Study information

Title	An observational study on growth in HIV-infected children and adolescents on antiretroviral therapy in Europe, with special reference to darunavir.
Protocol version	2.0
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Active substance	Darunavir
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Procedure number	EMEA/H/C/000707/MEA 069
Marketing authorisation holder(s)	Janssen-Cilag International NV
Research question and objectives	To what extent is the height of HIV-infected children in Europe aged <18 years affected by exposure to a darunavir-based ART regimen? The objectives of this study are to: (i) describe the 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; (ii) describe change in height for age z-score (HAZ) pre- and post-darunavir exposure in these children; (iii) compare the change in HAZ in those taking a darunavir-containing regimen to those taking other non-darunavir containing regimens (if a cohort with similar demographic and clinical characteristics to those taking darunavir can be identified), while adjusting for potential confounding factors including pre-regimen HAZ. The characteristics of the children taking the non-darunavir containing regimens will also be described.
Country(-ies) of study	Belgium Denmark France Germany Greece Italy Netherlands Poland Portugal Romania Russia Spain Sweden Switzerland Thailand Ukraine United Kingdom & Ireland
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Marketing authorisation holder(s)	Janssen-Cilag International NV

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List of abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
cART	Combination ART
DRV	Darunavir
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
HAZ	Height-for-age z-score
HICDEP	HIV Cohorts Data Exchange Protocol
HIV	Human Immunodeficiency Virus
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor

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Abstract

Title:	An observational study on growth in HIV-infected children and adolescents on antiretroviral therapy in Europe, with special reference to darunavir (DRV).
Rationale and Background:	The impact of long term ART on growth in HIV-infected children is poorly described. There is conflicting evidence on improved growth following exposure to NNRTI versus PI based regimens. The TMC114-TiDP29-C230 trial (DIONE) of DRV-containing first line therapy in antiretroviral naïve adolescents aged 12 to <18 years indicated no significant change in height for age z-score at 48 weeks. The European Medicines Agency requested further investigation on the effect of DRV on growth in HIV-infected children and adolescents. Currently (as of December 2013) among cohorts collaborating in EPPICC, a powered comparative study of DRV versus other ART drugs is not possible. This is due to an insufficient number of DRV-treated patients, their very complex ART histories (which presents challenges for identification of a comparison group), and in the most recent EPPICC data merger, a lack of pre and/or post-DRV height measures for some patients. However, the number of patients on DRV has increased by 40-45 patients per year over the last two years within the EPPICC network, and availability of height data on patients on DRV is anticipated to increase further due to planned addition of new cohorts to EPPICC, accrual of follow-up data on existing patients, and an increased emphasis on importance of the collection of height data for all future data mergers. Therefore this proposed study will be based on a data merger to be performed in 2016, to allow for the inclusion of an optimal number of valid DRV patient data and more robust analyses. This study aims to describe the height of HIV-infected children aged <18 years pre/post-darunavir exposure. Additional analyses will be performed to compare the height for age z-score (HAZ) of DRV treated patients to patients exposed to non-DRV containing regimens, should data allow.

Research Question and Objectives:

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

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 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.

Study Design:

Pooled analysis of individual patient data from longitudinal observational cohorts participating in the EPPICC pharmacovigilance programme will be conducted for all children initiated on cART.

Population / Setting:

HIV-1 infected children and adolescents aged <18 years at start of cART in Europe.

Eligibility Criteria:

All HIV-1 infected patients having initiated cART (composed of an NNRTI or boosted PI with ≥2 NRTIs, or ≥3 NRTIs including abacavir) at age <18 years.

Duration of Study:

The study will last for about 4 years, starting with the generation of the data on DRV utilization (December 2013), and ending with the availability of the final study report in Sept 2017.

Data Sources:

Cohorts collaborating in EPPICC will participate in this study, and include representation from Thailand and Russia. The cohorts are as follows:

- Belgium: Hospital St Pierre Cohort, Brussels
  Contact: Dr Tessa Goetghebuer
- Europe-wide: European Collaborative Study (including clinics in Belgium, Italy, Sweden, Denmark, Netherlands, Poland, Spain)
  Contact: Dr Claire Thorne
- French Paediatric study (EPF)
  Contact: Dr Josiane Warszawski
- German Competence Network on HIV infected children
  Contact: Dr Chris Koenigs
- Greece Cohort
  Contact: Dr. Vana Spoulou
- Italian Register for HIV infection in children
  Contact: Dr Maurizio de Martino, Dr Luisa Galli
- Netherlands: Amsterdam paediatric cohort
  Contact: Dr. Henriette Scherpbier
- Polish paediatric cohort
  Contact: Dr. Magda Marczynska
- Portugal: Centro Hospitalar do Porto
  Contact: Dr. Laura Marques
- Romania: "Victor Babes" Hospital Cohort, Bucharest
  Contact: Dr Dan Duiculescu, Dr Luminita Ene
- Russia: The Republican Hospital of Infectious Diseases, St Petersburg
  Contact: Drs. Konstantin Dodonov and Liubov Okhonskaia
- Russia: The City HIV Centre, St Petersburg
  Contact: Dr. Anna Samarina
- Russia: Kazan HIV Centre
  Contact: Dr. Firaya Nagimova
- Spain: Barcelona Cohort of HIV-infected Children (CoRISPE-2)
  Contact: Dr Ton Noguera
- Spain: Rest of Spain Cohort of HIV-infected Children (CoRISPE-1)
  Contact: Dr Pablo Rojo Conejo
- Swedish Cohort Study
  Contact: Dr. Lars Naver
- Swiss Mother and Child HIV Cohort Study (MoCHiV)
  Contact: Dr Christoph Rudin
- Programs for HIV Prevention and Treatment (PHPT), Thailand
  Contact: Dr. Gonzague Jourdain
- Ukraine Paediatric HIV Cohort Study, Odessa
  Contact : Dr Ruslan Malyuta
- UK / Ireland National Study of HIV in Pregnancy and Childhood (NSHPC)
  Contact: Dr Pat Tookey
- UK/Ireland Collaborative HIV Paediatric Study (CHIPS)
  Contact: Dr Ali Judd (CHIPS)

Data Sources: In addition by the time of the proposed data merger for this study it is anticipated that the national cohort from the Netherlands and an additional large cohort from France will have joined EPPICC and will collaborate.

Study Procedures: The data merger will take place in 2016. A standard operating procedure will be developed and the data merger will follow the HIV Cohorts Data Exchange Protocol (HICDEP).

Variables: Variables to be collected include: basic demographic details (date of birth, country of birth, sex, mode of infection, ethnicity, hepatitis B co-infection status); patient weights and heights at every clinic visit; ART dosing history, including reasons for stopping a drug.

Sample Size: The data merger for this study will be undertaken in 2016 to maximize the number of DRV-exposed patients and height measurements available for this study.

It is anticipated that between 200 and 250 children in EPPICC will be on a DRV containing regimen at this time. Assuming a mean change from baseline in HAZ of 0 in the comparator arm, a total sample size of 500 will provide 80% power to detect a difference in mean HAZ between groups of 0.25 or greater at a 5% significance level.

Differences that exceed 0.3 units of z-score (approximately 2 to 3 cm 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 is considered to be the minimum number required for the analysis of objective 3.

Matching / Statistical Methods: Standard descriptive statistics will be used to summarize demographic, clinical and drug utilization data for children taking DRV-containing and non-DRV-containing regimens within the EPPICC data set. Data on height will be transformed to height for age z-score (HAZ) based on the WHO Child Growth Standards and WHO Reference 2007.

Comparability of groups initiating DRV-containing and non-DRV-containing cART will be assessed using propensity scores. Providing there is sufficient overlap between the two groups, change in HAZ score will be compared using multilevel regression models to take account of the hierarchical structure of the data (repeated HAZ measurements for each child, and children within different cohorts). A fractional polynomial will be used to model change in HAZ over time, adjusting for baseline covariates related to demographic, HIV disease, treatment history and anthropometric characteristics. The use of multiple imputation to impute missing baseline covariates will be considered, as will sensitivity analyses excluding children with missing covariate data, and restricted to cohorts with data on pubertal stage only.

Milestones:	Pharmacovigilance reports on the progression of the number children on DRV-based regimens with height data appropriate for this analysis: Sept 2014 and Sept 2015
	SOP finalised: End of 2015
	Data merger: June 2016
	Data analysis: October 2016-June 2017
	Draft report: June 2017
	Final report: September 2017

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

Amendments and updates

Amendment or update number	Date	Section of study protocol	Amendment or update	Reason
1	Date	Text	Text	Text
2	Date	Text	Text	Text

Milestones

Milestone	Planned date
DRV Pharmacovigilance reports providing estimates of DRV-exposed patients with height data	September 2014, September 2015
SOP finalized	End of 2015
Data merger	June 2016
Cleaned dataset available	September 2016
Data analysis	October 2016 – June 2017
Draft report	June 2017
Final report	September 2017

Rationale and background

The impact of long term ART on growth in HIV infected children is poorly described. There is conflicting evidence on improved growth following exposure to NNRTI versus PI based regimens. The DIONE trial on DRV-containing first line therapy in 12 antiretroviral naïve adolescents aged 12 to <18 years indicated no significant change in height for age z-score at 48 weeks. The European Medicines Agency requested further investigation on the effect of DRV on growth.

Currently (as of December 2013) among cohorts collaborating in EPPICC, a powered comparative study of DRV versus other ART drugs is not possible. This is due to an insufficient number of DRV-treated patients, and their very complex ART histories (which presents challenges for identification of a comparison group). In the December 2013 EPPICC dataset, there were 158 patients who initiated on combination ART and started a DRV-based therapy aged<18 years, of whom 73 have been followed-up for ≥1 year after start of DRV. Fifty-four of the 73 patients had at least one height measurement at start of DRV and ≥1 measurement after at least 1 year on DRV: 8 of these patients were on DRV 1st line therapy, the remainder of second or subsequent line of therapy. Thus, so far, the majority of DRV patients are heavily treatment experienced with complex ART histories, making the identification of an adequate matching control group and an analysis appropriately adjusting for confounding factors extremely challenging.

Based on data from the last two years of mergers, the number of patients on DRV has increased by 40-45 patients per year within the existing EPPICC network. This is expected to continue to rise, and with the planned addition of new cohorts joining the EPPICC network, this number is likely to increase further. In addition, the existing patients exposed to DRV but with insufficient follow up time (<1 year) in the 2013 merger are likely to be eligible for analysis in future mergers. It is important to note that the EPPICC data mergers conducted to date were not intended to assess growth outcomes and therefore did not emphasise the need for growth data. As this is the outcome of interest for this study, the standard operating procedure will highlight the importance of complete height data for all future mergers.

Hence, the analyses will be based on a data merger performed in 2016, to allow for the inclusion of an optimal number of valid DRV patient data and more robust analyses. Meanwhile, the progression of the number of DRV-exposed children with height data appropriate for this analysis will be monitored and reported on in the 2014 and 2015 DRV pharmacovigilance reports.

This study aims to describe the height of HIV-infected children aged <18 years pre/post-darunavir exposure. Additional analyses will be performed to compare the HAZ of DRV treated patients to patients exposed to non-DRV containing regimens, should data allow.

Research questions and objectives

Research Question

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

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. To compare the change in HAZ in those taking a darunavir-containing regimen to those taking other non-darunavir containing regimens, adjusting for potential confounding factors including pre-regimen HAZ if a cohort with similar demographic and clinical characteristics to the group taking darunavir can be identified. The characteristics of the children taking the non-darunavir containing regimens will also be described.

Research Methods

1.1 Study Design

This is 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.

1.2 Population / inclusion criteria

For objectives 1 & 2: all HIV-infected children who initiated cART (composed of an NNRTI or boosted PI with $\geq$2 NRTIs, or $\geq$3 NRTIs including abacavir); and started a darunavir-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 $\geq$1 year subsequently.

For objective 3: all HIV-infected children aged <18 years at initiation of cART with at least one height measurement at the start of cART and at least one measurement $\geq$1 year subsequently.

1.3 Variables

Variables to be collected on all children will include: basic demographic details (date of birth, country of birth, sex, mode of infection, ethnicity, hepatitis B co-infection status); patient weights and heights at every clinic visit; ART treatment and dosing history (including start and stop dates, and reasons for stopping a drug); CDC disease stage; complete CD4s and viral loads. Where available, data on Tanner stage will also be collected.

Although the EPPICC cohorts have similar protocols, there are some variations with regard to specific data items that are routinely collected.

1.4 Data sources

Cohorts collaborating in EPPICC will participate in this study, and include representation from Thailand and Russia. The cohorts are as follows:

- Belgium: Hospital St Pierre Cohort, Brussels
  Contact: Dr Tessa Goetghebuer

- Europe-wide: European Collaborative Study (including clinics in Belgium, Italy, Sweden, Denmark, Netherlands, Poland, Spain)
  Contact: Dr Claire Thorne

- French Paediatric study (EPF)
  Contact: Dr Josiane Warszawski

- German Competence Network on HIV infected children
  Contact: Dr Chris Koenigs

- Greece Cohort
  Contact: Dr. Vana Spoulou

- Italian Register for HIV infection in children
  Contact: Dr Maurizio de Martino, Dr Luisa Galli

- Netherlands: Amsterdam paediatric cohort
  Contact: Dr. Henriette Scherpbier

- Polish paediatric cohort
  Contact: Dr. Magda Marczynska

- Portugal: Centro Hospitalar do Porto
  Contact: Dr. Laura Marques

- Romania: "Victor Babes" Hospital Cohort, Bucharest
  Contact: Dr Dan Duiculescu, Dr Luminita Ene

- Russia: The Republican Hospital of Infectious Diseases, St Petersburg
  Contact: Drs. Konstantin Dodonov and Liubov Okhonskaia

- Russia: The City HIV Centre, St Petersburg
  Contact: Dr. Anna Samarina

- Russia: Kazan HIV Centre
  Contact: Dr. Firaya Nagimova

- Spain: Barcelona Cohort of HIV-infected Children (CoRISPE-2)
  Contact: Dr Ton Noguera

- Spain: Rest of Spain Cohort of HIV-infected Children (CoRISPE-1)
  Contact: Dr Pablo Rojo Conejo

- Swedish Cohort Study
  Contact: Dr. Lars Naver

- Swiss Mother and Child HIV Cohort Study (MoCHiV)
  Contact: Dr Christoph Rudin

- Programs for HIV Prevention and Treatment (PHPT), Thailand
  Contact: Dr. Gonzague Jourdain

- Ukraine Paediatric HIV Cohort Study, Odessa
  Contact : Dr Ruslan Malyuta

- UK / Ireland National Study of HIV in Pregnancy and Childhood (NSHPC)
  Contact: Dr Pat Tookey

- UK/Ireland Collaborative HIV Paediatric Study (CHIPS)
  Contact: Dr Ali Judd (CHIPS)

In addition by the time of the proposed data merger for this study it is anticipated that the national cohort from the Netherlands and an additional large cohort from France will have joined EPPICC and will collaborate.

1.5 Study size and study termination

The data merger for this study will be undertaken in 2016 to maximize the number of DRV-exposed patients and height measurements available. If data available at the 2016 merger are

insufficient (less than 175 patients ever treated with DRV) to address objective 3, the study period will be extended by one additional year. The study will end when data are sufficient to meet this objective or at five years after the start (ie Sept 2018), whichever occurs first.

1.6 Data Management

A bespoke relational database in Microsoft Access software will be used. A detailed standard operating procedure (SOP) for data collection processes for the study will be developed and reviewed by all participating cohorts. The SOP will include the data specification (see Appendix), together with instructions on the data extraction and transfer procedures. An electronic data collection form will be provided for circulation by participating cohorts to the relevant treatment physicians to aid data extraction from patient records on variables not included in the cohort database (where applicable). Data formats based on the HIV Cohorts Data Exchange Protocol (HICDEP) will be used for this study.

The HICDEP format is based on a relational structure, and the data for this study will be collected in a series of tables, which are described in the Appendix, together with the lookup tables for the codes to be used. All available data on height are to be collected prior to start of ART up to the most recent follow-up visit.

The study team, which includes a database manager with extensive experience of designing and maintaining HIV databases for clinical trials and cohort studies, will obtain data from the participating cohorts through an electronic data merger of datasets according to the SOP. The database manager will remove any patient identifiers to ensure patient confidentiality. Data will then be subject to a battery of logical and consistency checks in order to assess accuracy and completeness; any data queries arising will be discussed and resolved with the relevant cohort data manager, before data are pooled into a joint study database.

1.7 Data Analysis

Statistical analysis of the pooled dataset will be carried out at the Medical Research Council Clinical Trials Unit at University College London (MRC CTU at UCL), using STATA software (StataCorp, College Station, Texas).

1.8 Statistical Methods

A more advanced statistical analysis plan (SAP) will be submitted once the protocol is agreed and further feasibility assessments are conducted with available data.

Objective 1
Baseline demographic characteristics (e.g. sex, age, ethnic group, mode of infection, ever AIDS diagnosis, pubertal stage, cohort) of participants will be described. Details of antiretroviral drug utilization / treatment history will be summarized, including : time from diagnosis of HIV infection to starting first ART/age at start of first ART; calendar year of ART initiation; exposure to NRTI, NNRTI, PI and other classes; length of time on therapy (overall and for each class of drug); number of drugs taken (overall and within class); number and cumulative length of all treatment interruptions (defined as stopping all drugs for more than 30 days) and duration of time on DRV and total daily dose of DRV. CD4 cell counts and viral load measurements and HAZ at ART initiation and “baseline” will also be described.

Objective 2
Data on height will be transformed to height for age (and gender) z-score (HAZ) (Vidmar 2013) based on the WHO Child Growth Standards (WHO 2006) and WHO Reference 2007 (de Onis

2007). A z-score of 0 represents the 50th percentile for the age and sex in the reference population, while a z score of -1 indicates that the child's height is one standard deviation below the median height in the reference population. Baseline HAZ will be taken as the nearest measurement to the time of starting DRV within the previous 6 months. Repeated measure analysis will be performed, modelling within patient HAZ change pre- and post-DRV exposure, adjusting for factors known to influence growth or factors related to disease progression and ART history.

Objective 3
A group of children taking non-darunavir containing regimens will be identified as a comparator group for this analysis. The comparability of the groups initiating non-DRV-containing and DRV-containing cART will be assessed using propensity scores (PS) (Rosenbaum 1983). The propensity score will be calculated using logistic regression of all variables considered to be related to a child receiving a particular treatment (i.e. those described under Objective 1) on treatment group. The PS distribution in each group will be compared using standard methods (Shadish 2010, Hade 2013). If there is sufficient overlap between the two groups the analyses will proceed as follows:

An ANCOVA analysis will compare change in post-DRV HAZ with the change in HAZ for the comparator group of children starting non-DRV-containing cART using a regression model adjusting for pre-regimen HAZ and other key variables including PS (logit transformed). Height measurements will be censored at time of regimen switch, death or last follow up visit. The assumption of non-informative censoring will be investigated, and the use of inverse probability weighting considered. Children starting DRV first-line will be excluded from this analysis and analysed separately data permitting.

A multilevel regression model will be used to take account of the hierarchical structure of the data (repeated HAZ measurements for each child, and children within different cohorts). A fractional polynomial (Royston 1994) will be used to model change in HAZ over time as this is not expected to be linear (Gosponer 2012). Baseline covariates as described above will be included in the model, including those summarising ART history. An interaction between (i) age and treatment group, and (ii) HAZ at ART initiation and treatment group will be investigated.

The use of multiple imputation to impute missing baseline covariates will be considered. Sensitivity analyses will be considered, a) excluding all children with any missing covariate data, b) on data from cohorts who collect data on pubertal stage only. An extension of the baseline covariate model using Marginal Structural Models (Robins 2000) to adjust for time varying confounders will be conducted, if appropriate, after descriptive investigation of the longitudinal data.

1.9 Quality Control

As stated above, data will be subjected to a battery of logical and consistency checks in order to assess accuracy and completeness; any data queries arising will be discussed and resolved with the relevant cohort data manager, before data are pooled into a joint study database. Further data checks will be conducted by the study statistician prior to data analysis.

1.10 Limitations of the research methods

The strength of this study is the large number of longitudinal observational paediatric HIV cohorts included in EPPICC. These cohorts routinely collect clinical, laboratory, and treatment data in HIV-infected children across Europe and thus the results derived from this study have

good generalisability to most European countries. As the participating cohorts assess the treatment and care of children with HIV served in routine clinical practice, this study provides data on the effect of darunavir on height in a “real world” setting.

With regard to limitations of the study, missing height data may lead to the exclusion of a proportion of paediatric patients from this analysis. The reporting of height measurements will be encouraged in the following ways: Representatives from the different cohorts participating in EPPICC meet face-to-face every 6 months. During these meetings scientific proposals and data management are discussed. The importance of height measurements for this DRV analysis can therefore be regularly emphasized. The importance of height measurements will be highlighted in the SOP, and an additional payment will be made for each participant with data corresponding to the minimum requirement for height measurements. It will be possible to monitor the level of reporting by checking the completeness of data submitted for interim analyses, allowing further reactive intervention if necessary.

Height change is known to be closely associated with age and onset of puberty. While it will be requested for Tanner stage data to be included, to assess onset of puberty, this data is expected to be incomplete and may be an important unmeasured confounder. Nutritional status has also been shown to be associated with growth in less-developed countries but is not collected within EPPICC and is not expected to have such a major confounding role. The majority of DRV patients in the EPPICC data set are heavily treatment experienced with complex ART histories, making the identification of an adequate matching control group and an analysis appropriately adjusting for confounding factors challenging. However, the complex analysis described in Section 12.8 addresses these points by formally assessing the suitability of the comparator group using Propensity Scores, and adjusting all comparisons for ART history and other confounding variables.

1.11 Other aspects

The number of DRV-treated patients in the EPPICC network with height data pre- and post start of DRV will be assessed on a yearly basis and reported on as part of the 2014 and 2015 DRV pharmacovigilance reports. This will allow for monitoring of the data to assess the feasibility of objective 3 within the stated timeframe. If data from the 2016 merger are insufficient to address objective 3, the study period will be extended. The study will end when data are sufficient to meet this objective or five years after the start of the study (ie Sept 2018), whichever occurs first.

Protection of human subjects

1.12 Good Pharmacoepidemiology Practices

The investigator will ensure that this study is conducted in accordance with the principles of the International Conference on Harmonization (ICH) guidelines, the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) and Good Pharmacovigilance Practices (GVP) and with the laws and regulations of the country in which the research is conducted.

1.13 Institutional Review Board (IRB) Review

The individual cohorts will be responsible to adhere to their appropriate local ethics approval procedures for this surveillance program (i.e. to contact their local ethics committee to determine whether additional protocol approval and additional informed consent form or an amendment to the existing protocol approval is required). Data received by the PENTA Foundation appointed team will be anonymized, and patient identifiers will be removed to ensure patient confidentiality.

1.14 Informed Consent

No informed consent will be obtained to participate in this secondary analysis of existing data. However informed consent may have been granted when original study data were collected, depending on the ethics approval procedures of each country.

1.15 Confidentiality

The patient identifiers in all data sources have been removed and the data will contain no patient identifiable fields.

Management and reporting of adverse events/adverse reactions

1.16 Adverse Event Reporting

This study is designed to assess the association between height change and DRV exposure based on aggregate analyses. The sponsor will report 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 which have been attributed to DRV will have already been reported by treating physicians according to country and European law.

Dissemination and communication of study results

Study results will be disseminated and communicated through the final study report. Study progress will be provided in the PSURs and RMPs for DRV. Additionally, findings of potential scientific or public health importance will be disseminated through conference presentations or journal articles as appropriate.

References

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Appendices

1.17 Appendix 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	MRC Standard Operating Procedure Version 1.0 2015 data merger	xxx	European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

1.18 Appendix 2: Preliminary analysis of EPPICC data (as of January 2014)

DARUNAVIR

Table 1.0 Ever taken Darunavir (DRV)

Ever take DRV	Freq.	Percent	Cum.
No	3,186	94.54	94.54
Yes	184	5.46	100.00
Total	3,370	100.00	

Table 1.1 Age >=18 when starting DRV – to exclude

type	Freq.	Percent	Cum.
second	6	23.08	23.08
third	20	76.92	100.00
Total	26	100.00	

Table 1.2 Type of DRV regimen for those starting <18 years

type	Freq.	Percent	Cum.
first	19	12.03	12.03
second	50	31.65	43.67
third	89	56.33	100.00
Total	158	100.00	

Table 2. DRV patients with no height data available at start and after start of DRV

cohort	Freq.	Percent	Cum.
No	10	100.00	100.00
Total	10	100.00	

Table 2.1 Number of height measurements by age among patients with a baseline height at start of DRV and ≥1 measurement after a year of DRV (measure OK n=54) Min/Max number of measurements per person by age

age_year	N(measureOK)	min(n_before)	max(n_before)	min(n_after)	max(n_after)
2	1	14	14	12	12
5	2	2	15	5	8
7	1	12	12	3	3
8	2	1	29	4	7
9	6	1	67	1	10
10	2	1	14	5	5
11	1	2	2	3	3
12	9	10	54	2	13
13	9	0	53	1	7
14	9	0	48	1	6
15	5	12	46	1	3
16	6	7	39	1	3
17	1	1	1	1	1
Total	54	0	67	1	13

ANNEX: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	5, 12
1.1.2 The objectives of the study?	X	☐	☐	6, 13
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	X	☐	☐	6, 13
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	X	☐	8, 13
1.2.3 if applicable, that there is no a priori hypothesis?	X	☐	☐	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	X	☐	☐	6, 7, 14
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	X	☐	☐	6, 14
2.2.2 Age and sex?	X	☐	☐	6, 14
2.2.3 Country of origin?	X	☐	☐	7, 14-15
2.2.4 Disease/indication?	X	☐	☐	6, 14
2.2.5 Co-morbidity?	X	☐	☐	8, 14
2.2.6 Seasonality?	☐	☐	X	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	6, 14

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	X	
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	X	☐	☐	6, 14
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X	☐	☐	8, 16, 17
3.4 Is sample size considered?	X	☐	☐	8, 15
3.5 Is statistical power calculated?	X	☐	☐	8

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	X	☐	☐	14-15
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	X	☐	☐	14-15
4.1.3 Covariates?	X	☐	☐	14-15
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	14
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	14
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	X	☐	☐	14
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	X	☐	☐	16
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	X	☐	☐	16
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	X	☐	☐	16
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	X	☐	☐	14
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	X	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	X	☐	☐	8, 16, 17
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	X	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	X	☐	☐	16

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	X	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	X	☐	

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address: 7.1.1 Selection biases?	X	☐	☐	18
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	X	
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	X	☐	☐	16-17
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	X	☐	☐	16-17
7.4 Does the protocol address other limitations?	X	☐	☐	17-18

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☐	X	☐	17
8.2 Is the choice of statistical techniques described?	X	☐	☐	17
8.3 Are descriptive analyses included?	X	☐	☐	16
8.4 Are stratified analyses included?	☐	X	☐	
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	X	☐	☐	17
8.5.2 Effect modifiers?	X	☐	☐	17
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	X	☐	☐	17
8.6.2 Effect modification?	X	☐	☐	17

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	16
9.2 Are methods of quality assurance described?	X	☐	☐	16, 17
9.3 Does the protocol describe quality issues related to the data source(s)?	X	☐	☐	14
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X	☐	☐	12, 15, 16, 18
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☐	☐	X	
9.5.2 Any progress report?	X	☐	☐	11, 18
9.5.3 End of data collection?	X	☐	☐	11
9.5.4 Reporting? (i.e. interim reports, final study report)	X	☐	☐	11
9.6 Does the protocol include a section to document future amendments and deviations?	☐	X	☐	
9.7 Are communication methods to disseminate results described?	X	☐	☐	21
9.8 Is there a system in place for independent review of study results?	X	☐	☐	21

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	X	☐	☐	19
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
10.3 Have data protection requirements been described?	X	☐	☐	16, 19

Comments:

MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen-Cilag International, NV
Address:	Turnhoutseweg 30, 2340 Beerse, Belgium
Contact Details:	Dr Magda Opsomer, mopsomer@its.jnj.com

Qualified Person Pharmacovigilance:

Name:	Dr Logesvaran Yogendran, MB BS MSc MRCP FFPM
Signature:	Electronic signature appended at the end of the protocol
Date:	

RESPONSIBLE PARTIES

Principal Investigator:	Dr Carlo Giaquinto
Coordinating Investigators:	Dr Ruth Goodall, Dr Ali Judd, and Dr Jeannie Collins
Contact person for this protocol:	Dr Ruth Goodall
E-mail address or telephone number of contact person:	r.goodall@ucl.ac.uk

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Principal Investigator:

Name (typed or printed): Dr Carlo Giaquinto

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): Magda Opsomer

Institution: Janssen Research & Development

Signature: Electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor; a protocol amendment will not be required.

LAST PAGE

SIGNATURES

Signed by	Date	Justification
Magda Opsomer	28Jul2015, 15:39:10 PM, UTC	Document Approval
Logesvaran Yogendran	19Aug2015, 20:53:17 PM, UTC	Document Approval