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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Prezista

darunavir

Procedure no: EMEA/H/C/000707/P46/073

Note

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

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1. Executive summary

This report covers the submission in accordance with Article 46 of Regulation (EC) No 1901/2006 of the final clinical study report of an observational study on growth in HIV-infected children and adolescents on antiretroviral therapy in Europe, with special reference to Darunavir.

The submission of the study protocol (EMEA/H/C/000707/MEA 69) "An observational study on growth in HIV-infected children and adolescents on antiretroviral therapy in Europe, with special reference to Darunavir" was requested as a post-authorisation commitment during the review of procedure EMEA/H/C/000707/II/0054 (type II variation to request an extension of the indication in the HIV infected treatment naïve patients aged ≥12 to <18 years).

No SmPC and PL changes are proposed.

2. Recommendation

In conclusion, there was no evidence that initiating a DRV-containing ART regimen had any impact on growth, positively or negatively. This lack of effect on growth is similar to that seen for other PIs.

The data submitted do not influence the benefit-risk balance for Prezista (darunavir) which remains unchanged. No changes to the current SmPC are warranted. The results of the study should be included in the RMP for Darunavir.

No further action is required.

3. Introduction

On 12 September 2017, the MAH submitted a completed paediatric study for Prezista (darunavir), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Prezista (darunavir) and that there is no consequential regulatory action.

4. Scientific discussion

4.1 Introduction

The MAH submitted a final report for:

An observational study on growth in HIV-infected children and adolescents on antiretroviral therapy in Europe, with special reference to darunavir.

The protocol for this observational study was agreed by PRAC in September 2014 (procedure EMEA/H/C/000707/MEA 69).

The final study report of the DIONE study was submitted by the MAH to the EMA on 7 November 2012 as part of a type II variation to request an extension of the indication in the HIV-infected treatment-naïve patients aged ≥12 to <18 years (procedure EMEA/H/C/000707/II/0054). In the DIONE study, the median height-for-age z-score (HAZ) at baseline was -0.4, which is close to but below the HAZ expected in uninfected adolescents and there was no significant change in HAZ-score at 48 weeks.

Therefore, EMA requested the MAH to include "growth abnormalities in the paediatric population" as an important potential risk in the Risk Management Plan and to further investigate the effect of DRV on growth in HIV-infected children and adolescents.

The MAH contracted the Paediatric European Network for Treatment of AIDS (PENTA) Foundation/European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) to conduct an observational study on growth in HIV-infected children and adolescents on ARV therapy in Europe. To place the potential effect of DRV on growth in context, analyses to investigate the wider effect of ARVs and different drug classes on growth in paediatric patients of different ages and treatment histories were also planned.

The DRV growth study in HIV-infected children and adolescents on ARV therapy in Europe conducted by PENTAEPPICC, has now been completed and is subject to this Article 46 submission.

The overall aim of this study was to investigate, among paediatric patients with HIV infection in a "real world" setting in 11 countries, how the height of HIV-infected children in Europe aged <18 years is affected by exposure to a DRV-based antiretroviral treatment (ART) regimen.

4.2 Clinical study

➢ Description

The overall aim of this study was to investigate, among paediatric patients with HIV infection in a "real world" setting in 11 countries (Belgium, Italy, Netherlands, Poland, Russia, Spain, Sweden, Switzerland, Thailand and the UK/Ireland), the following research question:

- ☐ How is the height of HIV-infected children in Europe aged <18 years affected by exposure to a darunavir-based ART regimen?

➢ Methods

- ➢ Objectives

1. To describe characteristics of HIV-infected children aged <18 years in Europe initiating treatment with a combination ART (cART) regimen and ever taking a darunavir-containing regimen, including a descriptive summary of their drug utilization data.
2. To describe the change in height-for-age z-score (HAZ) pre- and post-darunavir exposure.
3. If a cohort with similar demographic and clinical characteristics to children taking DRV can be identified, to compare the change in HAZ in those taking a darunavir-containing regimen to those taking other, non-darunavir protease inhibitor (PI) -containing regimens, adjusting for potential confounding factors including pre-regimen HAZ. The characteristics of the children taking the non-darunavir containing regimens will also be described. Children starting DRV first-line will be excluded from this analysis and analysed separately data permitting.

- Study design

A meta-analysis of individual patient data from longitudinal observational cohort studies participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). EPPICC conducts epidemiological research on the prognosis and outcome of HIV-infected pregnant women, children and children exposed to HIV in utero.

- Study population /Study size

Each cohort submitted individual patient data to the 2016 EPPICC data merger for all paediatric patients in their study who fulfilled the following inclusion criteria:

- HIV-infected paediatric patients who initiated on cART (composed of an NNRTI or boosted PI with ≥2 NRTIs, or ≥3 NRTIs including abacavir) aged <18 years,
- who started a DRV-containing regimen aged <18 years, with at least one height measurement prior to starting DRV, at the start of DRV and at least one measurement ≥1 year subsequently (Objectives 1 & 2)

  or

- started a PI-containing regimen aged <18 years, with at least one height measurement within the 2.5 years prior to starting the PI, and at least one measurement within 2.5 years after PI start (Objective 3)

For Objective 3 a matching process was used to select a control group starting non-DRV PI-containing regimens. Matches were identified using propensity scores based on cohort, age at ART initiation, initial ART regimen type, ART line number at start of PI and year of starting PI.

Differences that exceed 0.3 units of height-for-age z-score (HAZ) (approximately 2cm to 3cm in height) are considered to be of clinical concern. Assuming a mean change from baseline in HAZ of 0 in the comparator arm, 80% power and alpha=0.05, a total of 350 children (175 in each group) would give sufficient power to detect a difference in change in HAZ between groups of 0.3 or greater. Therefore, a sample size of 175 children on DRV was considered to be the minimum number required for the analysis of Objective 3.

- Variables

Data collected on patients receiving DRV and other PI-containing regimens included: demographics (age, sex, ethnicity, mode of infection); AIDS events and deaths during follow up; ART use (including start and stop dates, dosing and reasons for stopping a drug); and height, weight, viral load (HIV-1 RNA) and CD4 measurements at every visit. No information which could potentially identify patients, such as name or address, was collected.

- Outcomes/endpoints

The main outcome in this study was change in height, with height standardised using height-for-age z-scores (HAZ).

- Statistical Methods

Main summary measures: Patient characteristics are summarised as frequency (percentage), median [interquartile range (IQR)] or mean (standard deviation (SD)), as appropriate.

Mean changes in HAZ and regression model coefficients are summarised along with their corresponding 95% confidence intervals (CI) and p-values.

➢ Results

➢ Recruitment/ Number analysed

The results are based on data from 10 cohorts across 11 countries.

Overall, 996 patients had ever taken DRV with date of DRV start ranging from 05 March 2004 to 15 Nov 2016. Please see the patient flow chart for details on numbers of patients excluded and reasons.

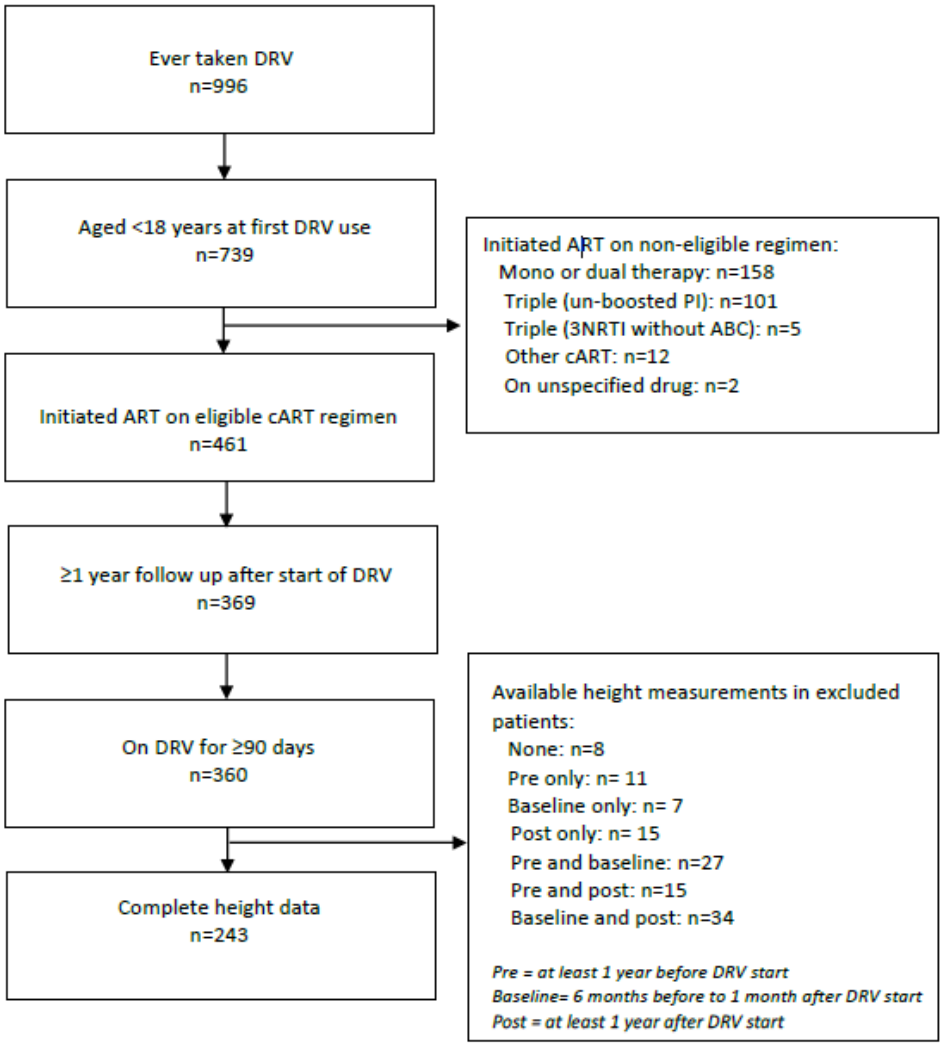


Figure 1: Flowchart of patient on DRV

Overall characteristics of patients with incomplete height data (n=117) were broadly similar to those with complete data (n=243). The only notable difference was that a higher proportion of patients with incomplete height data were naïve compared to patients with complete height data (21% vs. 8%). Consequently patients with complete height data tended to be on ART longer prior to DRV start (median 6.7 years [3.3,10.1] versus 3.9 years [0.2,7.8]) and were more likely to be exposed to drugs in each of the main classes. At the time of starting DRV, patients with complete data also had higher

CD4 counts (median 619 [373, 868] versus 382 [260, 633]) and CD4% (27% [21, 34] versus 21% [15, 29]) than those with missing height data.

The breakdown of characteristics by initial regimen revealed that patients who initiated on >3NRTIs were older at DRV start, started ART much earlier than other patients, and had different treatment histories to those starting a PI- or NNRTI-based regimen. As the number of patients in this group was relatively small (n=13) they were excluded from the main analysis.

Further analysis presented by the MAH has therefore been restricted to all patients (n=230) who initiated ART on a PI- or NNRTI-based regimen, and who had complete height data; 19 were treatment naïve and 211 treatment experienced at the time of starting DRV.

Rapporteur's Comments
The group of patients with three qualifying measurements available at the time of data analyses is 230 participants, which is higher than the minimum number of patients (175) specified in the agreed protocol.

- Baseline data

Darunavir group

Characteristics of the 230 patients: Just under half (46%) were male, the majority (83%) were black African, and most (93%) were identified as infected through mother to child transmission (MTCT), with similar proportions by treatment status. The large majority of patients (83%) were from the UK/Ireland. One patient died during follow up, however the cause of death was accidental and not related to HIV.

Overall, median age at ART initiation was 7.0 years [2.8, 10.6], and higher among the 19 patients who were treatment naïve when starting DRV (12.8 years [11.6, 14.7]) than the patients who were treatment experienced (6.5 years [2.4, 9.8]). Median age at DRV start was similar across the groups, at around 13 years of age.

Median viral load at ART initiation was similar across the groups, and among those who were treatment experienced, 62% had a viral load <400c/ml at DRV start.

Median CD4 count at ART initiation was similar, and higher at DRV start, among those with who were treatment experienced.

The treatment naïve patients had a mean height-for-age z-score of 0.04 (SD 0.76) at the time of ART/DRV initiation while for the treatment experienced patients at ART initiation, height was lower (at -0.83 (SD 1.34)) than what would be expected in uninfected children and adolescents of the same age. The median time between ART initiation and starting DRV in the treatment experienced patients was 6.8 years [3.7, 10.1] and during this time HAZ increased to -0.41 (1.17). Likewise, BMI-for-age z-score was also higher in the treatment naïve group compared to the treatment experienced group.

Treatment experienced patients were exposed to a median of 6 [4, 7] drugs before starting DRV. In this group, 29% initiated ART on a PI-based regimen and 71% on an NNRTI-based regimen. Forty-four per cent (44%) started taking DRV as part of their second ART line, 38% as third line and 18% as fourth or subsequent line. Overall, 100% had prior exposure to NRTIs, 77% to NNRTIs, 75% to PIs and 1% to other drug classes. In patients who had been exposed to NNRTIs, most had used one (median 1 [1,1]), with 60% taking nevirapine and 51% efavirenz, with a cumulative time on an NNRTI before starting DRV of 2.2 years [1.1,5.3]. In those who had taken a previous PI the median number of PIs was 1 [1, 2], taken for a total of 3.8 years [2.0, 6.1], with lopinavir the most commonly used PI (89%) followed by atazanavir (27%). Prior to starting DRV, one third (36%) of patients had a treatment

interruption of at least 30 days with the median total time off-treatment of 1.4 years [0.5, 2.7]. Thirty per cent (30%) of treatment experienced patients started DRV as part of simplified regimen while 15% switched to DRV following failure of the previous regimen dose.

One patient was prescribed DRV while under three years of age. This patient was female, from the UK and started ART at age three months on an NNRTI-based regimen and switched to a PI-based regimen containing lopinavir at age six months and then switched to DRV at age two years and two months. At DRV start she weighed 11 kg and was taking a 300mg/100mg b.d. dose. The reason for switch to DRV is not available.

Patients were on DRV for a median total time of 2.3 years [1.6,3.3] out of a total follow up time of 2.5 years [1.8,3.7] since DRV start; 9% had a treatment interruption after start of DRV, spending a total of 0.7 years [0.3,1.1] off treatment.

Rapporteur's Comments
As formulated in Objective 1, the MAH described the characteristics of the patients initiating treatment with a combination ART regimen and ever taking a DRV-containing regimen, including their drug utilization data.
The HAZ scores in the treatment naïve patients (0.04; SD 0.76) was higher compared to the treatment experienced group (-0.83; SD 1.34), however it is noted that there were only 19 naïve patients. The MAH further mentioned that during the median time between ART initiation and starting DRV in the treatment experienced patients, which was 6.8 years [3.7, 10.1], HAZ increased to -0.41 (1.17), which is to be expected. In addition, BMI-for-age z-score was also higher in the treatment naïve group compared to the treatment experienced group.

Control paediatric patients

A total of 211 propensity score matched controls were selected.

The baseline characteristics of treatment experienced patients and their propensity score matched controls are presented in Table 3 below.

Table 1: Characteristics of treatment experienced patients starting DRV and controls starting a PI other than DRV, <18 years of age

	Controls (n=211)	Treatment experienced at DRV start (n=211)
	n (column %) or median [IQR]	
Cohort		
Belgium	13 (6)	8 (4)
Italy	6 (3)	4 (2)
Poland	1 (0)	1 (0)
Spain	9 (4)	5 (2)
Sweden	7 (3)	9 (4)
Switzerland	6 (3)	4 (2)
Thailand	26 (12)	4 (2)
UK/Ireland	143 (68)	176 (83)
Male	103 (49)	97 (46)
Ethnic group		
White	17 (8)	10 (5)
Black African	139 (66)	173 (82)
Other	47 (22)	18 (9)
Unknown	8 (4)	10 (5)
Age		
Median age at ART initiation (years)	5.5 [1.7, 9.7]	6.5 [2.4,9.8]
Median age at PI start (years)	12.8 [11.6,14.7]	13.7 [12.0,15.2]
Time from ART initiation to starting PI (years)		
Median (IQR)	6.4 [3.7,8.6]	6.8 [3.7,10.1]
Height-for-age z-score		
Mean (SD) at ART initiation	-0.96 {1.44}	-0.83 {1.34}
Mean (SD) at PI start	-0.65 {1.24}	-0.41 {1.17}
Viral load at PI start[1] **(c/ml)**		
<400 c/ml	123 (58)	128 (62)
Year of switch to PI		
Median (IQR)	2012 [2010,2013]	2013 [2013,2014]
ART line at PI start		
Second	92 (44)	92 (44)
Third	87 (41)	81 (38)
Fourth	25 (12)	24 (11)
Fifth	7 (3)	14 (7)
Number of drugs prior to PI start		
Median (IQR)	6 [4,7]	6 [4,7]
Exposure to drug class by PI start		
NRTI	211 (100)	211 (100)
PI	155 (73)	159 (75)
NNRTI	170 (81)	162 (77)
Other	0 (0)	3 (1)

1. For VL the closest measurements to PI start within 6 months before to 1 week after are reported.

HAZ at ART start was missing for 67 (32%) of patients on DRV and 80 (38%) of controls. HAZ at PI start was missing for 26 (12%) of controls

Overall patients on DRV were more likely to be from the UK/Ireland and of black African ethnicity than the controls. Otherwise, the two groups were extremely similar. In 95% of those in the control group, and 96% of those on DRV, the PI was boosted, and the most common PI used in the control group was atazanavir (70%) followed by lopinavir (22%).

Rapporteur's Comments
The propensity score matched controls were selected according to the agreed protocol.
It is noted that the HAZ scores at start of ART and PI in the control group (-0.96 and -0.65, respectively) are slightly lower compared to the HAZ scores in the treatment experienced group (-0.83 and -0.41, respectively).

- Results of the HAZ scores

Darunavir group

Overall, from time of starting ART, patients in the DRV group had a median of 28 height measurements [18,40] compared to 28 [17,39] in the control group not taking DRV. Restricting follow-up time to +/- 2.5 years from start of DRV or other PI, patients in the DRV group had median 12 height measurements [7.5,14.5] compared to 9.5 [5,14.5] in the control group.

Height-for-age z-scores (HAZ) in the year before and after starting DRV, in treatment naïve and experienced patients are summarised in Table 1.

Table 2: Changes in height-for-age z scores one year before and after starting darunavir

	Treatment naïve at DRV start (n=19)				Treatment experienced at DRV start (n=211)			
	Mean {SD} or mean (95% CI)		Median [IQR]		Mean {SD} or mean (95% CI)		Median [IQR	
HAZ 1 year before starting DRV	0.08	{0.75}	0.22	[-0.56,0.65]	-0.40	{1.19}	-0.41	[-1.12,0.33]
HAZ at time of starting DRV	0.04	{0.76}	0.16	[-0.64,0.68]	-0.41	{1.17}	-0.50	[-1.16,0.32]
HAZ 1 year after starting DRV	0.03	{0.80}	-0.02	[-0.44,0.86]	-0.41	{1.11}	-0.56	[-1.09,0.30]
Change during 1 year before starting DRV (A)	-0.04	(-0.18,0.11)	0.01	[-0.20,0.09]	-0.01	(-0.05,0.04)	-0.03	[-0.21,0.16]
Change during 1 year after starting DRV (B)	-0.01	(-0.14,0.11)	-0.02	[-0.18,0.24]	0.00	(-0.04,0.04)	0.00	[-0.16,0.19]
Change after MINUS change before (B)-(A)	0.02	(-0.13,0.18)	0.04	[-0.12,0.25]	0.01	(-0.06,0.07)	0.01	[-0.18,0.25]

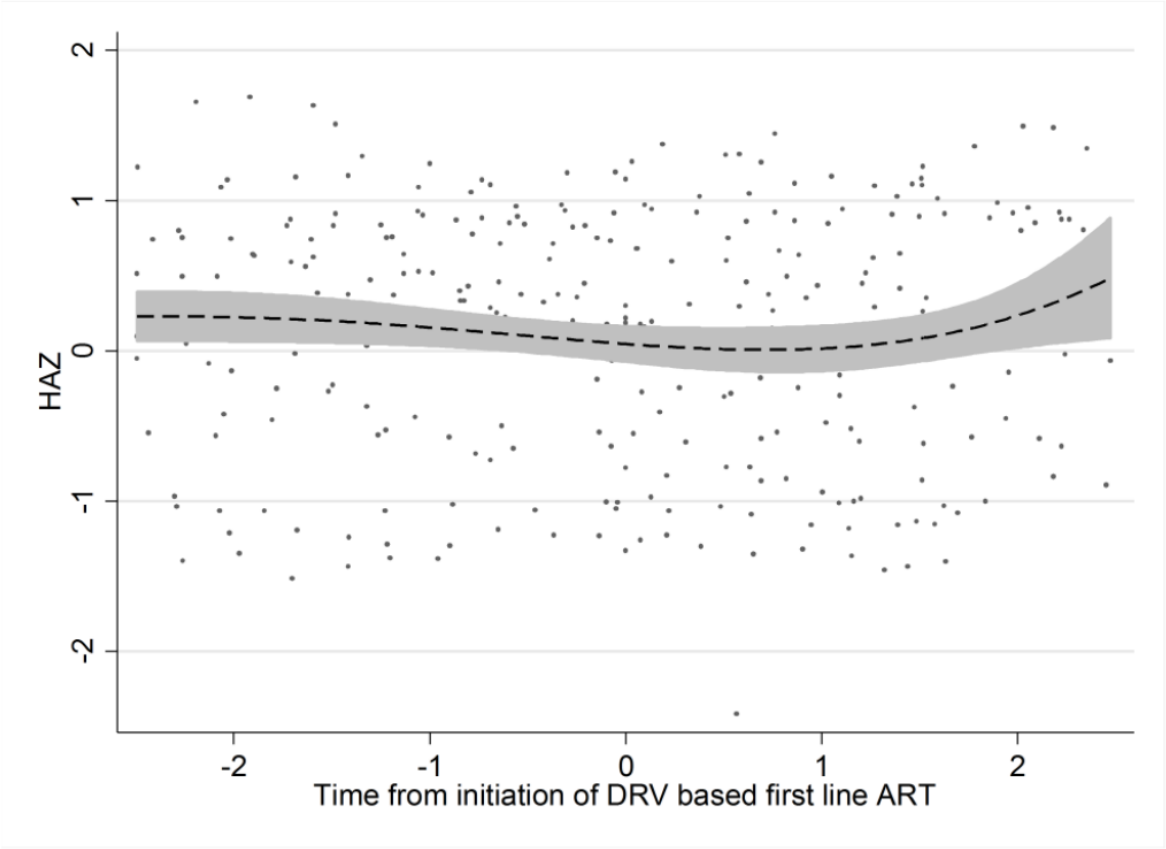
Notes: Height-for-age z-score at time of starting DRV was taken as the closest measurement to the date started within 6 months before to one month after.
All patients had at least one height measurement over one year before and one year after the start of DRV. To estimate height-for-age z-score at one year before and one year after DRV start the rates of change between the pre/post measurements and the measurement at DRV start were assumed to be linear. The actual time between the pre/post measurements and the measurement at DRV start was used to convert the absolute change to an annual rate of change from which height-for-age z-scores at one year before and after the baseline DRV measurement were estimated.

In treatment experienced patients, the mean HAZ was -0.40 one year before starting DRV, and -0.41 at both DRV start and one year after DRV start, with no evidence of any change in the one year period before or after starting DRV (mean change -0.01 (95% CI -0.05, 0.04) and 0.00 (-0.04, 0.04) respectively) or difference in the rate of change before and after starting DRV (0.01 (-0.06, 0.07)).

In treatment naïve patients where the HAZ score was higher at DRV start (mean 0.08), there was no evidence of any change in HAZ over the first year on treatment (mean change -0.01 (-0.14, 0.11)) and only a very small decrease in the year before starting treatment (mean change -0.04 (-0.16, 0.11)). Again there was no evidence that the rate of change differed in the two time periods (difference in rate of change 0.02 (-0.13, 0.18)).

In both treatment naïve and experienced patients the median HAZ reduced slightly from one year before (treatment naïve; median HAZ 0.22 [-0.56, 0.65], treatment experienced; -0.41 [-1.12. 0.33]) to time of DRV start (0.16 [-0.64, 0.68] and -0.50 [-1.16, 0.32]) and to one year after DRV start (-0.02 [-0.44, 0.86] and -0.56 [-1.09, 0.30]). However, the median change within patients before and after DRV start in both groups was approximately 0.

All HAZ measurements for treatment naïve patients up to 2.5 years before and after ART/initiation are shown in Figure 1. Results suggest that this group continued to grow at the expected rate (i.e. HAZ remained at roughly the same level), with a slight increase in HAZ observed after two years.



Note: HAZ scores of all patients who started DRV as part of their first line ART regimen are included (n=19)

Figure 1: HAZ scores (with fitted mean and 95% CI) among naïve patients within 2.5 years of initiation on DRV based first line ART

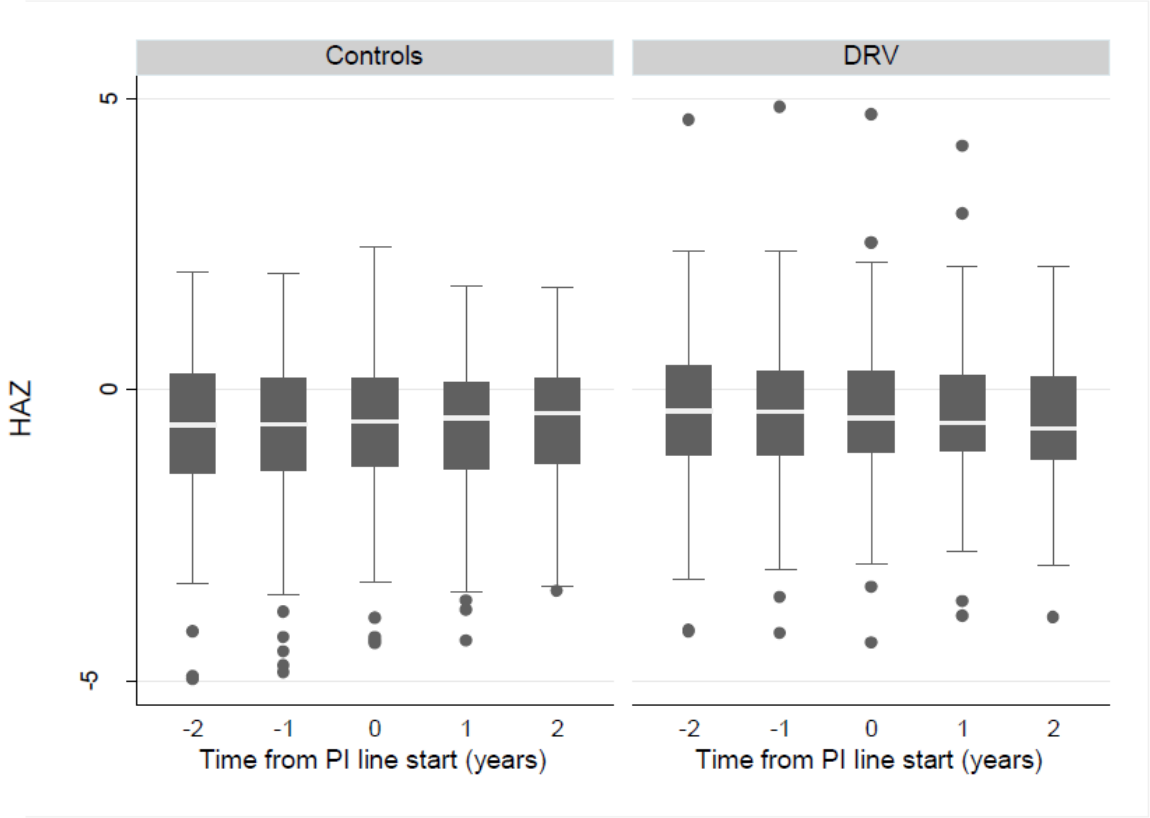
To formally test for any changes in HAZ in treatment experienced patients by key characteristics, a multivariable mixed effects linear regression model was fitted to the data, which allowed for a difference in the rate of change before and after DRV start while controlling for time on ART, age at ART start, initial regimen type, starting DRV after second-line, gender and suppressed viral load at DRV start. Overall, the regression coefficient for the change in HAZ before DRV start, was -0.004 ([95% CI - 0.040 to 0.030] p=0.800), and after DRV start -0.009 ([95% CI -0.058 to 0.041] p=0.723), indicating no change in HAZ in either period.

Rapporteur's Comments
In treatment experienced patients, the mean HAZ change in the one year period before or after starting DRV was -0.01 (95% CI -0.05, 0.04) and 0.00 (-0.04, 0.04) respectively. The difference in the rate of change before and after starting DRV was 0.01 (-0.06, 0.07).

In treatment naïve patients, the mean HAZ change in the one year period before or after starting DRV was -0.04 (-0.18, 0.11) and -0.01 (-0.14, 0.11) respectively. The difference in the rate of change before and after starting DRV was 0.02 (-0.13, 0.18).
Differences that exceed 0.3 units of HAZ score (approximately 2cm to 3cm in height) are considered to be of clinical concern.
It is agreed with MAH's conclusion that there was no evidence of any change in the growth in the patients treated with Darunavir.

Control paediatric patients

The HAZ scores at start of protease inhibitors (PI) and at one and two years before and after PI start in the DRV group and the control group are summarised in the boxplots in Figure 2. HAZ scores did not change over the follow-up time, were extremely similar for the DRV group and the control group.



Note: Boxplots summarise HAZ closest to each annual time point. A window of +/- 6 months was applied at all time points, apart from at start of PI where measurements were within -6 months to +1 month. Patients who initiated on an NNRTI or PI based regimen and did not take DRV in the first line and those on other PIs in the matched sample are included (n=211 per group)

Figure 2: Boxplot of HAZ from two years before to two years after start of DRV and other PIs

To determine whether change in HAZ scores was different before and after PI start in treatment experienced patients, and further whether the rate of change differed in those on DRV to the control group, a linear mixed effects model was fitted. There was no evidence of a difference in the rate of change in HAZ for those on DRV compared to the controls on other PIs (interaction term: PI type *

time since DRV start = -0.022 [95% CI -0.070, 0.027], p=0.381). The model also allowed for the rate of change in HAZ to differ after the start of PI compared to before, and an interaction term included in the model to allow the change in slope after PI start to differ between those on DRV and other PIs.

There was no evidence of any difference between those on DRV and those starting other PIs (beta=-0.039 [95% CI -0.105, 0.027], p=0.244). In fact, the results of the model indicate no change in HAZ across the time points before and after PI start, and across all patients.

Rapporteur's Comments
It is agreed that the HAZ scores were similar for the DRV group and the control group and the height of the patients did not change over the follow-up time.
It is agreed with the MAH that there is no evidence that Darunavir restricts the growth in paediatric patients as compared to other PIs.

Other analyses and adverse events/adverse reactions

From sensitivity analyses there was no evidence of any changes, or differences in changes, in HAZ over time or between PIs.

This study was designed to assess the association between height change and DRV exposure. Adverse events were not reported or analysed as part of this study. The sponsor reports aggregate study findings as study reports, not as individual spontaneous reports according to Johnson & Johnson safety reporting procedures.

In this study, it is not possible or appropriate to assess the causality of adverse events identified during data review. Additionally, individual patient adverse events attributed to DRV are reported by treating physicians according to country and European law.

Rapporteur's Comments
This is acknowledged. As commented in the protocol assessment report, it is accepted that the study results will be communicated on an aggregate level and that the epidemiological analysis of EPPICC data does not allow for causality assessment on an individual patient level.

4.3. Discussion on clinical aspects by the MAH

Characteristics of 230 HIV-infected children aged <18 years, who initiated ART on a PI-or NNRTI-based regimen, and who had complete height data, are presented in the clinical study report: 19 subjects were treatment-naïve and 211 were treatment experienced at the time of starting DRV. On average, DRV was started when patients were teenagers and had been on ART for a median of five years.

In treatment-experienced patients, the mean HAZ was -0.40 one year before starting DRV, and -0.41 at both DRV start and one year after DRV start, with no evidence of any change in the one (-0.04, 0.04) respectively. The lack of change in HAZ suggests that those taking DRV were growing at a similar rate to what would be expected in an uninfected population, both before and after starting DRV, and were neither catching up nor falling further behind from their HAZ at the beginning of the analysis window. Furthermore, when data from a control group of patients on non-DRV PI-containing regimens were analyzed, similar trends were observed with no differences between DRV and other PIs and no evidence of any change in HAZ, before and after the start of a new PI.

For the 19 treatment-naïve patients included in the study, there was also very little change in HAZ over the year before (mean change -0.04) and after (mean change -0.01) starting DRV. However, these patients had a baseline HAZ of 0.04, a similar height on average to that of an uninfected population. Therefore, any "catch-up" growth would not be expected, and the lack of change in HAZ indicates that these patients grew as expected.

Rapporteur's Comments
Overall, from the assessment of the final result of the study there is no evidence of an effect of darunavir-based ART regimen on the height of HIV-infected children in Europe aged <18 years.

5. Rapporteur's overall conclusion and recommendation

- **Overall conclusion**

There was no evidence that initiating a DRV-containing ART regimen had any impact on growth, positively or negatively. This lack of effect on growth is similar to that seen for other PIs.

The data submitted do not influence the benefit-risk balance for Prezista (darunavir) which remains unchanged. No changes to the current SmPC are warranted. The results of the study should be included in the RMP for Darunavir.

- **Recommendation**

No further action required.

6. Request for supplementary information as proposed by the rapporteur

None