma viral load (< 50 copies/ml) at Week 48. Virologic response defined as plasma viral load < 400 copies/ml at Week 48 was achieved by 58.8% of the patients. These results were confirmed by sensitivity analyses. The virologic response at 48 Weeks is in line with the relatively high virologic response found in (highly) treatment experienced adults. In addition, there was a clear immunological response with an overall shift towards a higher CD4 cell count.

Clinical safety

Patient exposure
Currently there is very limited experience in children –there is data from 77 HIV-infected patients aged 6 to 18 years on the selected dose, in addition to data on 73 children and adolescents enrolled in the compassionate use programme. This is not sufficient data to make reliable comparisons to other patient groups or treatments. However, the number of patients included in this trial is reasonable regarding the type of application, and similar as to other applications for ARV medicinal products such as PIs for similar paediatric indications. Originally, 24 weeks data were provided. Available data extend now to 48 week data. The safety data for the 24 week treatment period are summarised below.

Adverse events(AE)
During the treatment period, 71 of the 80 patients (88.8%) reported at least one AE. Most AEs were grade 1 or 2 in severity. Grade 3 or 4 AEs occurred in 18 (22.5%) patients. The most common AEs considered at least possibly related to darunavir were abdominal pain (4 patients, 5.0%), diarrhoea (2 patients, 2.5%), ALT increased, INR increased, LDL increased, epistaxis and rash (all in 2 patients, 2.5%).

Serious adverse events (SAE) and deaths
No deaths occurred during the 24 week period of trial TMC114-C212, SAEs were reported by 9 (11.3%) patients during the treatment period. One patient (1.3%) experienced increased ALT (grade 3) – this was the only SAE considered possibly related to treatment. All other SAEs were considered to be not or doubtfully related to darunavir. One patient permanently discontinued treatment due to an AE. This patient experienced grade 3 anxiety which was not considered related to trial treatment by the investigator.

Laboratory findings
The overall incidence of laboratory abnormalities was low. No clinically relevant mean changes from baseline were observed for any laboratory parameter. Most laboratory abnormalities were grade 1 or 2 in severity. Small median changes from baseline were observed for vital signs. None of the observed mean changes from baseline were considered clinically relevant.

As requested, the Applicant provided a more differentiated assessment of the safety according to age, weight/dose bands and mg/kg administered based on the 24 week and 48 week data. Any observed differences remained essentially descriptive and no conclusions could be inferred from these observations. The stratification according to dose (mg/kg) was not further considered as there was no relevant difference in exposure between the 2 groups. No new safety issues related to darunavir/ritonavir were identified from this additional post-hoc stratification of the Week 4 data.

During the 48 Week treatment period, 92.5% of patients reported at least 1 AE, with the most common AEs (at least 10.0%) being pyrexia, cough, upper respiratory tract infection, diarrhoea, vomiting, lymphadenopathy, herpes simplex, abdominal pain, pneumonia, sinusitis, tonsillitis, conjunctivitis and headache. Most AEs were grade 1 or 2 in severity. Twenty-one patients experienced a grade 3 or 4 AE, of which 5 were grade 4 and none was related to treatment. No patients died during the treatment period. SAEs were reported in 11 patients (13.8%) during treatment. All SAEs occurred in no more than 1 patient each. One SAE (increased ALT) was considered at least possibly related to investigational medication.

One patient permanently discontinued trial treatment due to an AE (anxiety) considered not related to investigational medication by the investigator. Rash-related events were reported in 11 patients (13.8%). Rash-related events considered at least possibly related to treatment were reported in 2 patients (2.5%). No grade 3 or 4 rashes occurred. The overall incidence of GI-related events was 33.8% with grade 2 as the worst severity rating. GI-related events considered at least possibly related to treatment were reported in 7.5% of patients. Haematology-related AEs in 9 patients (11.3%). Liver-, cardiac-, lipid-, and pancreas-related events were generally low in incidence (< 10%). The safety results in the 48 Week analysis were comparable to the Week 24 results and no new safety findings were observed.

Conclusion on Safety

There is very limited experience with Prezista in children and adolescents – currently there is data from 77 HIV-infected patients aged 6 to 18 years on the selected dose who were observed for 48 Weeks, in addition to data on 73 children and adolescents enrolled in the compassionate use programme. There is not enough data to make reliable comparisons to other patient groups or treatments.

The most common AEs occurring in more than 10.0% of patients during treatment were reminiscent of those in adult patients and included cough, diarrhoea, pyrexia, vomiting, and abdominal pain. The majority of AEs were grade 1 or 2 in severity. Grade 3 or 4 events were reported in 21 patients and were mostly not considered related to trial treatment. No patient died up to the cut off point (48 Weeks) and 11 patients (13.8%) reported a SAE. Only one patient permanently discontinued treatment due to an AE. This patient experienced grade 3 anxiety which was not considered related to trial treatment by the investigator. The adverse reactions seen are similar to what has been observed for Prezista up until now, and no new safety concerns emerged from the current study.

Compliance

The Applicant analysed compliance at Week 48 using 3 different methods: the adherence questionnaire from PENTA, sparse sampling of darunavir plasma concentrations and pill count.

An overview of the virologic response (viral load < 50 copies/ml) at Week 48 in relation to compliance as assessed by the adherence questionnaire showed a difference in response between compliant and noncompliant patients of overall approximately 7%, which illustrated that the questionnaire was not a sensitive method to measure compliance.

Darunavir plasma concentrations were measured. Patients were considered noncompliant if they had darunavir plasma concentrations < 550 ng/ml on any sparse sampling during the trial. A comparison of the virologic response (viral load < 50 copies/ml) at Week 48 in relation to compliance based on sparse sampling showed in both age groups that compliant patients (as defined by sparse sampling) had a response rate that was at least 40% higher compared to noncompliant patients.

Compliance was assessed via pill count and calculated as: (the actual amount taken / the amount to be taken) x 100%. The actual amount taken was calculated as: the number of pills dispensed – the number of pills returned. The amount to be taken was calculated as: the number of days since last dispensing x the number of pills to be taken per day. Based on this method, 28 patients were considered noncompliant, 4 (16.7%) of younger children and 24 (42.9%) of adolescents. A comparison of the virologic response (viral load < 50 copies/ml) at Week 48 in relation to compliance as assessed by pill count showed compliant patients to have a response rate that was 18% higher compared to noncompliant patients.

None of the 3 methods to measure compliance was completely reliable, but sparse pharmacokinetic sampling seemed to be the most effective measurement, as this was most strongly correlated with virological outcome. Notwithstanding the disadvantages of the different methods, the data demonstrated that compliance was more problematic in adolescents (than in younger children). More frequent sampling should be encouraged in future trials not only for pharmacokinetic reasons but also in the light of acquiring adherence data.

5. Pharmacovigilance system

The Applicant has provided documents that set out a detailed description of the system of pharmacovigilance (DDPS). A statement signed by the Applicant and the qualified person for pharmacovigilance, indicating that the Applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management plan

The Applicant provided an updated risk management plan (RMP), version 8.0, dated 9 February 2009, with amendments regarding the indication for children. A clear overview of the changes was provided. Earlier versions of the RMP were already assessed and found to be sufficient. Only the current amendments are discussed in this report.

Safety Specification
The following changes were made:

As requested by the CHMP, tables on dose by gender, and age by dose and by gender were added to the updated RMP.

- ***Section 1.3.1: Populations not studied:***

New text: 'The Phase II trial TMC114-C212 is ongoing to investigate the long-term (up to 48 weeks) safety and tolerability of darunavir/ritonavir in treatment-experienced, HIV-1 infected paediatric patients aged from 6-17 years (n=80). This trial is discussed in the Paediatric Investigation Plan (PIP) together with other planned studies in the paediatric population from 3 years of age and above.'

In response to CHMP questions, the Applicant added exposure data regarding the paediatric patients in the appropriate sections of the RMP, including compassionate use. The Applicant also addressed the missing data in children in the appropriate sections of the RMP.

- ***Section 1.4.3: Regulatory action taken:***

The Applicant added some regulatory actions taken since the last version of the RMP. This was agreed.

- ***Section 1.5: Adverse events/adverse reactions:***

The following was added in section 1.5.1: 'SOC General disorders and administration site reaction\ General Signs and Symptoms\Selected PT: Fat tissue increased.' The CHMP agreed to his addition.

Furthermore, section 1.5 was divided in two parts: adults and children. The following children section was added:
"Paediatric population:
The safety data of the phase II trial TMC114-C212 is used as primary safety dataset. When relevant, additional safety data obtained up to 29 February 2008, from the following trials and programs, are discussed:

- The ongoing trial TMC114-C212 after the cut-off date for the 24-weeks analysis (29 August 2007).
- The Compassionate Use Program (or exceptionally in the Expanded Access or Named Patient programs). In these Programs, 73 HIV-1 infected treatment experienced paediatric patients received treatment with darunavir/ritonavir as they had no treatment options due to virologic failure, or intolerance to multiple ARV regimens."

In 1.5.2 the identified and potential risks were presented separately for children.

As requested by the CHMP, in the updated RMP, development of drug resistance was re-graded from potential risk to identified risk, and the potential for off-label paediatric use in treatment naïve patients was included in section 1.9.5.

As the current data on children are too scarce to clearly identify all risks and upcoming new data will provide more information, the CHMP requested the Applicant to closely monitor all AEs and identify all possible new risks, also referring to the decision on the PIP 000038-PIP01-07 of the EMEA. The Applicant committed to closely monitor new safety data in specific paediatric trials and to stratify the data according to age groups.

Evaluation of the need for risk minimisation measures

It was agreed that the results of study TMC114-C212 do not indicate a different safety profile for children as compared with adults. However, this is based on very few data: only 24 children in the age of 6-12 years, and 56 in the age of 12-18 years. Therefore, properly estimated frequencies can not yet be added. The AEs in children have to be closely monitored and stratified in the age groups 6-12 and 12-18. On request of the CHMP, the Applicant committed to propose a long term study protocol using the PENTA registry. The draft protocol will be submitted to the CHMP for review (see also Letter of Undertaking).

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The Quality data presented within this extension application are considered satisfactory and support the addition of the 75 mg and 150 mg strengths.

Efficacy and Safety

Benefits
The biowaiver for the 75 and 150 mg tablet and the selected darunavir/ritonavir dose regimen for children were adequately justified.

Week 24 and 48 data on virologic and immunologic response of trial TMC114-C212 demonstrated that darunavir/ritonavir offers an effective treatment option in treatment-experienced HIV infected paediatric patients from 6 to 18 years of age at the recommended dose regimen. The virologic response defined as decrease from baseline of at least 1.0 $\log_{10}$ in plasma viral load was achieved by 65.0% of the patients, and 47.5% of patients achieved an undetectable plasma viral load (< 50 copies/ml) at Week 48. Virologic response defined as plasma viral load < 400 copies/ml at Week 48 was achieved by 58.8% of the patients. These results were confirmed by sensitivity analyses. The virologic response at 48 Weeks is in line with the relatively high virologic response found in (highly) treatment experienced adults. In addition, there was a clear immunological response with an overall shift towards a higher CD4 cell count.

Additional analyses with regards to virological efficacy data by weight band, mg/kg dose, and age to further justify the appropriateness of the selected regimens on the bases of week 24 and week 48 results in ART-experienced children favoured the choice of the higher dose level, especially in the younger age group. The adolescents group was more pre-treated and the lower response in this group could be explained at least partly by resistance to darunavir which was only seen in adolescents. The observed trend showing decreasing response with increasing weight band category especially at Week 48 evaluation reflects the age related observations associated with increased weight category. The evidence in favour of the efficaciousness of the higher dose was considered sufficient; although based on the limited paediatric data it was deemed acceptable in the light of the established efficacy of darunavir/ritonavir in (heavily) pre-treated HIV infected adult patients.

Risks
There is limited experience with Prezista in children and adolescents – currently there is data from 75 HIV-infected patients aged 6 to 18 years on the selected dose who were observed for 48 weeks, in addition to data on 73 children and adolescents enrolled in the compassionate use programme. There is not enough data to make reliable comparisons to other patient groups or treatments. However, the number of patients included in this trial was reasonable regarding the type of application, and similar as to other applications for anti retroviral drugs for treatment-naïve patients.

The most common AEs occurring in more than 10% of patients during treatment were comparable of those in adult patients and included cough, diarrhoea, pyrexia, vomiting, and abdominal pain. The majority of AEs were grade 1 or 2 in severity. Grade 3 or 4 events were reported in 18 patients and were mostly not considered related to trial treatment. No patient died up to the cut off point (24 weeks) and 9 patients (11.3%) reported a SAE. One patient permanently discontinued treatment due to an AE. This patient experienced grade 3 anxiety which was not considered related to trial treatment by the investigator. The adverse reactions seen are similar to what has been observed for Prezista up until now, no new safety concerns emerged from the current study.

During the 24 week study period, 22 patients out of 80 patients experienced virological failure; 15 of these were rebounders. It was unclear what proportion of the rebounders developed darunavir mutations, and whether issues related to adherence or possibly the adequacy of the dosage could have played a role in these cases.

The most relevant measurement of compliance –considered to be an extremely important aspect, especially in adolescents - was based on sparse pharmacokinetic sampling; it was most strongly correlated with virological outcome. Here, more frequent sampling should be encouraged in future trials not only for pharmacokinetic reasons but also in the light of acquiring adherence data. Furthermore, the highest pill burden was in the youngest age group (because they are not able to swallow the large tablets) yet they showed the highest virological response. This was explained by the fact that they are also the least pre-treated group. Children using the large tablets with less pill burden did not show better virological response. The pill-burden effect within an age category was not assessed.

Finally, the presented data suggested no connection between the development of darunavir RAMs and measurements of compliance by the darunavir plasma concentration measurement < 550 ng/ml. The data should be interpreted with caution because the groups are too small to draw robust conclusions. In conclusion, the issue of resistance development should be monitored like for the adult patients and resistance to darunavir in paediatric patients should be reported in the general evaluations of resistance to darunavir in the regular Periodic Safety Update Reports (PSURs) for Prezista (see also Letter of Undertaking).

Benefit-Risk Assessment

Week 24 and 48 data on virologic and immunologic response of trial TMC114-C212 demonstrate that darunavir/ritonavir offers an effective treatment option in treatment-experienced HIV infected paediatric patients from 6 to 18 years of age at the recommended dose regimen. Safety data up to 48 weeks of treatment did not reveal new safety issues. Also, the adverse reactions observed were comparable to those observed in adult patients. Nevertheless, there is only limited data in paediatric patients. Here, the Applicant committed to monitor the safety of Prezista including HIV resistance development in children and to report these issues in the regular PSURs for Prezista. Also, on request of the CHMP, the Applicant committed to propose a long term study protocol using the PENTA registry.

Given the agreed Pharmacovigilance measures, the CHMP concluded that the new strengths Prezista 75 mg and 150 mg, co-administered with low dose ritonavir, can be used safely and efficaciously in the targeted ART- experienced paediatric population.

The final agreed wording for the indication is as follows:

"Prezista, co administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV 1) infection in antiretroviral treatment (ART) experienced adult patients, including those that have been highly pre-treated, ***and for the treatment of HIV 1 infection in ART experienced children and adolescents from the age of 6 years and at least 20 kg body weight.****"*

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Prezista 75 mg and 150 mg film-coated tablets, co-administered with 100 mg ritonavir in combination with other ARV medicinal products in the treatment of HIV-1 infection in ARV treatment of ARV experienced HIV-1 infected paediatric patients aged 6 to 18 years was favourable and therefore recommended the granting of the MA.