12 October 2017
EMA/CHMP/54377/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pegasys

International non-proprietary name: peginterferon alfa-2a

Procedure No. EMEA/H/C/000395/II/0091

Note

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

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APASL	Asian Pacific Association for the Study of the Liver
BSA	Body surface area
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CHMP	Committee for medicinal products for human use
ERA	Environmental risk assessment
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
GCP	Good Clinical Practice
HAI	Histology activity index
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
IFN	Interferon
IU	International units
LSM	Liver stiffness measure
MAA	Marketing Authorization Application
NA	Nucleos(t)ide analog
OR	Odds ratio
PD	Pharmacodynamic
PDCO	Paediatric Committee
PEG-IFN	Pegylated interferon alfa-2a
PI	Product information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
RMP	Risk management plan
SmPC	Summary of Product Characteristics
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 8 November 2016 an application for a variation.

The following variation was requested:

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

Extension of Indication to include paediatric patients from 3 to less than 18 years of age with Chronic Hepatitis B in the immune-active phase for Pegasys; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from study YV25718. The Package Leaflet is updated in accordance. An updated RMP (version 8.0) is submitted in consequence.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	8 November 2016
Start of procedure:	26 November 2016
CHMP Rapporteur Assessment Report	27 January 2017
PRAC Rapporteur Assessment Report	27 January 2017
PRAC members comments	1 February 2017
PRAC Outcome	9 February 2017
CHMP members comments	13 February 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 February 2017
Request for supplementary information (RSI)	23 February 2017
CHMP Rapporteur Assessment Report	21 June 2017
PRAC Rapporteur Assessment Report	21 June 2017
PRAC members comments	28 June 2017
PRAC Outcome	6 July 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur Assessment Report	13 July 2017
2nd Request for supplementary information (RSI)	20 July 2017
PRAC Rapporteur Assessment Report	18 September 2017
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	18 September 2017
PRAC Outcome	28 September 2017
CHMP members comments	2 October 2017
Updated CHMP Rapporteur Assessment Report	5 October 2017
Opinion	12 October 2017

2. Scientific discussion

2.1. Introduction

Pegasys (pegylated interferon alpha 2a, PEG-IFN α2a) was approved in 2002 for the treatment of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) in adults and has ever since, together with peg-IFN α2b, replaced the use of non-pegylated interferons due to their improved pharmacokinetic properties (weekly injections) and due to their consequent better efficacy.

In 2013 an extension of indication was approved for Pegasys, for the treatment of hepatitis C in children aged 5 years and above. That indication was approved for the other approved pegylated IFN (PEG-IFN α2b) already in 2008. Prior studies conducted with interferons in children serve as an important source of safety information, including long term safety data on a fairly sufficient number of children treated with PEG-IFN α2b, where 40/48 patients who had received 48 weeks of PEG-IFN α2b treatment were followed for 5 years. These data were previously assessed by the CHMP and are now

also published (Haber et al, Jan 2017). In general the safety profile, known to be somewhat problematic, is considered to be similar for the different interferons. This includes a substantial risk to reduced final height of the individual, in particular if treatment is given during periods of growth spurts (puberty), which is a major safety issue in children and adolescents.

This application concerns an extension of indication for the treatment of chronic hepatitis B in children aged 3 years and above (including adolescents); specifically Hepatitis B eantigen (HBeAg) positive children with increased transaminases as a marker for entering/being in the immune active stage.

Children with CHB were either vertically infected at the time of birth, or horizontally infected in early childhood. In the high epidemic area of South East Asia, vertical transmissions stand for the majority of cases. In contrast, at least historically, horizontal transmission has been the dominant type in e.g. southern Europe and African countries.

Apart from PEG-IFNs, a number of nucleo(t)side analogues are also approved in the EU for the treatment of CHB. As opposed to PEG-IFNs (an immune therapy), it is currently not clear for how long treatment with nucleos(t)ide analogues should be continued. For adult HBeAg positive patients, therapy may be stopped after 1 year of viral suppression following HBe-seroconversion. However, the risk for virological relapse (e.g. from undetectable DNA levels to levels >10.000 IU/ml) is in the order of 50% or higher (e.g. Qiu et al 2016, Chen et al 2015). Similar data for paediatric patients are not available. In summary, in practice, therapy with direct acting antivirals does not have a specified duration and is in most cases used indefinitely to suppress viral replication.

The natural course of HBV disease, studied in a number of cohorts, was presented at the time of the initial marketing authorisation and is discussed in the Pegasys EPAR. In summary, patients vertically infected would be in the majority of cases in the immune tolerant phase throughout childhood and adolescence (HBeAgen positive, but with normal ALTs). During this stage there is no indication for treatment with the presently available therapies. For those infected in early childhood, the immune tolerant phase is shorter, and this stage is more or less lacking in those infected in adult life.
The proportion of children with an indication for treatment within childhood or adolescence would therefore likely be higher for children infected post-partum. More exact figures for typical time points for these stages by route of transmission are hard to find in the published literature, since the studies of main interest around the natural course of the infection (population based surveys, for example by McMahon 2001) are scarce and lack details, while clinically based surveys may be based on cohorts of children not necessarily representative for the whole group (rather selected for reasons of elevated transaminases). The immune active stage (entrance marked by increasing alanine aminotransferase (ALT) levels) is associated with a risk for liver injury, and therapy with IFN may shorten that stage, lowering the risk of inflammation and consequently lowering risk of fibrosis development. The main objective with PEG-IFN therapy is to accelerate that process; very few patients, however, achieve Hepatitis B s antigen (HBsAg) seroconversion (around 3% in adult studies), which is the ultimate goal of therapy for chronic hepatitis B.
When looking at long term outcomes in children not given therapy, but followed up at clinics, two publications with a very long term follow-up were found in the literature.

- Wu et al (JPGN Volume 54, Number 1, January 2012, Taiwan single centre) reported on 104 HBeAg positive children, with a mean initial age of 7 and a mean follow-up of 24 years, with assessments of serology etc. every 6-12 months. The vast majority had HBV subtype B (n=96), 75% were suspected to have been infected vertically. None of the subjects received antiviral agents or immune therapy prior to HBeAg seroconversion. During follow-up

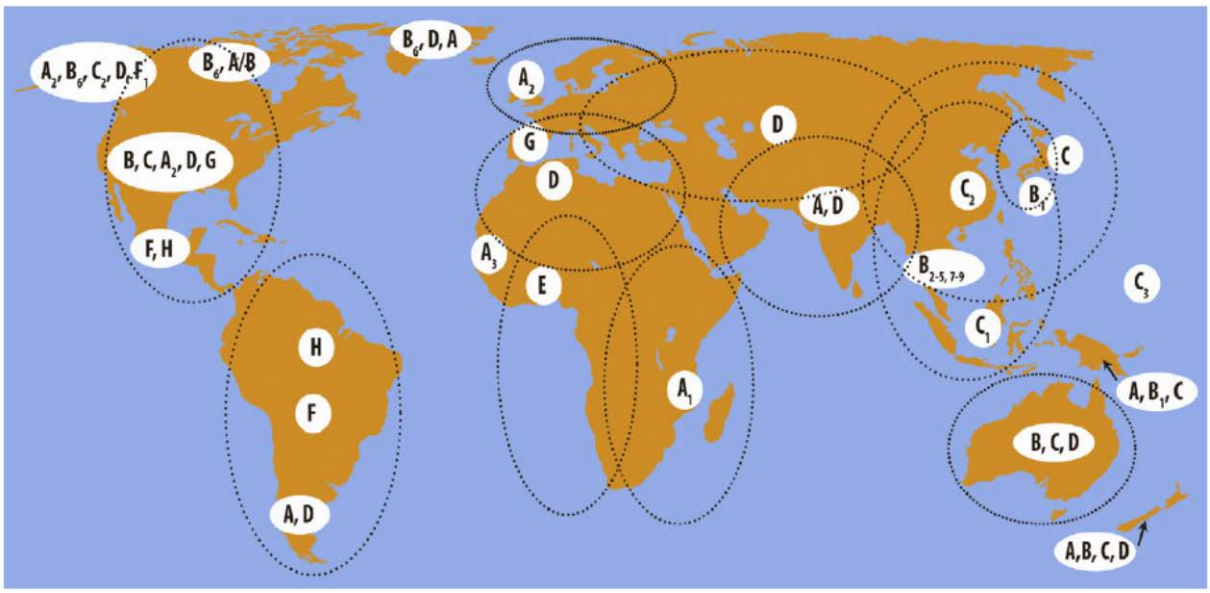
spontaneous HBe seroconversion (loss of HBeAg and developing of the corresponding antibody) occurred in 80% (n=83) of the subjects, at a median age of 15 (range 1 to 33). Of note, this group was selected (having at least some ALT elevation when referred to the center).

- Bortolotti reported similar data from a 29-year longitudinal study (Italian single centre), concerning 91 HBeAg positive children, also with a mean age of 7 years at study entry. These children were (likely) predominantly horizontally infected, and in practice all were infected with HBV genotype D (typical for this region). During follow-up HBe seroconversion was documented for all 89 with > 1 year of follow-up. Seven children were treated with standard IFN (24 weeks) due to sustained HBeAg positivity, none of them responded, but had a spontaneous clearance later; another 14 received other treatments (however none received direct acting antivirals). Of 64 untreated children without baseline cirrhosis, 59 remained as stable inactive carriers following HBe seroconversion and without evidence of marked liver injury, the others had further reactivations. Four children (age 4.5 ± 4.2 years) had cirrhosis at baseline, of whom 2 developed hepatocellular cancer, 9 and 16 years after HBe seroconversion. The mean age for HBe seroconversion was 11 years for those who converted in that system but remained active carriers.

In adults, response to PEG-IFN therapy differs by HBV genotype. This is discussed in some detail in the efficacy section of this assessment report, but overall the highest HBe seroconversion rates have been seen in patients with genotypes A and B, followed by genotype C and with the lowest rates in genotype D-infected patients. To what extent this is an effect by HBV genotype per se, or rather/also an effect by other baseline demographics that happen to be associated to HBV genotype is not fully elucidated, as the mechanistic basis for these circumstances is not known.

New HBV genotypes were discovered in more recent years; to date 9 genotypes have been defined (McMahon, 2015). Of note, data on outcomes with PEG-IFN has basically been presented for genotypes A-D, very scarcely for the others.

Figure 1: Worldwide distribution of HBV genotypes



2.2. Non-clinical aspects

No new non-clinical data have been submitted for the new paediatric indication. The MAH has submitted a justification for not providing a full environmental risk assessment (ERA). This justification was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The EMA 2006 guideline on Environmental Risk Assessment (ERA) for non-GMO human medicinal products [EMEA/CHMP/SWP/4447/00 corr. 2; ref. 1] requires an ERA for the marketing authorisation application (MAA) of all new medicinal products in the European Union. For proteins and peptides, however, the "ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment".

Interferon alfa-2a (CAS no. 76543–88–9, molecular mass ~19 kDa), the pharmaceutical active ingredient in Pegasys, is a recombinant human cytokine signalling protein with antiviral and immunomodulating properties. Pegasys (polyethylen glycol–IFN α2a or PEG-IFN α2a) is a molecule of interferon alfa-2a conjugated with a branched polyethylene glycol chain of approximately 40 kDal. Pegylation of proteins has been specifically developed for medical applications as it strongly extends the human half-life of elimination, delaying both enzymatic metabolism and urinary excretion. Hence, pegylation increases the therapeutic efficacy through prolonging the period between administrations, meaning that the active substance needs to be administered less often while active therapeutic concentrations are maintained throughout.

Environmentally Relevant Properties of Interferon alfa-2a and Peginterferon alfa-2a

IFN α2a is not mutagenic, not teratogenic and not known to be reprotoxic or carcinogenic or to have endocrine activity. Being a protein, it is not bioavailable by oral administration (as it would be digested) but must be given by injection. It is rapidly metabolised in the human body and therefore it will not bioaccumulate, but it will be excreted in the form of non-recognisable and non-functional fragments.

IFN α2a was tested as the formulated solution for ready biodegradability (OECD test guideline 301F) and for acute ecotoxicity towards algae (Scenedesmus (= Desmodesmus) subspicatus, OECD 201) and waterflea (Daphnia magna, OECD 202) [8], all under GLP, for classification and labelling purposes as well as for an initial environmental risk estimation.

The formulated solution as a whole and, factoring in the biochemical oxygen demand in the blank control as well as the theoretical oxygen demand by the excipients, the active pharmaceutical ingredient IFN α2a itself, proved to be readily biodegradable according to the OECD criteria. Hence, any active substance that might theoretically escape human metabolism may be expected to be removed during sewage treatment.

IFN α2a solution was not significantly toxic to algae and daphnids, with both 50% effect values (ErC50 respectively EC50) greater than the only tested concentration of 100 mg IFN α2a/l. While these are only acute endpoints, they do support a low risk for unexpected aquatic ecotoxicity of IFN α2a.

These results align well with several other protein active pharmaceutical substances that were tested for ready biodegradability and acute ecotoxicity. All unaltered protein active substances, without exception, proved to be readily biodegradable, resulting in extremely low predicted environmental concentrations in receiving waters. Also, acute ecotoxicity was not remarkable for any of the unaltered protein active substances.

PEG-IFN α2a is not mutagenic and is not known to be reprotoxic or carcinogenic, nor is it known to bioaccumulate, despite the prolonged elimination half-life due to the pegylation. Like IFN α2a, it is not suspected of endocrine activity.

PEG-IFN α2a was tested in a ready biodegradability Closed Bottle test (OECD 301D) with a very low concentration of activated sludge bacteria (0.1 ml of coarsely filtered secondary effluent from a municipal sewage works in the Netherlands per litre) under GLP. Standard Pegasys solution was used and the degradation values were corrected for oxygen demand in the blank control, for the theoretical oxygen demand by the excipients and for nitrification (ThODNO3). The test showed 19% respectively 22% degradation at PEG-IFN α2a initial concentrations of 8.2 mg/l respectively 3.36 mg/l in 28 days. At both test concentrations a plateau corresponding to approximately 20% biodegradation was already reached by day 7 and 14, respectively.

Acute ecotoxicity tests with daphnids (Daphnia magna, OECD 202) and fish (Cyprinus carpio, OECD 203) were performed under GLP for Classification and Labelling purposes as well as for an initial environmental risk estimation. Both tests showed no adverse effects at the tested nominal concentration of 300 mg PEG-IFN α2a/l, corresponding to 100 mg IFN α2a moiety/ l. While these endpoints are only acute, they do support a low risk for unexpected aquatic ecotoxicity of Pegasys.

Conclusion on Environmentally Relevant Properties

Taken together, the two ready biodegradability tests make it likely that the partial degradation observed in the Closed Bottle test with PEG-IFN α2a corresponds to biodegradation of the IFN α2a moiety. This conclusion is supported by the three facts, (1) that this partial degradation was reached quite rapidly, within 7–14 days into the test, (2) that IFN α2a itself is readily biodegradable [6] and (3) that while long-chained polyethylen glycols basically are biodegradable, their degradation proceeds the slower the longer the polyethylen glycol chain length is. However, no substance-specific analysis was performed in the Closed Bottle test with PEG-IFN α2a to corroborate this hypothesis.

Moreover, both PEG-IFN α2a and IFN α2a are not mutagenic and are not known to be reprotoxic or carcinogenic, moreover, they are not suspected of having bioaccumulative properties, nor endocrine activity. Last, based on a limited set of acute test data, there is no indication of any high or specific ecotoxicity for both compounds.

In addition to the considerations regarding the environmental properties of PEG-IFN α2a, Pegasys has been on the market in Europe for about 15 years. Therefore, available sales data in European countries for the years 2005–2015 were obtained from IMS Health, Inc., with the data covering the following 24 countries: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

In January 2015, these countries were estimated by Eurostat, the EU Statistics Office, to have a combined population of 508'930'708 inhabitants. Excluding some non-EU ex-Yugoslavian states, this figure corresponds to 97.4% of the combined EU–28 plus EFTA (IS+LI+NO+CH) population of 527'381'309 inhabitants. Therefore, the data are regarded as representative for Europe as a whole.

Total Pegasys sales amounts in kg relating to the interferon alfa-2a moiety per annum and country for the above representative European countries range from 0.116 kg to 0.331 kg within the period 2005 to 2015. As these figures only capture the IFN α2a moiety, a multiplication by a factor of 3 will give the total amounts for PEG-IFN α2a. This conversion is included in the derivation of the realistic worst-case predicted environmental concentrations (PECs) for surface water below.

European surface water PECs were derived based on the converted sales data per annum and country, which were transformed from kg to ng, divided by the population of the respective country for that

year, by 365 days per annum, by a default EU wastewater volume of 200 l per inhabitant and day, and by a default EU surface water dilution factor of 10. As usual for an initial worst-case PEC derivation neither removal in patient metabolism nor during sewage treatment was included.

The spreadsheet calculates surface water PEC values for total PEG-IFN α2a ranging from a minimum of 0.000101 ng/l (nanograms per litre) to a maximum of 0.010058 ng/l for single countries in the period of 2005 to 2015. Hence, the actual-use-based surface water PECs were a factor of 1000 to 100'000 below the 2006 EMA ERA Guideline 'action limit' of 10 ng/l.

Conclusion

With the documented-use-based surface water PECs for PEG-IFN α2a being at least a factor of 1000 below the EMA 'action limit', even an additional paediatric patient population with chronic hepatitis B in the immune-active phase will not significantly increase those PECs. Therefore, the EMA ERA Guideline Phase 1 'action limit' for the PEG-IFN α2a PEC will not be reached by far.

In addition, PEG-IFN α2a (and IFN α2a) is not mutagenic and not known to be reprotoxic or carcinogenic, also, it is not suspected to have bioaccumulative properties nor endocrine activity. On the other hand, there are experimental data suggesting that the pharmacologically active moiety of Pegasys, IFN α2a, will be rapidly biodegraded. Moreover, based on acute tests, there is no indication for high unexpected ecotoxicity. Therefore, due to its nature, PEG-IFN α2a (and IFN α2a) is unlikely to result in a significant risk to the environment. This conclusion confirms the general finding that monoclonal antibodies and other biologics (protein or peptide) active pharmaceutical substances do not pose a risk to the environment.

Based on the data presented above, the CHMP agreed that no full ERA according to the 2006 EMA ERA Guideline (corr. 2) is required for the additional indication for Pegasys in paediatric patients from 3 years of age and older with chronic hepatitis B in the immune-active phase.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted for the new paediatric indication and CHMP agreed that none were required. The MAH has submitted a justification for not providing a full environmental risk assessment. This justification was considered acceptable by the CHMP.

2.2.3. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, CHMP considered that the extension of the currently approved indication for Pegasys is not likely to lead to a significant increase in environmental exposure further to the use of Peginterferon alfa-2a.

CHMP agreed that Peginterferon alfa-2a is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Overview of clinical studies

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
YV25718	To compare HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) between a group treated with PEG-IFN monotherapy and an untreated control group.	Randomized, controlled, parallel-group, open-label, multicentre study of pegylated Interferon alfa-2a (PEG-IFN) treatment compared to untreated control	PEG-IFN, dosed according BSA: 45, 65, 90, 135 or 180 µg for BSA 0.51-0.53, 0.54-0.74, 0.75-1.08, 1.09-1.51 or >1.51 m2, respectively	161	Male and female paediatric patients aged 3 to < 18 years of age with chronic hepatitis B in the immune active phase	48 weeks

Anti-HBe= hepatitis B envelope antibody; BSA=body surface area; HBeAg= hepatitis B e antigen; pegylated Interferon alfa-2a=PEG-IFN

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of pegylated interferon alfa-2a PEG-IFN α2a (PEG-IFN in tables and text below) in paediatric patients with chronic hepatitis B (CHB) was evaluated as part of study YV25718.

Data

Study YV25718 was a randomized, controlled, parallel-group, open label, multicentre study of PEG-IFN α2a treatment compared to an untreated control. A more detailed description of the study is provided in section "Clinical Efficacy" of this assessment report. Patients without advanced fibrosis were randomized 2:1 to either active treatment (Group A) or to an untreated control arm (Group B). Patients with advanced fibrosis were assigned to a third treatment arm (Group C). Treatment lasted for 48 weeks with a follow up period of 24 weeks (data available) and subsequently an extended planned follow up period of 4.5 years (data not available). Patients in the untreated control group (Group B) who had not experienced HBeAg seroconversion were offered active treatment with PEG-IFN after completing the principal observation period (48 weeks after randomization).

The PK sub-study aimed to confirm adequate PEG-IFN exposure following administration of a new BSA-category dosing regimen in paediatric patients with CHB.

The dosing regimens based on the BSA categories are summarized in the following table:

Table 2 Paediatric Dosing Regimen Based on BSA categories

Dose (µg)	BSA Range (m^2)
45	0.51–0.53
65	0.54–0.74
90	0.75–1.08
135	1.09–1.51
180	>1.51

BSA = body surface area (estimated using the Mosteller formula)

For participating patients, PK samples were collected at week 1 and week 24 pre-dose (0), and 24-48, 72-96, and 168 hours after administration of PEG-IFN. Pre-dose samples were also collected at weeks 4, 8, and 12 within 6 hours prior to PEG-IFN administration. Subjects were to take all doses of PEG-IFN associated with both pre- and post-dose PK sampling at the clinic.

Methods

Bioanalysis

The serum concentrations of PEG-IFN were assessed by a quantitative enzyme-linked immunosorbent assay (ELISA). The assay was conducted using 100 µL of 5-fold diluted human serum. The lower limit of quantification in undiluted serum was 250pg/mL. The calibration range was 250 pg/mL to 5000 pg/mL. The precision and accuracy of the assay, as determined from the analysis of quality control samples were satisfactory throughout the study and ranged from 5.4% to 9.9% (precision) and from -4.9% to -1.5% (accuracy, RE).

Population PK modelling

- Data and exclusions

A population PK model of PEG-IFN in paediatric patients was developed based on data from study YV25718 and data in adults originating from four clinical studies. The data in adults were initially used to develop the structural population PK model of PEG-IFN including covariates, and the data from study YV25718 were then added to develop a population PK model of PEG-IFN in paediatric patients and adults.

The table below summarizes the adult studies included in the PopPK analysis together with the paediatric study YV25718.

Table 3 Summary of study designs of clinical studies [included in the PopPK analysis]

Study	Population	Subjects	Design	Relevant treatment	Collection time
NP17354	CHC	N = 46	Open-label, parallel group	180 µg PEG-IFN once weekly for 8 weeks plus ribavirin	Profiles at week 1 and week 8
NP17355	CHC with renal disease	N = 63	Non-randomized, parallel group	180 µg and 135 µg (ESRD) PEG-IFN once weekly for 12 weeks plus ribavirin	Profiles at week 1 and week 12
PP22512	CHB	N = 13	Open-label, randomized	360 µg PEG-IFN once weekly for 2 weeks	Profiles at week 1
PP22612	CHB	N = 8	Open-label, randomized	180 µg PEG-IFN once weekly for 48 weeks	Samples every 8 weeks
YV25718	Children with CHB	N = 31	Open-label, randomized	PEG-IFN once weekly for 48 weeks based on BSA categories: Dose (µg) / BSA range (m^2) 45 / 0.51 - 0.53 65 / 0.54 - 0.74 90 / 0.75 - 1.08 135 / 1.09 - 1.51 180 / > 1.51	Profiles at week 1 and week 24 Samples every 4 weeks

Nonlinear mixed effects modelling (with software NONMEM) was used to analyse the sparse dose-concentration-time data and derive PK parameters (e.g., clearance [CL/F], volume of distribution [V/F], AUC, etc.) using a population PK modelling approach.

Based on the exploratory graphical analysis, five outlying data points and all quantifiable pre-first dose concentrations were deleted from the dataset. In addition, two data points were removed as the Conditional Weighted Residual (CWRES) was > 4 and eight data points were removed as CWRES was < -4. In the NONMEM runs, all plasma concentrations below the lower limit of quantification (LLOQ) were excluded. Data from subject ID 127 were excluded in the NONMEM runs as only one data point was available. Finally, all data from subject ID 7320 of study YV25718 were excluded in the NONMEM runs as this subject was defined by the bioanalytical lab to be non-evaluable due to high interference peak at baseline. As a summary, from 160 subjects with at least one quantified concentration and 3131 data points, 172 previously excluded data points in the original file, 15 detected outliers, 371 BLQ data points and two subjects with 10 data points were excluded.

- Modelling procedure

Data from the clinical studies NP17354, NP17355, PP22512 and PP22612 were used first to develop a structural population PK model of PEG-IFN in adults. A covariate analysis was then performed and subsequently the data of paediatric study YV25718 were added with the aim of developing a population PK model for PEG-IFN in children including selected covariates. Finally, model evaluation was carried out using visual predictive check (VPC) to assess the model's ability to simulate the same data that have been used for the model development. The heterogeneous designs between the studies were taken into account.

The influence of continuous and categorical covariates was tested for their significance and clinical relevance on parameter with random effects: clearance (CL) and volume of distribution (V). The covariates that were tested in the model were sex, age, race, body mass index (BMI), body surface area (BSA), body weight (WT), lean body weight (LBW), creatinine clearance (CLCR), and infection with HCV versus HBV. Forward addition and backward deletion of covariates was performed by using stepwise covariate model building (SCM). Forward covariate selection was performed using a p-value

of p< 0.05 as the selection criterion. Subsequently, backwards deletion was per formed using a p-value of p< 0.01 as the selection criterion.

Standard methods were used to evaluate models including residual error diagnostic plots, difference objective function value between competing models, standard error of estimates and model convergence. To evaluate the predictive performance of the model, a visual predictive check (VPC was performed on the final model parameter estimates.

- Modelling results

The structural population PK (popPK) model of PEG- IFN in adults consisted of a one compartment disposition model with a sequential zero- first order absorption and an endogenous IFN level. As PK data from a renal impairment study were included, the effect of creatinine clearance (CLcr) on clearance (CL) was incorporated into the model from the beginning of model development onwards. As the model in adults was planned to be used as a basis for developing a population PK model of PEG-IFN in children, the effects of body weight (WT) on CL and volume of distribution (V) were also included from the beginning of model development onwards.

The final population PK model to describe the pharmacokinetics of PEG- IFN in adults and children was a one-compartment disposition model with sequential zero- first order absorption. CL was impacted by CLcr and WT, and V was impacted by WT. An ‘endogenous’ level of IFN was included in the model and was estimated to be 0.25 ng/mL. No additional covariates were identified in the covariate modelling for the combined adult/children model. The parameter estimates are shown in the following table:

Table 4 PEG-IFN parameter estimates for the final population PK model (run 140) in adults and children

Thetas (Fixed effects)		Estimate	SE	SE (%)	95 % CI	
θ1	Central volume (L)*	14.8	1.53	10	11.8	17.8
θ2	Clearance (L/h)**	0.0733	0.0042	6	0.065	0.081
θ3	Lag time (h)	0 FIX				
θ4	0 order absorption duration (h)	6.61	0.894	14	4.9	8.4
θ5	Absorption rate constant (h-1)	0.0228	0.0026	11	0.018	0.028
θ8	Creatinin clearance impact on θ2**	0.0698	0.0697	100	-0.067	0.206
θ9	Endogeneous INF (ng/ml)	0.253	0.0408	16	0.173	0.333
θ10	Weigth impact on θ1*	1.52	0.181	12	1.165	1.87
θ11	Weigth impact on θ2**	0.75 FIX				
Etas (Random effects)		**Estimate**	**SE**	**SE (%)**	**IIV (%)**	
η1	Central volume (L)	0.575	0.120	21	76	
η2	Clearance (L/h)	0.135	0.0323	24	37	
η3	Lag time (h)	0 FIX				
η4	0 order absorption duration (h)	1.24	0.224	18	111	
η5	Absorption rate constant (h-1)	0.811	0.247	30	90	
η13	Endogeneous INF (ng/ml)	0.441	0.135	31	66	
Etas (Random effects)		**Estimate**	**SE**	**SE (%)**	**IOV (%)**	
η6-8	Bioavailability	0.255	0.0327	13	50	
η9-10	0 order absorption duration (h)	0 FIX				
η11-12	Absorption rate constant (h-1)	0.833	0.132	16	91	
Sigmas (Residual error)		Estimate	SE	SE (%)	Residual variability	
θ6	Additive	0.158	0.0016	1	0.16 (ng/ml)	
θ7	Proportional	0.193	0.0034	2	19 (%)	

* V for typical subject = θ1*((WT/84)**θ10)

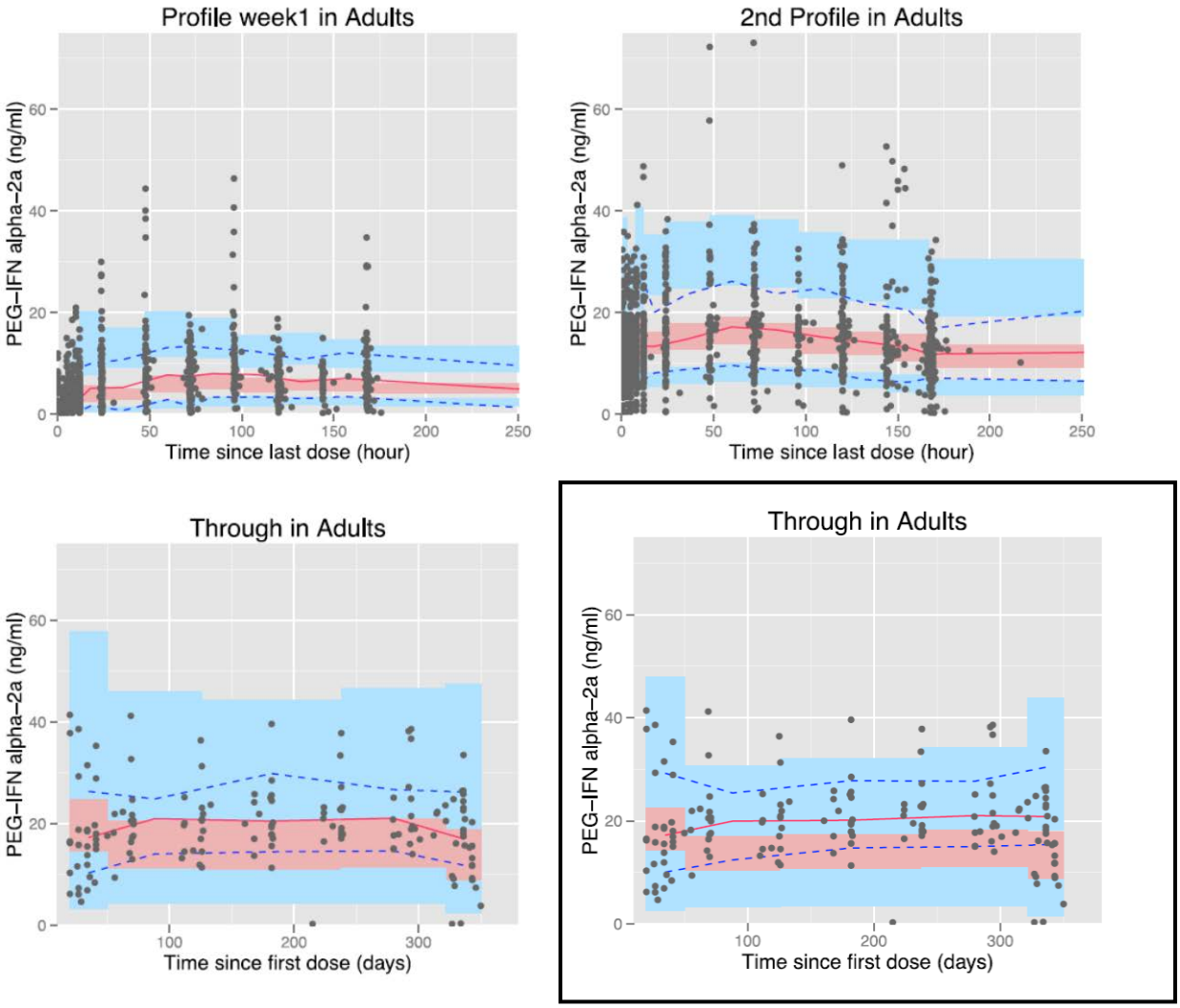
** CL for typical subject = θ2*((CRCL/114.8)**θ8)*((WT/84)**θ11)

The population PK model estimates of typical clearance and volume of distribution were largely consistent with the estimates in the EPAR of 2005. Parameter precision was acceptable except for the effect of creatinine clearance on the clearance of PEG-IFN. In that case the relative standard error is 100% and the confidence interval included 0 (null effect). Further, the effect of body weight on the volume of distribution was estimated to 1.52 which should be compared to the theoretical value of 1.0. This would predict lower trough values in adults compared to children which may or may not be a reason for the under prediction of trough concentration in adults seen in the VPCs.

A visual predictive check for the final population PK model of PEG-IFN in adults was performed and the results are presented in the figure below. For purpose of comparison, the corresponding VPCs of adult

trough values are included for the final adult model (lower left) and for the combined model of adult and children (lower right), respectively.

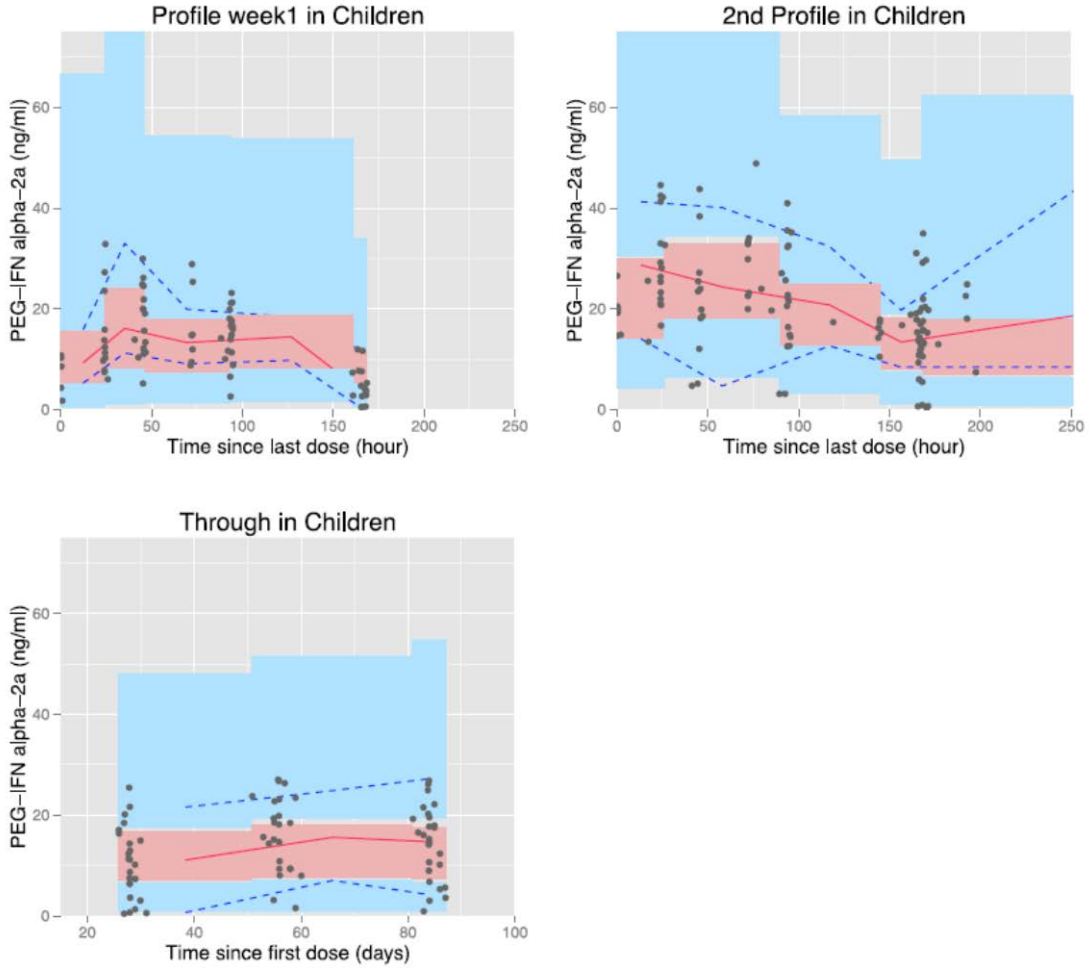
Figure 2 VPCs for the final model in adults (top row and lower left panel) along with VPC af trough in adults for the final adult/children model (lower right panel).



Grey circles are observed data. Solid red lines are the median of the observed data. Dashed blue lines are 10th-90th percentiles of the observed data. Pink areas around the observed median and blue areas around the observed 10th- 90th percentiles are the respective predicted 95% confidence intervals.

The PopPK modelling was carried out using standard methods which was considered adequate by the CHMP. The visual predictive check for the adult model showed a slight but consistent under prediction of the central tendency in plasma PEG-IFN concentration. For the combined model for adults and children, this trend was more evident when looking at adult trough values. Also, the plot of conditional residual error vs. time shows evidence of under prediction of the PEG-IFN concentration at later time points (not shown).

The results of the VPCs for the final model in adults and children are presented in the following figure. Of note, only the VPCs for data from children are shown.



During the assessment, CHMP highlighted that the PopPK model of combined adult and children data is important for justifying the dosing regimen in children. It was considered important that the influence of body size (e.g. BSA or body weight) on PK parameters was modelled in a proper way. The MAH elaborated the rationale for estimating the relation for one of the exponents and not for the other, and the discrepancy between observed and simulated data seen for trough concentration in adult patients. A VPC of trough values in adults for a model where the allometric exponents were both fixed to their theoretical values (0.75 and 1.0, respectively) was also submitted and assessed at request of CHMP.

Attempts were made to fix the allometric exponents for their theoretical values (i.e.: 0.75 for CL and 1 for V) during the PopPK model development. An allometric exponent higher than the theoretical value seemed required to describe the influence of covariates on the PK properties of PEG-IFN. Although, the physiological reasons for this finding were not fully elucidated, fixing the exponent for volume to the theoretical value of 1 had no impact on the main results of the PopPK analysis which is that the applied BSA category-based dosing of PEG-IFN in children results in similar PK exposures between paediatric and adult patients.

Taken together, the data showed that the model fit was not improved using a fixed theoretical allometric exponent on volume of distribution. Further, it was shown that the under prediction of trough concentration was not related to the allometric exponent being fixed or not. This was considered adequate by the CHMP.

Pharmacokinetic sub-study to study YV25718

A total of 31 patients from 6 centres participated in the PK substudy. Seventeen, nine and five patients were from Group A, the Switch arm and Group C, respectively.

The median (range) age was 7 years (3 years to 17 years). Nine patients were < 5 years of age, 11 patients were between 5 years and 12 years of age and 11 patient < 12 years of age. Approximately one third of the patients were female.

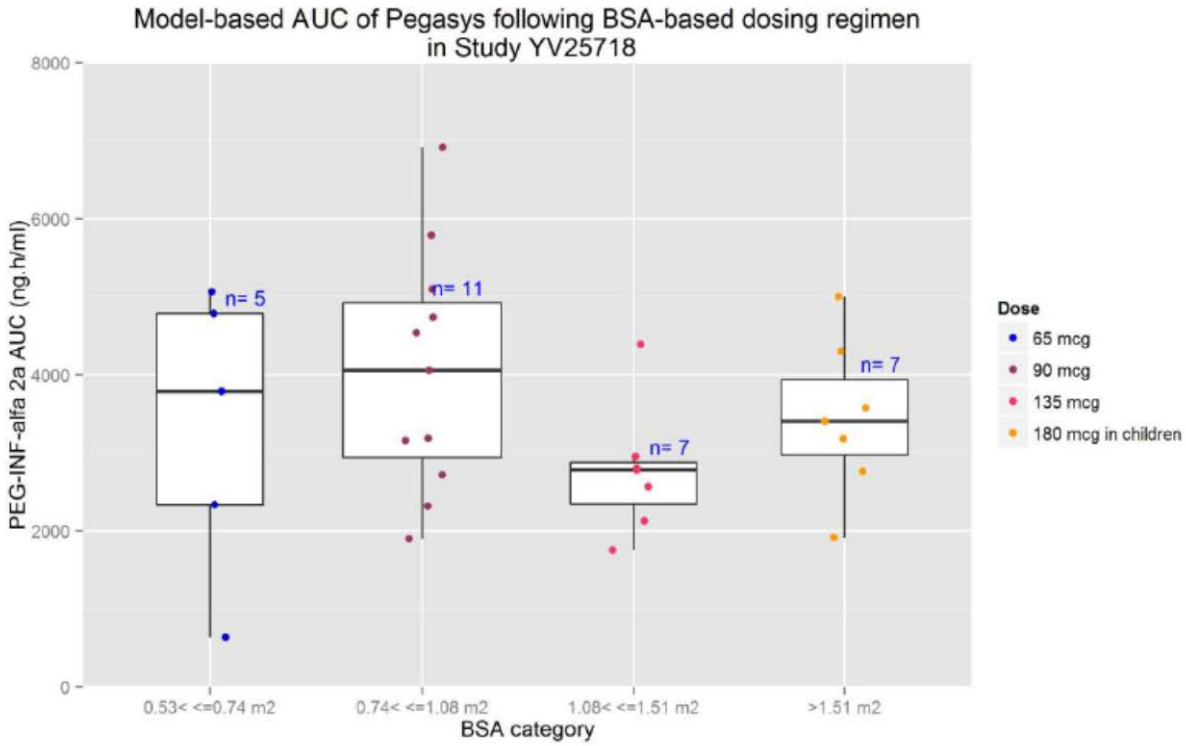
The median (range) body weight was 27 kg (15 kg to 87.5 kg). The median (range) body surface area (BSA) was 0.987 m2 (0.62 m2 to 2.06 m2).

Paediatric PK parameters were estimated from sparse PK data using the population PK model. One of the 31 participating patients was deemed non-evaluable and excluded from PK analyses. A summary of estimated PEG-IFN exposures (AUC) is shown in the following table and figure.

Table 5 Summary of Estimated PEG-IFN AUC at Steady-State in Paediatric Patients with CHB following BSA-Category Based Dosing

BSA (m^2)	Estimated AUC (h.ng/mL)				
	0.54 – 0.74	0.75 – 1.08	1.09 – 1.51	> 1.51	All
N	5	11	7	7	30
Mean	3320	4037	2765	3448	3484
Median	3784	4055	2780	3400	3184
CV%	56%	38%	30%	29%	40%
Minimum	633	1897	1750	1914	633
Maximum	5064	6916	4392	5000	6916

Figure 3 Box-plots of the predicted steady-state AUC by BSA-based dosing category



A comparison between the predicted exposures at steady state by study is shown in the following table below in order to compare adults and children:

Table 6 Summary of predicted steady-state AUC by study

Study	Predicted AUCss (ng.h/mL)					
	Adults					Children
	NP17354	NP17355*	PP22512	PP22612	All	YV25718
N	45	31	13	7	96	30
Mean	2451	2877	3834	3153	2827	3484
Median	2467	2564	3871	3088	2751	3184
CV%	37%	47%	30%	31%	42%	40%
Minimum	249	271	2110	1451	249	633
Maximum	4310	6872	5962	4221	6872	6916

In general, a higher mean exposure was predicted for children while the maximal exposure was similar between adults and children. The minimum exposure in children was higher than the minimum exposure in adults. The variability in terms of CV% was similar.

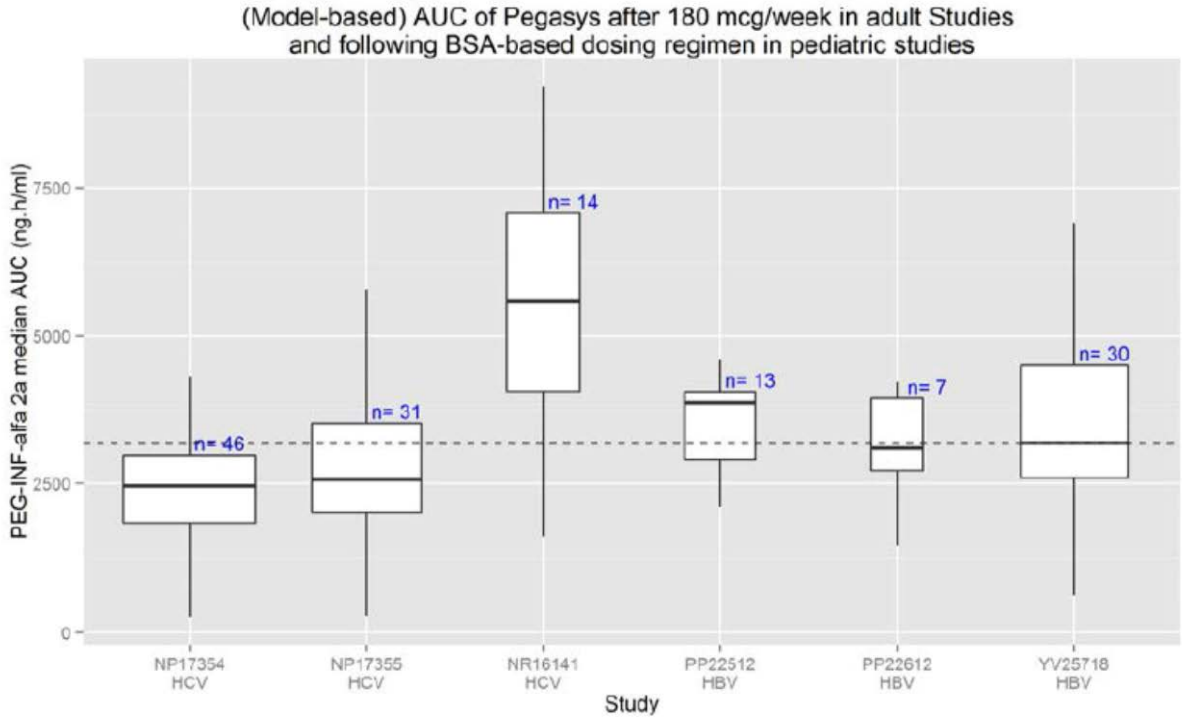
During the assessment, the MAH examined the goodness of fit in view of the rather limited number of subjects included and of the sparse PK sampling. Inspection of the separate VPCs provided by the MAH for children showed that the simulations were consistent with observed data. In addition, inspection of the individual plots of observed data at week 1 and week 24 with population and individual predictions for the final run showed that the final population PK model is able to adequately describe the PEG-IFN concentration-time data.

The low exposures observed in some paediatric patients were not considered to be a consequence of dose reduction or treatment interruption but rather reflect the high between- and within-patient variability in PEG-IFN pharmacokinetics observed in adults.

CHMP agreed that the assessed data showed the ability of the model to describe PK data in children.

Comparison was made to historical data including the study in children with hepatitis C (NR16141). The following figure shows the exposure from both pediatric studies and from adult hepatitis C and hepatitis B studies. The median AUC_{SS} in study NR16141 was 5583 h*ng/mL, while the median AUC_{SS} was 3184 h*ng/mL in study YV25718.

Figure 4 PEG-IFN exposure from both pediatric studies and from adult hepatitis C and hepatitis B studies



Note: the thick line represents the median, the upper and lower quartiles are represented by the upper and lower end of the box and the min and max by the end of the lines. The dashed line represents the median from study YV25718.

The marketing authorisation holder of Pegasys considered that the observed difference in exposure between studies YV25718 and NR16141 was mainly due to random variation (sample size effect). Nevertheless, since overexposure may be of concern, CHMP considered that the reasons for the observed difference had to be further explored, to allow the model predicted exposure for the younger children to be trusted.

During the assessment, the MAH explained that the PK data of the paediatric CHB study YV25718 were pooled with multiple-dose PK data from other clinical studies that were conducted within the last 10 years. Older clinical studies were not selected, as the collection of date and time of events informing the PK events, such as dosing and PK sampling, were not considered optimal. Uncertainties in PK sample collection times and also in compliance could significantly impact the robustness of a population PK model and could also artificially increase variabilities and uncertainties, especially when sparse PK samples are collected. The paediatric CHC study NR16141 was conducted more than 14 years ago and the PK sample collection was relatively sparse. This study was therefore not selected to be included in the current population PK analysis. It was also established, based on the population PK analysis of this study, that the PK time course profiles could not be always properly described due to rather large intra-patient variability in some patients, potentially due to limited compliance to the weekly dosing regimen. To further illustrate why PK data collected in study NR16141 data were excluded from a pooled analysis, a comparison of the raw PK data between NR16141 and YV25718 using dose-adjusted concentration plot as well as a comparison of the raw PK data of NR16141 with the population PK prediction of NR16141 using the population PK model build on YV25718 data were conducted.

In addition it was confirmed that PK data collected in the paediatric CHC study, and in particular the data collected after multiple dosing, were not in accordance with the current understanding of the PK properties of PEG-IFN in paediatric CHB patients as well as in adult CHC and CHB patients. While the higher than expected accumulation in the paediatric CHC study could not be fully elucidated, the lack of concordance of the estimated CL in the paediatric CHC study with the allometric relationship (contrary to the CHB paediatric study) as well as the lack of PK differences between adult CHC and CHB patients, were interpreted to increase the likelihood that this higher than expected accumulation could be due to limited compliance to the weekly dosing regimen in the paediatric CHC study.

Moreover, it was noted that the PK results in CHB were consistent in paediatric and adult patients and that, in addition, the PK results in adults are consistent for the CHB and CHC populations. The only dataset that did not fit this consistent picture were the results of study NR16141. The new information from CHB paediatric trials was considered important and was consistent with the decision made by the CHMP in 2013 to select the CHC dosing in children in the Pegasys SmPC on the basis of the doses tested in the paediatric Phase III clinical trial (NV17424) (rather than based on the PK results from study NR16141).

CHMP agreed to the MAH position that inclusion of the data from the NR16141 to the YV25718 analysis would have resulted in population pharmacokinetic estimates which would not have been truly representative of the pharmacokinetics of PEG-IFN in children and that this approach was therefore not warranted.

During the assessment of the present extension of indication procedure, CHMP also requested further clarification on the indication proposed by the MAH for the treatment of children aged 3 years and above with CHB, with a posology covering a BSA from 0.54, in view of the currently approved indication for chronic hepatitis C, which was limited from 5 years of age and a BSA of 0.71, due to uncertainties about exposure in smaller children.

The MAH explained that the proposal for the CHB indication with a lower limit of 3 years was based on the results of study YV25718 which enrolled patients from 3 to 17 years of age. Patients from each protocol-defined BSA category were enrolled in the trial, with the exception of the BSA category 0.51-0.53, where no patients were enrolled. The population pharmacokinetic analysis, conducted in a substudy (N=31) also included all BSA categories > 0.53 m2. Using the BSA category based dosing regimen resulted in similar exposure across all BSA categories studied. In contrast, data for the hepatitis C paediatric indication were based on results of two studies: Study NV17424, the pivotal Phase 3 study - originally designed and conducted by the US National Institute of Health, with no PK sampling - and the pharmacokinetic study NR16141. In study NV17424, patients were enrolled with ages ranging from 5 to 17 years and BSA ranging from 0.71-2.18 m2. In study NR16141 (N=14), patients were enrolled with ages ranging from 2 to 8 years and BSA ranging from 0.6 to 1.3 m2. The lower BSA range was therefore determined by the smallest set of patients included in the trials.

CHMP agreed to the above rationale. A further discussion on a potential harmonisation of the lower age limit and BSA between the two paediatric indications was not considered warranted.

2.3.3. Discussion on clinical pharmacology

The PK of PEG-IFN in children was investigated in study YV25718 where 31 children from 3 years to17 years of age received weekly doses of PEG-IFN by the subcutaneous route according the following BSA based dose categories:

Dose (μg)	BSA Range (m^2)
45	0.51–0.53
65	0.54–0.74
90	0.75–1.08
135	1.09–1.51
180	>1.51

BSA = body surface area (estimated using the Mosteller formula)

Relatively sparse plasma sampling was performed in a sub-study to determine the PK of PEG-IFN in the children. The data was modeled together with adult data and individual steady state exposure was predicted using the model and individual PK observations. This was considered to be adequate provided that the model fits the data well.

The population PK model based on combined adult and children data is important for justifying the dosing regimen in children. The exposure is intended to be similar between adults and children and the model is used for simulation of the exposure in the different BSA categories. It is therefore important that the influence of body size (e.g. BSA or body weight) on PK parameters is adequately modelled. The allometric exponent for the relation between body weight and clearance was fixed to 0.75 while the relation between volume of distribution and body weight was estimated to 1.52. The rationale for estimating the relation for one of the exponents and not the other was unclear to CHMP, as the volume of distribution influences the trough concentration and a discrepancy between observed and simulated data was seen for trough concentration in adult patients. Therefore, CHMP requested a VPC of trough values in adults for a model where the allometric exponents were fixed to their theoretical values (0.75 and 1.0, respectively).

During the procedure, the MAH provided additional graphics and modelling results to justify the rationale for estimating the relation for one of the exponents. Collectively, the data showed that the model fit appeared not to be improved using a fixed theoretical allometric exponent on volume of distribution. Further, it was shown that the under prediction of trough concentration did not seem to be related to this allometric exponent being fixed or not. This was considered adequate by the CHMP.

Another issue that was discussed and clarified regarding the model fit was the number of children included in the population PK data set (n = 31). Since this number of subjects was rather limited and PK sampling was sparse, a more thorough examination of the goodness of fit was considered warranted by CHMP, especially since some of the individually predicted PK profiles differed from the population prediction. To address this concern, the MAH provided more detailed analyses (VPCs) to show the ability of the model to describe PK data in children. The additional plots showed that an adequate fit was achieved overall. New individual goodness-of-fit plots were also provided and these also showed an adequate fit of the model to the data.

In light of the limited number of children included in the population PK data, another clarification point raised during the assessment was the exclusion of study NR16141 (conducted in paediatric CHC patients) from the population PK analysis. The marketing authorisation holder was required to justify the rationale for exclusion of this study from the population PK model, especially since exposure in these children was 25% to 70% higher than that observed in adults and that over-exposure was of concern.

The MAH provided the rationale as to why the data from study NR16141 was not included in the population PK analysis. The data from this study were modelled together with data from paediatric patients with CHB (study YV25718) to allow for a comparison between the population PK analysis

results excluding or including study NR16141. Despite differences that were observed in the modelled apparent clearance in study NR16141 compared to other available PK data, CHMP agreed that the MAH approach of excluding the data from study NR16141 from the population PK analysis was acceptable.

CHMP also noted during the assessment the differences between the proposed indication for paediatric CHB compared to the existing paediatric indication for CHC (for CHB from 3 years of age, with a posology covering a BSA from 0.54 versus from 5 years of age and a BSA of 0.71 for CHC). The MAH explained that the proposal for the CHB indication with a lower limit of 3 years was based on the results of study YV25718 which enrolled patients from 3 to 17 years of age. In contrast, data for the hepatitis C paediatric indication were based on results of two other studies: Study NV17424, the pivotal Phase 3 study, and the pharmacokinetic study NR16141 which employed different entry criteria than the paediatric CHB study YV25718. Consequently, the BSA and age limit for treatment were based on the inclusion criteria of the study as well as the observed range of BSA and age. The population model, which fits the data, does suggest consistent PK in the studied range. From a PK point of view the proposed age and BSA limits were considered acceptable by CHMP.

2.3.4. Conclusions on clinical pharmacology

CHMP agreed that the PK of PEG-IFN α2a in children with chronic hepatitis B in the immune-active phase aged from 3 to less than 18 years has been adequately described using population PK modelling of combined adult and children PK data.

2.4. Clinical efficacy

The data in support for this extension of indication come from a multi-centre open label study. Children without severe fibrosis were randomized (2:1) to Pegasys for 48 weeks or to no treatment; it was not considered ethical to have a placebo-controlled study for reasons easy to understand. As described below, those allocated to no treatment had a chance to receive therapy post week 48. Those with severe fibrosis (F3) received active therapy at study entry.

2.4.1. Main study – study YV25718

Centres and countries: Australia (2 sites), Belgium (2), Bulgaria (2), China (10), Germany (1), Israel (3), Italy (1), Poland (3), Russia (4), Ukraine (2), United Kingdom (3), and the US (4)

Period of trial: July 2012 (first patient enrolled), January 2016 (cut-off for primary analysis)

The study concerns the outcomes with 48 weeks of peg-IFN alpha 2a therapy (Pegasys, dose by BSA bands), or no treatment, randomised (2:1), in children 3- <18 years of age with e-antigen positive CHB in the immune-active phase.

Study participants

Main inclusion criteria

A patient was included if the answer to all of the following statements was “yes”:

- Positive HBsAg for more than 6 months, and positive HBeAg plus HBV-DNA >2000 IU/ml at screening
- A liver biopsy performed within 2 years prior to baseline to confirm the presence of advanced fibrosis [allocation to placebo not ethic] or exclude cirrhosis [not to be included in this study]. For patients with advanced fibrosis, a liver biopsy had to have been performed within 9 months prior to baseline.

- Compensated liver disease (Child-Pugh Class A)
- ALT > upper limit of normal (ULN) but ≤10 X ULN as determined by two abnormal values taken ≥14 days apart during the preceding 6 months (at least sample obtained ≤35 days prior to the first dose).

Main exclusion criteria

- History or other evidence of a medical condition associated with chronic liver disease other than CHB, including the presence of antibodies to HCV or HDV.
- HIV co-infection.
- Neutrophil count < 1.5 x 10^9 cells/L, platelet count < 90 x 10^9 cells/L or hemoglobin < lower limit of normal (LLN). Screening albumin < lower limit of normal or total bilirubin > ULN.
- Evidence of renal impairment
- History of immunologically mediated disease
- Major depression or history of psychiatric disorder
- Thyroid disease poorly controlled on prescribed medications or clinically relevant abnormal thyroid function tests
- Poorly controlled diabetes

Treatments

Patients without advanced fibrosis were randomized 2:1 to PEG-IFN treatment (Group A) or untreated control (Group B), respectively. Untreated controls without a spontaneous HBeAg seroconversion during the 48 weeks of principal follow-up were offered therapy; an offer that remained for 1 year post primary follow-up.

Patients with advanced fibrosis were assigned to PEG-IFN treatment (Group C), since it was considered un-ethical to withhold treatment for these subjects. Advanced fibrosis was defined as a liver biopsy with Metavir score 3 (out of 4), or Knodell fibrosis score 3, Modified Ishak fibrosis score 4, Batts & Ludwig score 3, or Scheuer score 3.

Pegasys (groups A and C) was given for 48 weeks, dosed in line with that used in the pivotal paediatric hepatitis C-infection study (with no subjects included for the lowest BSA band):

Dose (µg)	BSA Range (m^2)
45	0.51-0.53
65	0.54-0.74
90	0.75-1.08
135	1.09-1.51
180	>1.51

For Group A, Group B non-switch, and Group C patients, the study duration was approximately 6 years (5 years of follow-up post treatment). For Group B switch patients, the total study duration was up to approximately 8 years to enable a 5 year follow-up post therapy.

Criteria for Dose Modification or Withdrawal from Treatment

Stopping rules and dose modifications were generally in line with the recommendations in the present Pegasys SmPC.

Outcomes/endpoints

Primary efficacy analysis

- HBeAg seroconversion (loss of HBeAg and presence of anti-HBe), 24 weeks post therapy

Patients with missing values of primary endpoint (including patients in group B who started PEG-IFN treatment prior to Week 24 of follow-up) were considered as non-responders.

Sensitivity analyses were carried out with the approach of last observation carried forward (LOCF). An additional post-hoc analysis was also performed by excluding Group B patients who switched before Week 24 of follow-up from ITT population.

Secondary efficacy analysis

- HBeAg seroconversion (outside the 24 week time point)
- HBsAg seroconversion (loss of HBsAg and presence of anti HBs)
- Loss of HBsAg (without development of anti-HBs)
- Proportion of patients with normal ALT
- Suppression of HBV-DNA to < 20,000 IU/mL, < 2,000 IU/mL, undetectable, and change from baseline.
- Combined endpoint of HBeAg seroconversion and HBV-DNA response
- Quantitative values of serum ALT, HBV-DNA, HBeAg, and HBsAg, and their change from baseline.

Sample size

161 patients, including at least 145 without advanced liver fibrosis or cirrhosis

Randomisation

151 patients without advanced fibrosis were enrolled and randomized (101 in Group A and 50 in Group B). An additional 10 patients with advanced fibrosis were enrolled in Group C.

Stratification was performed by genotype (A vs. non-A) and ALT level (< 5 × the ULN vs. ≥ 5 × the ULN). Subjects with advanced fibrosis (assessed by liver biopsy performed within 9 months prior to baseline) were assigned to PEG-IFN treatment (Group C: advanced fibrotic arm).

Treatment group assignment was centralized by Interactive Voice or Web Response System (IxRS).

Statistical methods

The estimates of the common odds ratio, adjusted by stratification factors, were reported accompanied by the associated 95% confidence intervals.

P-values for the binary secondary efficacy endpoints were calculated using Fisher's exact test. Efficacy assessments at later time points will be reported in the final CSR. Descriptive statistics were used to summarize safety parameters by group during the treatment/principal observation period and initial 24 weeks of follow-up. Laboratory data not reported in International System of Units (SI units) were converted to SI units before further processing.

For the growth analysis, the gender specific Centres for Disease Control and Prevention (CDC) Growth Charts were used as reference to calculate the height (weight, BMI) for age percentile and height (weight, BMI) for age z-score.

Safety assessments collected during the 4.5-year extended, long-term follow-up period will be reported in the final CSR.

Conduct of the study

The protocol was amended once prior to enrolment of the first patient. Subsequently, three amendments were implemented.

With regard to the study design, CHMP noted that the treatment duration was that recommended for adults, and that Pegasys was dosed in children with the aim of mimicking the exposure in adults. The choice of HBV-DNA level (>2000 IU/ml) used as inclusion criterion was discussed by CHMP (see further).

CHMP also acknowledged that an important aspect of a long term follow-up is to further evaluate the effects of PEG-IFN on height development. The data already generated and evaluated from children treated with PEG-IFN α2b (5 year follow-up presented) were considered trustworthy by CHMP when evaluating that aspect of safety, as it was considered that long term effects on height would not differ by the type of interferon used.

The study endpoints were endorsed by CHMP.

Results

Baseline data

211 patients were screened with 45 screening failures (not fulfilling entry criteria/not willing to participate).

Asian sites recruited the highest number (76 randomized patients overall, 69 in China), followed by Europe (57 randomized patients, with 18 in the Russia and 13 in the Ukraine). Nine of the 10 patients with advanced fibrosis (Group C) were enrolled in Asia.

As seen in the next two tables, main demographics and disease characteristics (including degree of ALT increase and HBV genotype) was fairly well balanced between arms A and B.

Summary of Demographic Data (ITT population)

	Group A n=101	Group B n=50	Group C n=10
Age (year), mean (SD)	10.4	11.2	6.7
<5	14 (14%)	9 (18%)	4 (40%)
≥5 and <12	39 (39%)	11 (22%)	5 (50%)
≥12	48 (47%)	30 (60%)	1 (10%)
Male sex	64 (63%)	32 (64%)	8 (80%)
Race:			
Asian	56 (55%)	33 (66%)	7 (70%)
Black or African American	7 (7%)	1 (2%)	1 (10%)
Multiple	1 (1%)	0	0
White	32 (32%)	15 (30%)	2 (20%)
Other	5 (5%)	1 (2%)	0
Weight, kg median	37.2	47.2	20.5
Min-max	12-80	13-94	15-67
Height, cm median	145	156	125
Min-max	93-186	94-187	93-172
Body surface area group (m2):			
0.51-0.53	0	0	0
0.54-0.74	9 (9%)	9 (18%)	2 (20%)
0.75-1.08	31 (31%)	9 (18%)	6 (60%)
1.09-1.51	30 (30%)	12 (24%)	1 (10%)
>1.51	31 (31%)	20 (40%)	1 (10%)
Weight for age z-score, mean (SD)	0.096 (1.159)	-0.028 (1.148)	0.187 (1.141)
Height for age z-score, mean (SD)	0.254 (1.162)	-0.037 (1.178)	0.586 (0.947)

SD = standard deviation.

Disease characteristics

Baseline ALT	Group A (101)	Group B (50)	Group C (10)
< 1X ULN	7 (7)	5 (10)	10 (100)
>=1xULN - <2xULN	41 (41)	19 (38)	
>=2xULN - <5xULN	43 (43)	17 (34)	
>=5xULN - <10xULN	8 (8)	9 (18)	
HBV genotype A	9 (9)	3 (6)	1 (10)
B	21 (21)	6 (12)	1 (10)
C	34 (34)	23 (46)	6 (60)
D	31 (31)	18 (36)	2 (20)
E/other	6 (6)	0	0 (0)
Fibrosis score F0	13 (13)	6 (12)	0
F1	51 (51)	27 (54)	1 (10)*
F2	36 (36)	17 (34)	0
F3	0	0	9 (90)
F4	0	0	0
Mode of transmission			
perinatal	31	13	5
transfusion	2	5	
other percutaneous	8	7	
unknown	58	24	5
other	1	1	
Family history of HBV	101	50	10

*one patient with an F1 fibrosis score was erroneously placed and dosed in Group C.

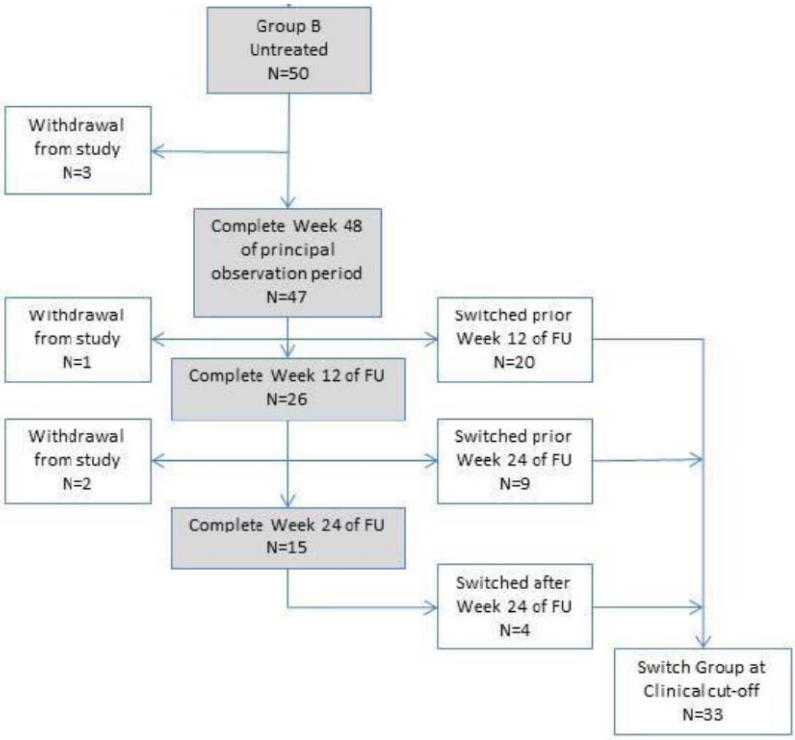
The inclusion criteria were considered liberal. A number of children had normal ALT levels at baseline, and around half had an ALT level of < 2 X ULN. As expected, the majority had minimal fibrosis (F0 or F1).

Disposition of subjects

Out of 101 subjects in group A, 96 were treated for 45-48 weeks (1 for 3 months, 1 for 6 months and 3 for just over 48 weeks). Out of the 10 with severe fibrosis (C), 9 received 45-48 weeks of therapy, and the 10th 49-52 weeks.

Only 2 patients in Group A prematurely discontinued treatment; AE 1, physician decision 1 (treatment deemed unnecessary). Both patients completed Week 24 of follow-up.

The disposition of group B, including decision to start therapy post week 48, is shown below.



Loss of HBeAg at week 72 (48 weeks + 24 weeks of FU) was seen in 26% of those treated versus in 3/50 (6%), table below) controls, where controls who had started treatment prior to this time point were counted as non-responders, as well as those without an assessment at this time point. Using a last observation carried forward with regards the latter increased the number of responders by 1 patient in each group (26.7% vs. 8%).

HBeAg loss was seen in 3/21 controls (14.3%) who did not start Pegasys prior to the assessment of the primary end point.

Efficacy Endpoints at 24 Weeks after the End-of-Treatment: ITT Population (Group A and B)

	Group A (N=101) (95% CI)[a]	Group B (N=50) (95% CI)[a]	Odds Ratio (95% CI)	p-value
Primary Endpoint				
HBeAg seroconversion	26 (26) [18, 35]	3 (6) [1, 17]	5.4 [2, 19]	0.0043[f]
Secondary Endpoints				
Loss of HBeAg	26 (26) [18,35]	3 (6) [1,17]	5.4 [2,29]	0.004
HBsAg seroconversion	8 (8) [4,15)	0 (0) [0, 7]	-	0.054
Loss of HBsAg	9 (9) [4,16]	0 (0) [0, 7]	-	0.030
Normal ALT	52 (51) [41,62]	6 (12) [5,24]	7.8 [3,24]	<0.0001
HBV-DNA < 20000 IU/mL	34 (33)	2 (4)	12	<0.0001
< 2000 IU/mL	29 (29)	1 (2)	19.7	<0.0001
undetectable	17 (17)	1 (2)	9.9	0.007
HBeAg seroconversion and HBV-DNA < 20000 IU/mL	23 (23)	2 (4)	7.1	0.003
HBeAg seroconversion and HBV-DNA < 2000 IU/mL	20 (20)	1 (2)	12.1	0.002

95% CI of response rate is calculated by Clopper-Pearson method. HBeAg/HBsAg seroconversion is defined as loss of these antigens and the presence of anti-HBe/anti-HBs

In Group C, HBeAg seroconversion was observed in 3 (30.0%) patients (95% CI, 6.7%-65.3%) at 24 weeks after the end of treatment period.

CHMP noted that the overall HBe conversion rates in these children after 48 weeks of therapy were lower than those seen in adult patients in the pivotal studies of PEG-IFN α2a and 2b (HBeAg positive previously untreated patients). CHMP agreed that the difference was likely driven by the fairly large number of children included with next to normal ALT values (as a marker of minimal immune activation), and a very low response rate in children with genotype D.

Per Protocol (PP) Population

The PP population included 91 patients in group A and 43 patients in group B, others were excluded (10% and 14% respectively) for the below reasons. The rates of HBeAg seroconversion in the PP population remained similar (26 vs. 7%).

	Group A	Group B
ALT <= 1xULN or ALT > 10xULN at screening and baseline	1(1%)	0 (0%)
HB < lower limit of normal (LLN) at screening	4 (4%)	6 (12%)
Neutrophil count < 1.5 x 10^9 cells/L at 1 screening	1 (1%)	0 (0%)
Received <39 doses or <= 80% of treatment duration of PEG-IFN	2 (2%)	NA
Received IFNs, or HBV nuke within 6 months prior to BL	2 (2%)	1 (2%)

HBeAg Seroconversion at 24 Weeks post treatment: ITT, PP Population and Sensitivity Analyses

	Analysis	Group A (Peg-IFN)	Group B (untreated)	P-value (CMH test)
ITT	ITT, switchers = failure W24 missing = failure	26/101 (25.7)	3/50 (6.0)	0.0043
Planned Sub-Population	Per protocol	24/91 (26.4)	3/43 (7.0)	0.0100
Planned Sensitivity	LOCF	27/101 (26.7)	4/50 (8.0)	0.0080
Post hoc Sensitivity	switched excluded	26/101 (25.7)	3/21 (14.3)	0.2305

In Group C, HBeAg seroconversion was observed in 3 (30.0%) patients (95% CI, 6.7%-65.3%) at 24 weeks after the end of treatment period.

Efficacy in selected subgroups

The following table shows HBeAg seroconversion rates by relevant baseline parameters. Many of them would be connected, such as race and HBV genotype (and not shown here, mode of transmission).

Age wise, younger paediatric patients had improved efficacy response compared with older pediatric patients (HBeAg seroconversion rates: < 5 years [42.9%], 5-11 years [25.6%], > 12 years [20.8%]), in line with previous studies with IFNs that demonstrated better efficacy in younger pediatric patients (Sokal et al. 2013). It is noted that the response in patients with genotype D (most likely Caucasians in this study) was low. Likewise, those children with minimal ALT increases responded less well, in line with what is known from adults.

	Group A (N=101)		Group B (N=50)			
	n	HBeAg Seroconversion	n	HBeAg Seroconversion	Odds Ratio	(95% CI)
Age groups						
Age < 12	53	16 (30.2%)	20	1 (5.0%)	8.22	(1.08,362.4)
Age >= 12	48	10 (20.8%)	30	2 (6.7%)	3.68	(0.69,36.67)
Age < 5	14	6 (42.9%)	9	0 (0.0%)	-	(-)
Age >= 5	87	20 (23.0%)	41	3 (7.3%)	3.78	(1.01,20.97)
Baseline BSA						
0.51-0.53	0	0 (0.0%)	0	0 (0.0%)	-	(-)
0.54-0.74	9	3 (33.3%)	9	0 (0.0%)	-	(-)
0.75-1.08	31	11 (35.5%)	9	1 (11.1%)	4.40	(0.46,212.7)
1.09-1.51	30	7 (23.3%)	12	1 (8.3%)	3.35	(0.34,164.4)
>1.51	31	5 (16.1%)	20	1 (5.0%)	3.65	(0.36,181.8)
Baseline BMI						
< 18.5	61	19 (31.1%)	27	2 (7.4%)	5.65	(1.18,53.32)
18.5 - <25.0	34	4 (11.8%)	18	0 (0.0%)	-	(-)
25.0 - 30.0	5	2 (40.0%)	4	1 (25.0%)	2.00	(0.06,156.7)
> 30.0	1	1 (100%)	1	0 (0.0%)	-	(-)
Race						
ASIAN	56	19 (33.9%)	33	2 (6.1%)	7.96	(1.67,74.39)
CAUCASIAN	32	5 (15.6%)	15	1 (6.7%)	2.59	(0.25,131.2)
OTHER	13	2 (15.4%)	2	0 (0.0%)	-	(-)
Sex						
F	37	10 (27.0%)	18	1 (5.6%)	6.30	(0.75,289.0)
M	64	16 (25.0%)	32	2 (6.3%)	5.00	(1.04,47.27)
HBV genotype						
A	9	3 (33.3%)	3	1 (33.3%)	1.00	(0.04,78.43)
B	21	7 (33.3%)	6	0 (0.0%)	-	(-)
C	34	13 (38.2%)	23	1 (4.3%)	13.62	(1.69,604.5)
D	31	3 (9.7%)	18	1 (5.6%)	1.82	(0.13,101.2)
OTHER	6	0 (0.0%)	0	0 (0.0%)	-	(-)
Baseline ALT						
<1xULN	7	0 (0.0%)	5	0 (0.0%)	-	(-)
>=1xULN - <2xULN	41	9 (22.0%)	19	0 (0.0%)	-	(-)
>=2xULN - <5xULN	43	15 (34.9%)	17	1 (5.9%)	8.57	(1.08,383.0)
>=5xULN - <10xULN	8	2 (25.0%)	9	2 (22.2%)	1.17	(0.06,20.75)
>=10xULN	2	0 (0.0%)	0	0 (0.0%)	-	(-)
Baseline log10(HBVDNA)						
<= median	48	16 (33.3%)	27	3 (11.1%)	4.00	(0.97,23.44)
> median	53	10 (18.9%)	23	0 (0.0%)	-	(-)

The inclusion criteria to this study were seen as liberal with regards to ALT levels to be included and the MAH was asked to discuss. It was clarified that the inclusion criteria used in study YV25718 were chosen to ensure patients were in the immune-active phase of the disease (i.e. defined by positive HBeAg, HBV DNA >2000 IU/mL, ALT elevated, active inflammation on liver biopsy [McMahon 2008]). The ALT criterion aligns with the previous adult Pegasys CHB studies. Moreover, this ALT inclusion criterion is consistent with the current treatment guidelines (i.e. AASLD [Terrault et al 2016], EASL [EASL 2017], APASL [Sarin et al 2016]), which state that patients with minimally elevated ALT levels (1-2 × ULN) can still be considered for treatment. Indeed, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2013 paediatric CHB guideline treatment algorithm advocates liver biopsy and subsequent treatment consideration in children with elevated ALT levels (Sokal et al 2013). The indication wording now includes that there is evidence of **persistently** elevated ALT levels and included references to sections 4.4 and 5.1.

Further, a fairly high number of children with genotype D were included, and results did not seem to favour the use of PEG-IFN therapy in that group (e.g. having side effects in mind). The MAH showed more details on these patients.

The distribution of HBV genotypes by region/country in study YV25718 is displayed in the following table:

Table 7 Distribution of HBV Genotypes by Region/Country in Study YV25718

Summary of HBV Genotype by Region, Country, and Investigator Number: All Patients
Protocol: YV25718

Group A PEG-IFN (N=101)

Region Country Investigator Number	HBV genotype A (N=9)	HBV genotype B (N=21)	HBV genotype C (N=34)	HBV genotype D (N=31)	HBV genotype OTHER (N=6)	Total (N=101)
Asia	0	15 (71.4%)	29 (85.3%)	4 (12.9%)	0	48 (47.5%)
China	0	15 (71.4%)	29 (85.3%)	0	0	44 (43.6%)
Israel	0	0	0	4 (12.9%)	0	4 (4.0%)
Australia And New Zealand	0	1 (4.8%)	3 (8.8%)	1 (3.2%)	2 (33.3%)	7 (6.9%)
Australia	0	1 (4.8%)	3 (8.8%)	1 (3.2%)	2 (33.3%)	7 (6.9%)
Europe	8 (88.9%)	1 (4.8%)	1 (2.9%)	26 (83.9%)	3 (50.0%)	39 (38.6%)
Belgium	3 (33.3%)	0	1 (2.9%)	1 (3.2%)	1 (16.7%)	6 (5.9%)
Bulgaria	0	0	0	3 (9.7%)	0	3 (3.0%)
Germany	0	0	0	1 (3.2%)	0	1 (1.0%)
United Kingdom	0	1 (4.8%)	0	3 (9.7%)	1 (16.7%)	5 (5.0%)
Poland	3 (33.3%)	0	0	0	1 (16.7%)	4 (4.0%)
Russian Federation	1 (11.1%)	0	0	12 (38.7%)	0	13 (12.9%)
Ukraine	1 (11.1%)	0	0	6 (19.4%)	0	7 (6.9%)
North And South America	1 (11.1%)	4 (19.0%)	1 (2.9%)	0	1 (16.7%)	7 (6.9%)
United States	1 (11.1%)	4 (19.0%)	1 (2.9%)	0	1 (16.7%)	7 (6.9%)

Group B Untreated (N=50)

Region Country Investigator Number	HBV genotype A (N=3)	HBV genotype B (N=6)	HBV genotype C (N=23)	HBV genotype D (N=18)	Total (N=50)
Asia	1 (33.3%)	6 (100.0%)	19 (82.6%)	2 (11.1%)	28 (56.0%)
China	0	6 (100.0%)	19 (82.6%)	0	25 (50.0%)
Israel	1 (33.3%)	0	0	2 (11.1%)	3 (6.0%)
Australia And New Zealand	0	0	2 (8.7%)	1 (5.6%)	3 (6.0%)
Australia	0	0	2 (8.7%)	1 (5.6%)	3 (6.0%)
Europe	2 (66.7%)	0	1 (4.3%)	15 (83.3%)	18 (36.0%)
Belgium	0	0	1 (4.3%)	1 (5.6%)	2 (4.0%)
Bulgaria	0	0	0	1 (5.6%)	1 (2.0%)
Germany	0	0	0	1 (5.6%)	1 (2.0%)
United Kingdom	0	0	0	1 (5.6%)	1 (2.0%)
Italy	1 (33.3%)	0	0	1 (5.6%)	2 (4.0%)
Russian Federation	0	0	0	5 (27.8%)	5 (10.0%)
Ukraine	1 (33.3%)	0	0	5 (27.8%)	6 (12.0%)
North And South America	0	0	1 (4.3%)	0	1 (2.0%)
United States	0	0	1 (4.3%)	0	1 (2.0%)

Group C PEG-IFN (N=10)

Region Country Investigator Number	HBV genotype A (N=1)	HBV genotype B (N=1)	HBV genotype C (N=6)	HBV genotype D (N=2)	Total (N=10)
Asia	1 (100.0%)	1 (100.0%)	6 (100.0%)	1 (50.0%)	9 (90.0%)
China	0	1 (100.0%)	6 (100.0%)	0	7 (70.0%)
Israel	1 (100.0%)	0	0	1 (50.0%)	2 (20.0%)
Europe	0	0	0	1 (50.0%)	1 (10.0%)
Russian Federation	0	0	0	1 (50.0%)	1 (10.0%)

Patients enrolled in Europe (37.7% of the ITT population in study YV25718) accounted for a high proportion of the patients with genotype D infection (83.9% in Group A, 83.3% in Group B and 50.0% in Group C). Within the European region, most of the patients with genotype D infection were enrolled in Russia and the Ukraine (18/26 [69%]). The high prevalence of genotype D infection in these countries is in line with recent epidemiological observations (Bissinger et al 2015).

Exploratory subgroup analyses of the primary endpoint of HBeAg seroconversion by genotype were supportive of a treatment benefit across HBV genotypes B, C and D. In the case of HBV genotype A, an odds ratio (OR) of 1.0 was observed, but the number of patients with this genotype was too low (9 in Group A and 3 in Group B) to enable a meaningful assessment of the treatment effect. In the specific case of HBV genotype D, which is considered as a less responsive genotype (Sunbul 2014), a

less profound treatment effect on HBeAg seroconversion rate was observed (9.7%) comparing to HBV genotypes B and C (33.3%-38.2%).

The MAH also analysed to what extent factors other than genotype D may explain HBeAg seroconversion rate of <10% in this study. Baseline characteristics of the treated patients with HBV genotype D were compared with those with non-D genotypes to investigate whether any baseline factors that are predictive of worse response may have contributed to the lower response rate in HBV genotype D patients.

Table 8 Demographic Characteristics of HBV Genotype D Patients in Study YV25718: ITT Population

Demographics by HBV Genotype: ITT Population
Protocol: YV25718

	Group A PEG-IFN (N=101)		Group B Untreated (N=50)	
	HBV Genotype D (N=31)	HBV Genotype non-D (N=70)	HBV Genotype D (N=18)	HBV Genotype non-D (N=32)
Age(yr)				
n	31	70	18	32
Mean (SD)	10.65 (4.28)	10.30 (4.72)	11.22 (4.93)	11.19 (5.13)
Median	11.00	10.50	12.50	13.50
Min - Max	4.0 - 17.0	3.0 - 17.0	3.0 - 17.0	3.0 - 17.0
Age group(yr)				
n	31	70	18	32
<5	3 (9.7%)	11 (15.7%)	2 (11.1%)	7 (21.9%)
>=5 and <12	13 (41.9%)	26 (37.1%)	6 (33.3%)	5 (15.6%)
>=12	15 (48.4%)	33 (47.1%)	10 (55.6%)	20 (62.5%)
Sex				
n	31	70	18	32
Male	22 (71.0%)	42 (60.0%)	10 (55.6%)	22 (68.8%)
Female	9 (29.0%)	28 (40.0%)	8 (44.4%)	10 (31.3%)

Table 9 Baseline Disease Characteristics of HBV Genotype D Patients in Study YV25718: ITT Population

Baseline Characteristics by HBV Genotype: ITT Population
Protocol: YV25718

	Group A PEG-IFN (N=101)		Group B Untreated (N=50)	
	HBV Genotype D (N=31)	HBV Genotype non-D (N=70)	HBV Genotype D (N=18)	HBV Genotype non-D (N=32)
Log10(HBVDNA+1) at Baseline (Log10 IU/mL)				
n	31	70	18	32
Mean (SD)	8.549 (1.129)	7.892 (0.848)	8.327 (1.284)	7.904 (0.755)
Median	8.731	7.898	8.869	8.023
Min - Max	4.24 - 10.99	5.77 - 10.43	4.18 - 9.55	5.53 - 9.04
Log10(HBeAg+1) at Baseline (Log10 PEIU/mL)				
n	25	67	15	28
Mean (SD)	2.636 (0.448)	2.773 (0.519)	2.516 (0.757)	2.597 (0.598)
Median	2.726	2.916	2.756	2.785
Min - Max	1.78 - 3.24	1.46 - 4.10	1.10 - 3.45	1.05 - 3.45
Log10(HBsAg+1) at Baseline (Log10 IU/mL)				
n	31	70	16	28
Mean (SD)	4.702 (0.400)	4.136 (0.718)	4.765 (0.633)	4.165 (0.685)
Median	4.754	4.204	4.985	4.187
Min - Max	3.77 - 5.32	1.34 - 5.51	3.66 - 5.63	2.24 - 5.08
ALT at Baseline (ULN)				
n	31	70	18	32
Mean (SD)	2.100 (1.774)	3.080 (2.696)	2.076 (1.147)	3.329 (2.237)
Median	1.625	2.365	1.808	2.500
Min - Max	0.60 - 9.20	0.93 - 17.93	0.87 - 4.21	0.93 - 9.00
ALT at Baseline				
n	31	70	18	32
<1xULN	6 (19.4%)	1 (1.4%)	4 (22.2%)	1 (3.1%)
>=1xULN - <2xULN	14 (45.2%)	27 (38.6%)	5 (27.8%)	14 (43.8%)
>=2xULN - <5xULN	9 (29.0%)	34 (48.6%)	9 (50.0%)	8 (25.0%)
>=5xULN - <10xULN	2 (6.5%)	6 (8.6%)	0	9 (28.1%)
>=10xULN	0	2 (2.9%)	0	0

Differences of note included fewer patients infected with HBV genotype D versus non-D aged less than 5 years (3/31 [9.7%] versus 11/70 [15.7%]), more patients with baseline ALT < 1xULN (6/31 [19.4%] versus 1/70 [1.4%]) or with minimally elevated ALT (≥ 1xULN – 2xULN) (14/31 [45.2%] versus 27/70 [38.6%]), slightly higher baseline HBsAg level (mean $\log_{10}$[HBsAg+1] 4.70 versus 4.14), and baseline HBV-DNA (mean $\log_{10}$[HBV-DNA+1] 8.55 versus 7.89). Baseline HBeAg level was similar (mean Log_{10}[HBeAg+1] 2.64 versus 2.77). Since, in general, lower baseline ALT level, higher HBV-DNA and higher HBsAg level are associated with poorer response to PEG-IFN treatment, these factors may have contributed to the lower HBeAg seroconversion rate observed in patients with HBV genotype D in YV25718 study.

In a further effort to understand what factors may influence response in patients with genotype D, baseline and demographic characteristics of these patients were analyzed by whether patients achieved HBeAg seroconversion at Week 24 of follow-up. However, as only 3 out of 31 patients with genotype D experienced seroconversion, it was not possible to draw reliable conclusions from this analysis. The MAH further noted that the 9.7% response rate observed in the paediatric study YV25718 was in line with the results of a meta-analysis of pivotal and post-marketing data exclusively in patients treated with PEG-IFN, recently undertaken by the MAH, in which the response rate was 10.3%. Despite the limitations of these analyses, CHMP agreed that genotype D will be included in the approved paediatric indication and that section 5.1 of the Pegasys SmPC will show response rates by genotype.

Furthermore, the MAH provided data on the treatment of HBV genotypes other than A-D. Despite the fact that the included numbers were low, CHMP agreed that the approved paediatric indication for Pegasys in CHB paediatric patients will also include these patients.

Comparison of efficacy to that obtained in adult patients treated with PEG-IFN

The indication for Pegasys in adult e-antigen positive patients was based on the results in study WV16240. This study evaluated PEG-IFN α2a + placebo or lamivudine versus lamivudine. Additionally, a phase IV study (WV19432) compared the efficacy and safety of PEG-IFN α2a for 24 or 48 weeks at doses of 90 or 180 µg weekly for the same population.

Notable differences in baseline demographics between the present pediatric study and these studies were the proportion of genotype D-infected (31% versus 3-7% in studies WV16240 and WV19432), baseline HBeAg-levels being 4-fold higher in the paediatric patients (2.87 in study YV25718 versus 2.25 Log10 IU/mL in study WV16240), and the lack of cirrhotic patients in the paediatric study (around 5% in the adult studies).

Efficacy Endpoint	YV25718 n=101	WV16240 n = 271	WV19432[a] n = 130
HBeAg seroconversion	25.7%	32.1%	36.2%
HBV-DNA <20 000 IU/mL	33.6%	31.7%	42.3%
HBV-DNA <2 000 IU/mL	28.7%	23.6%	30.0%
Loss of HBeAg	25.7%	33.6%	36.2%
Loss of HBsAg	5.9%	3.3%	2.3%
HBsAg seroconversion	7.9%	3.0%	2.3%
Normal ALT	51.4%	41.0%	52.3%

[a] Values for 180 µg dose 48 week treatment arm (per protocol population).

As already mentioned, the least favourable outcome in the paediatric study was seen in patients with genotype D-infection. When looking at published data for outcomes by genotype in HBeAg positive adult patients treated with PEG-IFN α 2a or 2b +/- lamivudine, for 48 weeks the following HBe seroconversion rates were presented.

		Peg2b +/- lam (a)	**Peg2a +/- lam (b)**
Genotype	**A:**	42/90 (47)	16/41 (39)
	B:	10/23 (44)	47/158 (30)
	C:	11/39 (28)	93/318 (30)
	D:	26/103 (25)	4/20 (20)

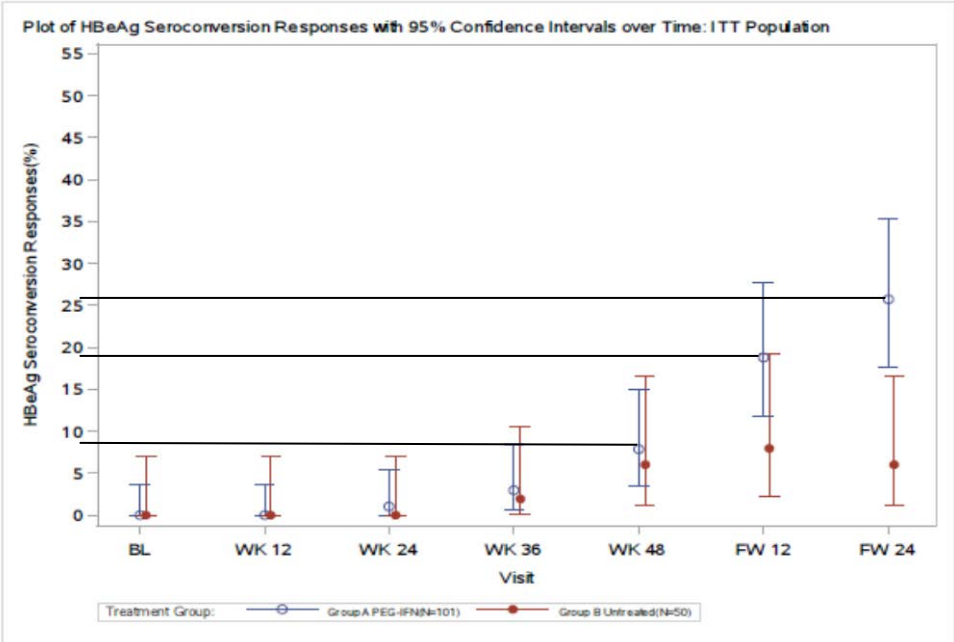
a) Janssen, Lancet 2005, b) Lau, NEJM 2005

In summary, the number of children with genotype A was too small for a comparison, the outcome in genotype B and C was in line with that seen in adults, and the outcome in genotype D (9%) seems considerably lower.

Time for HBeAg seroconversion

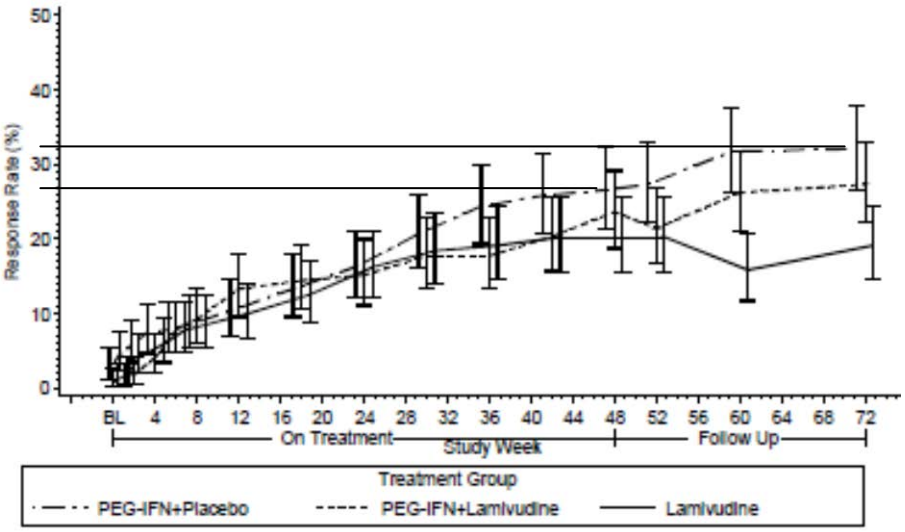
In the paediatric patients HBeAg seroconversion largely occurred post-treatment, whereas in adults, HBeAg seroconversion was observed to increase similarly during and after treatment, figures below.

HBeAg Seroconversion over Time: ITT Population (YV25718, pediatric)



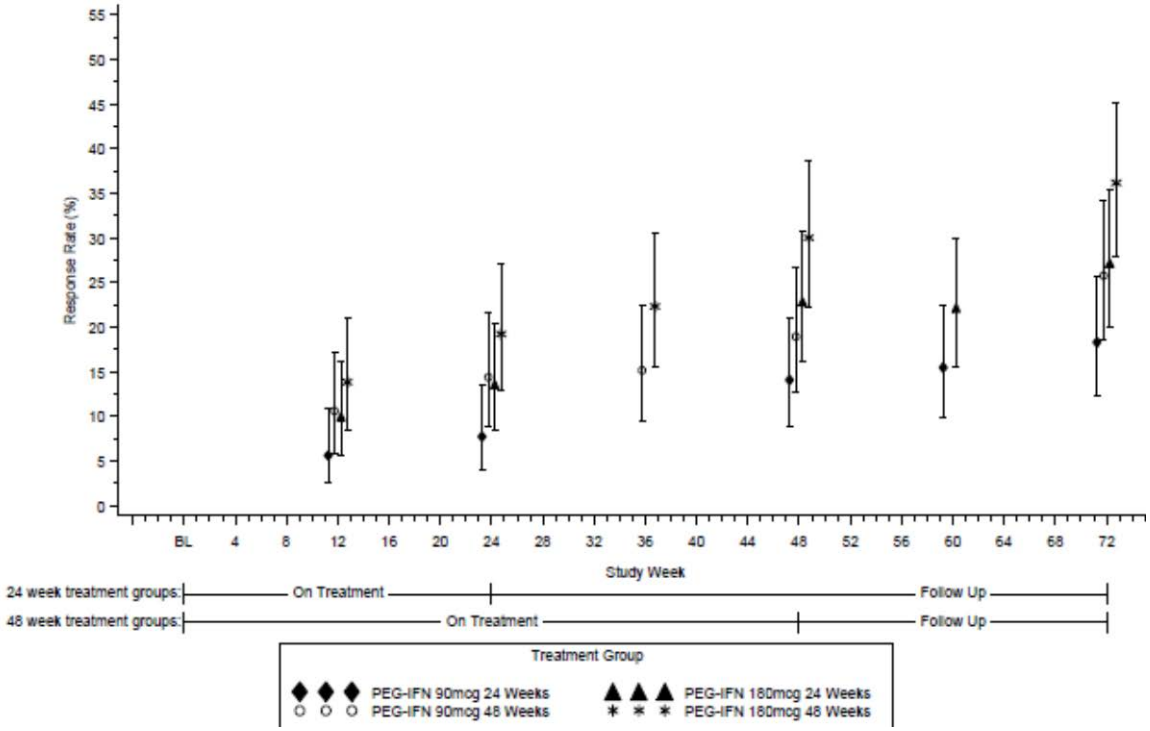
CHMP noted that a lower proportion of the children had an HBeAg seroconversion during treatment (around 7%, compared to around another 20% post treatment) and asked the MAH to discuss. It was clarified that timing of HBeAg seroconversion in study YV25718 occurred largely after the end of treatment in study YV25718 in contrast to the adult studies. Off-treatment serological and virological responses continued to increase at Year 1 of follow-up, similar to adult long-term follow-up study WV16866 which showed that HBeAg seroconversion rates continue to increase several years post PEG-IFN treatment.

HBeAg Seroconversion over Time: ITT Population (WV16240, adult pivotal)



Source: WV16240 CSR Figure 5

HBeAg Seroconversion over Time: PP Population (WV19432, adult phase 4)

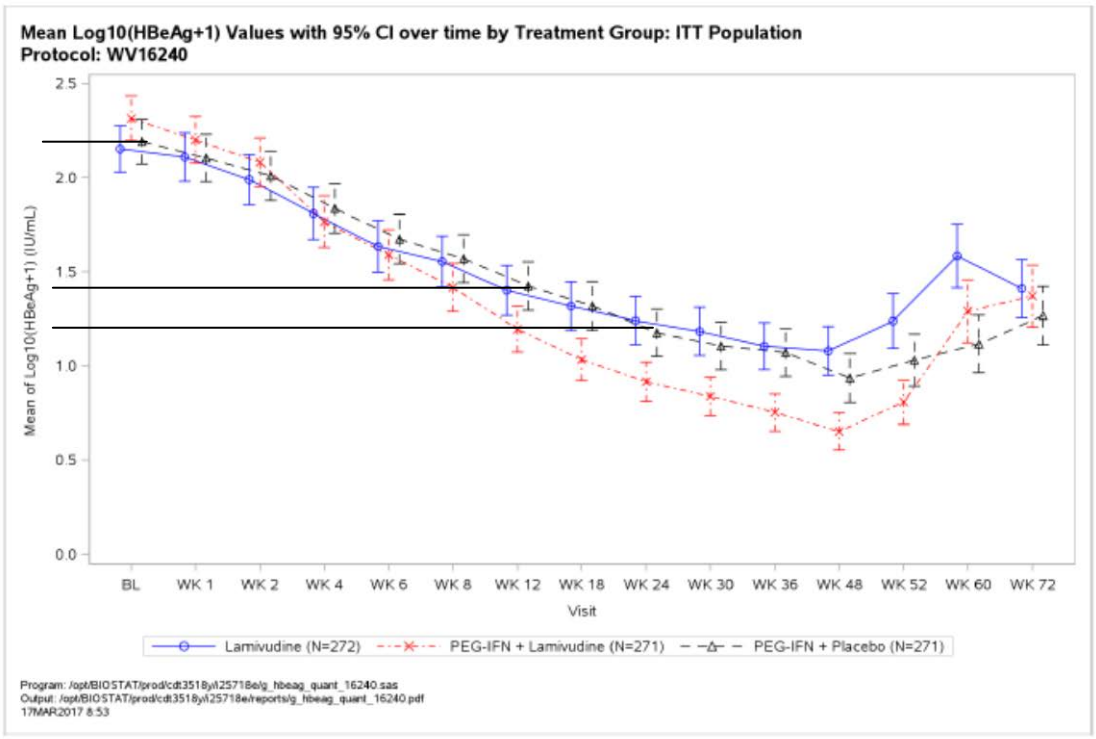


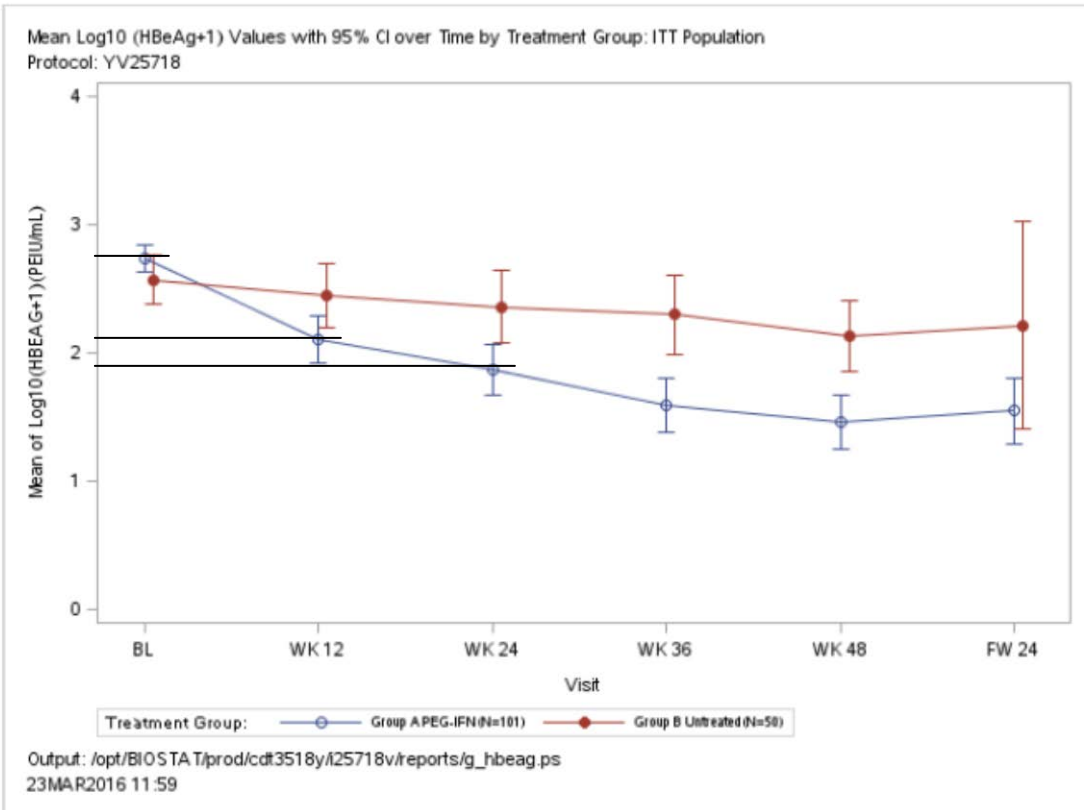
Source: WV19432 CSR Figure 4

CHMP questioned during the procedure whether this late response in HBe seroconversion was a result of high baseline HBe levels in children. The MAH provided HBe- and HBV-DNA levels for studies YV25718 (paediatric) and WV16240 (adults), at baseline, during treatment and during follow-up, for all patients, and separate for the responders (HBe seroconverters).

HBeAg seroconversion largely occured post-treatment in paediatric patients, whereas in adults, HBeAg seroconversion increased rapidly during early treatment and continued after treatment. This observation was further investigated by analysing individually the kinetics of the components of this composite endpoint. The presence of anti-HBe increased in paediatric patients and adults during and after treatment by Week 24 of follow-up. Likewise, mean HBeAg levels in paediatrics and adults declined during treatment to a minimum at Week 48 of treatment and slightly rebounded by Week 24 of follow-up. The main observable difference was that baseline HBeAg levels were approximately 4-fold higher in paediatric patients compared to adults: 2.87 versus 2.25 $\log_{10}$ IU/mL respectively.

Figure 5 Mean Log_{10} (HBeAg+1) Values over Time for Adults (Study WV16240) and Pediatric Patients (Study YV25718)





Additional plots of log_{10} (HBeAg+1) mean values over time for adults (study WV16240) and pediatric patients (study YV25718) by responders (HBeAg seroconversion at Week 24 of follow-up) and non-responders are presented in the following.

Figure 6a) Study WV16240

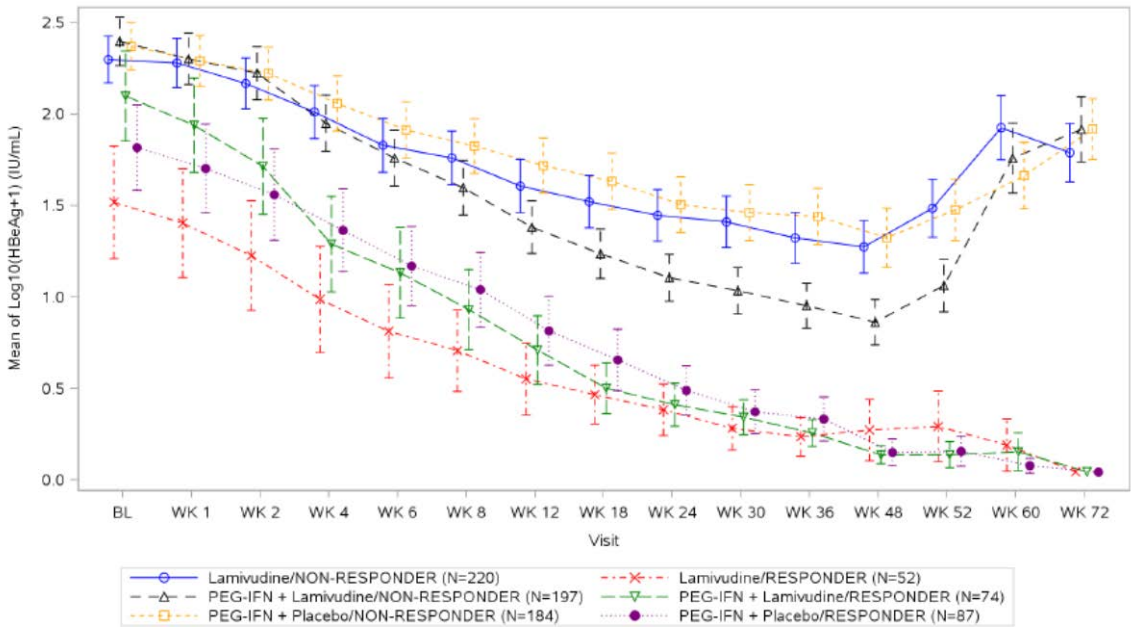
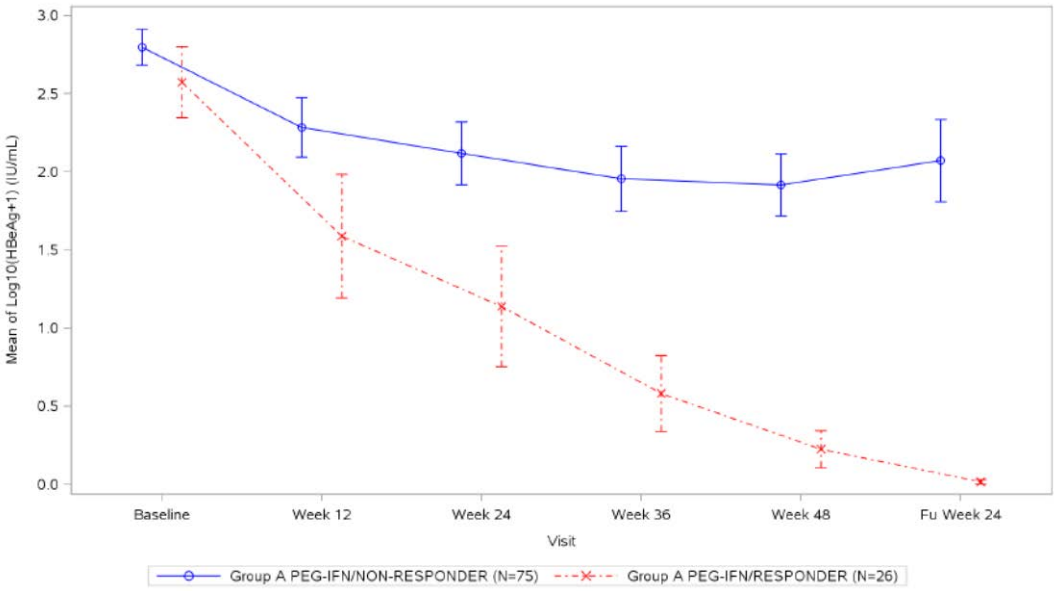


Figure 6b) Paediatric Study YV25718 (Group A, PEG-INF Treatment)



With regard to the HBV DNA Levels in adult and paediatric patients, it was clarified that PEG-IFN induces early reductions of viral DNA in serum (virological response) and viral DNA continues to decrease with treatment to rebound slightly post-treatment and stabilize to lower levels as compared with baseline or untreated control. The change in mean HBV DNA levels over time was of similar magnitude during treatment in both adults (study WV16240) and paediatric patients (study YV25718) with values moderately rebounding post-treatment.

CHMP concluded that the mean baseline HBeAg levels were higher in the paediatric study compared with the levels observed in adults, and this may have affected the delayed HBe-seroconversion in paediatric responders compared with adult responders. The difference in decline of HBeAg and HBV DNA between responders and non-responders opens for predictions of the likelihood of response early during treatment (for example at week 12).

CHMP noted that an increased probability of HBsAg conversion was seen with Pegasys treatment, and asked the MAH to discuss during the procedure qHBsAg at baseline and on-treatment as a predictor of HBsAg loss, as well as other disease and demographic predictors of HBsAg loss, as well as potential on-treatment predictors. Exploratory analyses of data from study YV25718 provided by the MAH showed that although baseline qHBsAg was not a predictor for HBeAg seroconversion, HBV-DNA<2000 IU/mL and HBsAg loss at Week 24 of follow-up, lower on-treatment qHBsAg (at Week 12 or Week 24) were associated with higher likelihood of achieving serological or virological response. Furthermore on-treatment qHBeAg, baseline BMI, BSA and baseline HBV-DNA level were shown by the exploratory analyses to be associated of HBsAg loss at Week 24 of follow-up.

CHMP acknowledged this and agreed that interpretation of these findings needs to be treated with caution given the limited amount of data and the exploratory nature of the analyses.

At request of the CHMP the MAH provided an analysis regarding HBV-DNA as an on-treatment predictor of response in HBeAg positive children. Low numbers were acknowledged.

Treatment response (HBeAg seroconversion) by change in HBV-DNA up to Week 12 of treatment (<1 $\log_{10}$ decline, >1 but <2 $\log_{10}$ decline, >2 $\log_{10}$ decline) is presented in the following table.

Table 10 Response at Week 24 of Follow-up by Decline from Baseline in HBV DNA at Week 12 of Treatment

Log_{10}(HBV-DNA+1)(IU/mL)	Responder	Non-responder
All genotypes (N=101)		
<1 log_{10} decline	6 (13.6%)	38 (86.4%)
1 - <2 log_{10} decline	5 (20.8%)	19 (79.2%)
≥2 log_{10} decline	15 (50.0%)	15 (50.0%)
Missing	0	3 (100.0%)
All	26 (25.7%)	75 (74.3%)
Genotype-A (N=9)		
<1 log_{10} decline	0	6 (100.0%)
1 - <2 log_{10} decline	2 (100.0%)	0
≥2 log_{10} decline	1 (100.0%)	0
All	3 (33.3%)	6 (66.7%)
Genotype-B (N=21)		
<1 log_{10} decline	1 (16.7%)	5 (83.3%)
1 - <2 log_{10} decline	1 (20.0%)	4 (80.0%)
≥2 log_{10} decline	5 (50.0%)	5 (50.0%)
All	7 (33.3%)	14 (66.7%)
Genotype-C (N=34)		
<1 log_{10} decline	3 (30.0%)	7 (70.0%)
1 - <2 log_{10} decline	2 (16.7%)	10 (83.3%)
≥2 log_{10} decline	8 (66.7%)	4 (33.3%)
All	13 (38.2%)	21 (61.8%)
Genotype-D (N=31)		
<1 log_{10} decline	2 (10.0%)	18 (90.0%)
1 - <2 log_{10} decline	0	5 (100.0%)
≥2 log_{10} decline	1 (20.0%)	4 (80.0%)
Missing	0	1 (100.0%)
All	3 (9.7%)	28 (90.3%)

In the genotype-specific analysis, 2 patients with mixed genotype and 4 patients with genotype E are not shown

The Applicant evaluated the performance characteristics (NPV, sensitivity, specificity) as a predictor of response using decline in HBV DNA of <1 log_{10} or <2 log_{10} at Week 12 by genotype in paediatric patients.

In addition, the predictive values of the parameters derived in the adult meta-analysis were tested on the paediatric data set; HBV DNA >8 log_{10} IU/mL and HBsAg >20,000 IU/mat at week 12, restricted to genotypes B and C.

It is acknowledged that statistical analyses around stopping rules were based on small numbers and should be interpreted with caution. Nevertheless, the response at week 24 in those with <1 log10 decline in HBV-DNA at week 12 (seen in overall 44/101 patients) seems poor, and the chance to

achieve a response is considered more decent in those with >2 log10 decline at week 12 (seen in 30/101 patients). Of note, the safety profile of peg-IFN is problematic, therapy is long and the disease course is mild in the vast majority of children. For transparency and to support an informed decision who to treat, at request of the CHMP, the data reflected in the table above are presented and commented in section 5.1 of the Pegasys SmPC.

Liver Elasticity Substudy

Liver Stiffness Measure (LSM) was assessed at baseline, Week 48 and Week 24 of follow-up in 75 patients (44 in Group A, 25 in Group B and 6 in Group C). Baseline data were available for 68 patients (40 in Group A, 22 in Group B and 6 in Group C) and data at Week 24 of follow-up were available for 53 patients (42 in Group A, 5 in Group B [the lower number is due to patients who switched to treatment with PEG-IFN at the end of the principal observation period], and 6 in Group C).

At baseline, median LSMs were similar across subgroups according to age, BMI and fibrosis score (range 4.9-6.6 kPa) and slightly higher in patients with advanced fibrosis (7.1 kPa).

LSM values steadily declined during PEG-IFN therapy in contrast to untreated patients, where values increased to Week 48, suggesting an improvement in underlying liver histology of PEG-IFN treated paediatric patients.

CHMP agreed that the outcome in the liver elasticity substudy was expected, i.e. to see a lowering of LSM values as an effect of therapy, likely as a consequence of lowered inflammation (rather than fibrosis during this short time span). The values seen at baseline in patients with “advanced fibrosis” indicate a slight mismatch as compared to LSM values presented in HBV-infected adults with F3 fibrosis (where 7.1 kPa would be equivalent to F2 fibrosis).

2.4.2. Discussion and conclusions on the clinical efficacy

The main goal of PEG-IFN therapy in HBeAg positive HBV infection is to shorten the immune active phase, i.e. to shorten the time to HBeAg seroconversion in patients who have entered the immune active stage, in order to prevent development of liver fibrosis, and reach a low viral replication. The overall HBeAg seroconversion rate seen in children in study YV25718 is comparable, although somewhat lower, to rates obtained in adult patients. Similar to adults, response rates were low in those children with the lowest baseline ALT increases. Therefore, the ALT inclusion criterion that was used in the study was discussed by CHMP; a repeated value, at least 2 weeks apart, higher than the upper limit of normal prior to study entry (maximum 6 months from the first sample). It was clarified that the inclusion criteria used in study YV25718 were chosen to ensure patients were in the immune-active phase of the disease. The ALT criterion aligns with the previous adult Pegasys CHB studies and is consistent with the current treatment guidelines. Nevertheless, to ensure that children with a low need for therapy and low probability of response are not treated in clinical practice, section 4.1 of the SmPC was revised, to clarify that the indication only concerns HBeAg positive children with persistently raised ALT levels (i.e. marker of immune active phase) and includes references to sections 4.2, 4.4 and 5.1.

The HBeAg seroconversion rate in children infected with HBV subtype D was very low (around 10%), and lower than results yielded in adults (20-25%).

The MAH was asked to elaborate on whether the viral subtype per se seems to explain this finding, or whether other baseline factors (such as normal or minimally increased ALT levels) were seen in these children as compared to the others. CHMP agreed that the latter seemed to at least partially explain the very low response rate in this study, indirectly linked to difference in opinion around who to

treat/recruit by region. Of note, the difference in response rates by genotype has been less marked in adult studies. A genotype specific indication is not deemed necessary. Upon request the data is transparently presented in the Pegasys SmPC (section 5.1).

CHMP noted that an increased probability of HBsAg conversion was seen with Pegasys treatment. Exploratory analysis of data from study YV25718 showed that baseline qHBsAg was not a predictor for HBeAg seroconversion, HBV-DNA levels and HBsAg loss at Week 24 of follow-up.

The time for HBe seroconversion in relation to therapy differed markedly in these children versus in adults. In adults treated for 48 weeks seroconversion was for the most achieved during therapy, with an additional 5% or so during the next 12 weeks of follow-up, and no further increase thereafter. In the paediatric study the HBe conversion rate at week 48 was low (around 8%), increasing to around 18% at 12 weeks FU and to 26% at 24 weeks of follow-up. It may be that this is explained by the very high HBV (and HbeAg) levels at baseline in children. The proportion of responders at 48 of FU was presented during the procedure. The trend of increasing response rates was maintained in Group A (n=101), at 1 year of follow up 32/101 had achieved HBeAg seroconversion. The study has a 5 year follow-up, and the pattern of HBV replication and the frequency of flares/relapses back to immune activation over time is important to follow.

The difference in decline of HBeAg and HBV-DNA between responders and non-responders opens for predictions of the likelihood of response early during treatment. Despite the exploratory nature of the analyses and small n numbers, the response in patients with lower decline in HVB-DNA at week 12 seemed poorer compared to those patients who achieved a steeper decline in HBV-DNA. For transparency, this is reflected in section 5.1 of the Pegasys SmPC.

Outcomes of interest in study YV25718 have been presented at the AASLD conference 2016, and will be presented as full length journal article, planned to be published within 2017. Overall, efficacy of PEG-IFN alpha 2a given for 48 weeks yielded similar results in HBeAg-positive children as previously shown in adult patients. It is therefore considered an option for the treatment of carefully selected children, where attention should be paid to updated HBV treatment guidelines.

2.5. Clinical safety

Introduction

The (somewhat problematic) safety profile of Pegasys in adult patients is well known. Data are also available from a limited number of children who were treated for hepatitis C-infection as part of clinical trials. Throughout the safety assessment below, comparisons are made to adult data, which were presented as part of the application. For adult data, reference is made to the two pivotal studies of Pegasys for the treatment of CHB (WV16140 and WV16141, concerning HBeAg positive and HBeAg negative patients, respectively). With regards to prior paediatric data the MAH refers to the paediatric study NV17424 (Pegasys +/- ribavirin for 48 weeks for the treatment of hepatitis C in children). NV17424 enrolled 114 children/adolescents aged 5-18 years, whereof 31 received Pegasys monotherapy for 48 weeks. However, during that study different terms were used when reporting AEs, and different reference values/methods were used for the assessment of some lab parameters. In addition, children were given either ribavirin (an agent associated with a number of side effects) or placebo in addition to a. This may have influenced the reporting of AEs (also in the placebo arm). In summary, since the number of patients in that paediatric study was also fairly low, a comparison is mainly done to the adult data with regard to safety.

A specific issue for interferon therapy in children is the risk of a negative impact on length development, in particular when treatment is given during the growth spurt in during puberty. This risk is already highlighted in the Pegasys SmPC (as Pegasys is already approved for the treatment of hepatitis C infection in children aged 5 and above).

Conclusions on the impact of PEG-IFN therapy on final height needs long term follow-up. Such 5-year data have been presented to the Agency and have as well been published (Haber et al, 2017) for children who were treated for hepatitis C with PEG-IFN α2b. The analysis of these data showed that a substantial proportion of children have a rather profound decrease in height per age percentiles, and that no relevant catch up in length is seen beyond 2 years of follow-up. In a short summary, 40% (19/48) of the children had a > 15 percentile height-for-age decrease from pre-treatment to the end of 5 year long-term follow-up compared to pre-treatment baseline percentiles; 13% (6/48) had a decrease from pre-treatment baseline > 30% height-for-age decrease. This is equivalent to a reduction of around 4 cm and 6-10 cm in final height. The Pegasys MAH has also previously shown such data for children treated for hepatitis C with a (PED-C study). Unfortunately, the interpretation of long term follow-up data in this case was hampered by a high rate of loss to follow-up. Out of 114 patients treated in that study, screening for long term FU was done for 57 patients who had been treated for 48 weeks, of whom 23 patients completed the 5-year follow-up. As there is no mechanistic reason to believe that the impact of different PEG-IFNs-alfa on growth differ, data on the impact of height obtained with other IFNs need to guide the interpretation of this safety issue until the Pegasys MAH generates and presents more substantial data for assessment.

The safety data from study YV25718 is presented in the following.

Patient exposure

111 patients were included. 105 patients were administered Pegasys for the planned duration; 2 stopped early and 4 were treated somewhat longer (49-52 weeks).

Adverse events

The overall AE frequencies, below, are similar to those seen in adults. Of note, only 1 single patient stopped therapy due to an AE, a low figure as compared to that rate in adult studies.

	PEG-IFN (N=111)
Total number of patients with at least one adverse event	96 (86.5%)
Total number of events	754
Total number of patients with at least one	
Serious AE	6 (5.4%)
AE leading to withdrawal from treatment	1 (0.9%)
AE leading to dose modification/interruption	8 (7.2%)
Related AE	90 (81.1%)
Severe AE (at greatest intensity)	8 (7.2%)

AEs reported in ≥5% of patients treated with peg-IFN for 48 weeks, children/adolescents vs adults

Adverse Event	Children/adolescents (N=111) YV25718, Groups A+C PEG-IFN No. (%)	Adults (N=448) WV16140 (HBe+) PEG-IFN + lamivudine placebo No. (%)
Pyrexia	57 (51)	240 (54)
Headache	34 (31)	119 (27)
Myalgia	-	117 (26)
Fatigue	9 (8)	109 (24)
Alopecia	7 (6)	81 (18)
Anorexia	-	71 (16)
Asthenia	10 (9)	54 (12)
Arthralgia	-	51 (11)
Abdominal Pain	19 (17)	46 (10)
Diarrhea	-	44 (10)
Dizziness	7 (6)	40 (9)
Nausea	10 (9)	38 (8)
Pruritus	-	36 (8)
Insomnia	-	35 (8)
Injection Site Reaction	-	34 (8)
Upper Respiratory Tract Infection	9 (8)	30 (7)
Rash	11 (10)	30 (7)
Rigors	-	29 (6)
Pharyngolaryngeal Pain	-	26 (6)
Cough	17 (15)	25 (6)
Malaise	-	23 (5)
Gingival Bleeding	-	23 (5)
Dyspepsia	-	22 (5)
Vomiting	17 (15)	
Influenza like illness	15 (14)	-
ALT increased	11 (10)	-
AST increased	11 (10)	-
epistaxis	10 (9)	-
decreased appetite	7 (6)	-
nasopharyngitis	7 (6)	-
rhinorrhea	6 (5)	-

Note: The table was made on the basis of AEs reported in the adult studies, and terms not listed but reported in the paediatric study were added on the lower rows (vomiting and rows below).

Around half of the patients in the present study were below the age of 12. Of the most frequently reported individual terms in Group A (patients without severe fibrosis), the following were reported more frequently in patients aged <12 compared with patients ≥12 years of age:

- pyrexia (68% vs 27%)
- cough (19% vs 8%)
- vomiting (21% vs 6%) and rash (15% vs 4%)

In contrast, the following events were reported more frequently in patients of ≥12 years of age:

- headache (35% vs 25%)
  influenza-like illness (23% vs 8%)

Serious Adverse Events

6/111 (5%) of patients in groups A+C experienced SAEs, none of which caused a stop of treatment, and all had resolved by 24 weeks of FU; the age was above 12 years in 4 out of 6 cases.

- 4 Infections: HBV 1, Latent TB 1, Micosporum infection 1, Tonsillitis 1
- 1 ALT/AST increased
- 1 osteochondrosis

Of note, in the CHB adult pivotal studies, 27 patients (6%) experienced SAEs in the PEG-IFN monotherapy arm.

Adverse Events that Led to Withdrawal of Study Treatment

One patient (1%) withdrew from study treatment due to a non-serious AE. The patient, a 5-year-old girl, experienced increased ALT and AST (> 10 x ULN) which were considered related to the study drug by the investigator. The event resolved after 8 weeks.

Of note, in the CHB adult pivotal studies, 21 patients (5%) in the PEG-IFN monotherapy arms discontinued study treatment prematurely for safety reasons.

Adverse Events and Laboratory Abnormalities that Led to Dose Modification of Study Treatment

Twenty-nine patients (26%) experienced an AE or laboratory abnormality that led to a dose modification Lab concerns low neutrophils, 14 (13%) or increased ALT levels, 13 (12%), and AEs concerned pyrexia, disturbance in attention and learning disorder, abdominal pain, neutropenia, and infection (respiratory tract infection and varicella).

Of note, in study WV16240 (adults, HBeAg-positive) 40% had dose modifications in the PEG-IFN monotherapy arm, mainly due to neutropenia, 22%, and ALT increase, 12%.

The proportion of young patients in need of dose modifications was similar or lower than the proportion seen in adult studies. This is further discussed under the “laboratory abnormalities” subheading.

AEs of special interest

Ophthalmological Disorders

13/111 patients (12%) reported an eye disorder during the study, none serious, of which 4 were considered to be related to study drug (eye pain, eyelid edema, retinal hemorrhage and retinal edema). None of these events led to discontinuation of PEG-IFN or dose modification.

Of note, in the CHB adult pivotal studies 7% experienced eye disorders in the PEG-IFN monotherapy arm, most commonly blurred vision (2%) and eye pain (2%). In the CHC pediatric study, eye disorders were reported for 8 patients (15%) in the PEG-IFN plus RBV combination arm, and 7 patients (23%) in the PEG-IFN monotherapy arm, most commonly conjunctivitis (4% and 19%) and eye pain (2% and 3%).

Psychiatric / neurologic events

Twelve patients (11%) reported a psychiatric disorder; depressed mood and depression were reported in one patient each. Both these events were considered related to study treatment, were mild and had resolved by the end of treatment.

41 patients (37%) reported a nervous system disorder, mainly headache (31%).

Of note, in the CHB adult pivotal studies, 17% of patients reported psychiatric disorders in the PEG-IFN monotherapy arms, mainly insomnia (8%) and depression (4%).

Thyroid Disorders, including lab abnormalities

Two patients (2%) had increased TSH reported as AEs; no other AEs related to thyroid function occurred. The events resolved without treatment, without modification or discontinuation from treatment with PEG-IFN:

- The first patient had a single high TSH value at Week 48 and positive TPO antibody at Week 24 and Week 48, but FT3 and FT4 within normal range.
- The second patient had FT3, FT4 and TSH values outside normal range and positive TPO antibody during treatment; high FT3 was detected at baseline, and FT3, FT4 and TSH returned to normal range by Week 24 of follow-up.

Of note, in the CHB adult pivotal studies, 3 patients (<1%) experienced hypothyroidism and 6 patients (1%) experienced hyperthyroidism (i.e. reported as AEs).

46 patients (41%) had at least one post-baseline thyroid lab abnormality (at least one value of FT3, FT4 or TSH outside of the normal range up to Week 24 of follow-up). The most frequently reported value was high FT3, which was reported in 40 patients (36%). Of note, 15 patients (37.5%) had a high FT3 abnormality at baseline. 14 patients (13%) had last or replicated high FT3 abnormality. None of the patients had high FT4 abnormalities or reported an event of hyperthyroidism.

Overview of Thyroid Function Laboratory Abnormalities, Group A + C

	Time-point			
		Post-Baseline		
Parameter	**Baseline[a]**	**Single (not Last)**	**Last/replicated**	**Any**
FT3 – low	-	2 (1.8%)	-	2 (1.8%)
FT3 – high	15	27 (24.5%)	14 (12.6%)	40 (36.0%)
FT4 – low	-	1 (0.9%)	1 (0.9%)	2 (1.8%)
FT4 – high	-	-	-	-
TSH – low	-	6 (5.4%)	-	6 (5.4%)
TSH – high	-	6 (5.4%)	1 (0.9%)	7 (6.3%)

Six patients (5.4%) had low TSH abnormalities, all single events and without FT4 3 increases at the same time point. High TSH levels were observed in 7 patients and in 2 this was reported as an AE (mentioned above).

No thyroid function laboratory abnormality led to dose modification. Four PEG-IFN-treated patients reported TPO antibodies, two of whom had all FT3, FT4 and TSH values within normal range; the other two patients had TSH value above normal and reported AEs, as mentioned.

In summary, the majority of thyroid laboratory abnormalities were isolated and single events of high FT3 values not accompanied by TSH or FT4 abnormalities. None of these abnormalities was reported as an AE, except two high TSH abnormalities AEs which did not require treatment.

Despite the rather high incidence of lab abnormalities (including at baseline) seen in this study, since the risk for thyroid disorder during/following therapy with interferons is well established and is already handled in the Pegasys SmPC, and despite noting difficulties in comparing the results to the adult ones and to the ones generated in the paediatric CHC study, CHMP considered that further discussion on the topic was not warranted.

Laboratory abnormalities

Only lab chemistry of higher interest is discussed below. No clinically relevant changes were seen in haemoglobin or creatinine and thyroid parameters were discussed above.

Neutrophils

Interferons carry a well-established risk for neutropenia. Below the lowest post-baseline neutrophil count for groups A+C are shown. These changes reversed by Week 24 of follow-up, and no patient had a neutrophil count below 0.25 x 10^9 cells/L at any time during the treatment and 24-week follow-up periods. Neutrophil counts less than 0.75 x 10^9 cells/L were clinically manageable with appropriate dose modifications. As seen previously, no severe infections were reported during the study. The occurrence and degree of neutropenia is in line with that seen in the adult studies.

Neutrophil Levels (x10^9 cells/L)	(N=111)
Normal, >= 2.0	8 (7.2%)
1.5 - <2.0	12 (10.8%)
1.0 - <1.5	45 (40.5%)
0.75 - <1.0	24 (21.6%)
0.5 - <0.75	17 (15.3%)
<0.5	5 (4.5%)

ALT flares

In study YV25718, as an inclusion criterion, patients had to have ALT > ULN but <10 × ULN within 35 days of baseline. The highest post-baseline values greater than 5.0 × ULN were reported in 65 patients (59%) in the pooled safety population. For most patients with post-baseline ALT ≥ 5.0 × ULN, ALT levels returned/were returning to baseline at Week 24 of follow-up except for 2 patients, who had a peak ALT value at Week 24 of follow-up but with normal bilirubin.

None of the ALT flares met the modified Hy's law criteria and there was no evidence of hepatic decompensation. Modified HY´s law criteria were defined as ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN or with clinical jaundice, ALP levels not taken into account.

The following table shows that the pattern (frequency, level and time for event) of ALT flares was similar in the paediatric and adult patients in the pivotal studies, YV25718 and WV16140.

ALT flares during therapy and follow-up, pediatric vs adult e-antigen positive CHB patients

ALT Flares	Paediatric (YV25718)		Adults (WV16140)
	Group A+C n = 111	Group B (control) n=50	PEG-IFN + Placebo n = 448
During Treatment:			
>5x ULN	57 (51.4%)	14 (28.6)	188 (42.0%)
>10x ULN	19 (17.1%)	3 (6.1%)	70 (15.6%)
During Follow-up:			
>5x ULN	19 (17.1%)	N/A (many started therapy)	110 (24.6%)
>10x ULN	5 (4.5%)		46 (10.3%)

Platelets

Post-baseline platelet counts in the range of 50.0- ≤75.0× 10^9 cells/L and 20.0 - ≤50.0 × 10^9 cells/L (this event reported as AE) were reported in one patient each. In both cases, platelet counts recovered to normal range without any dose reductions, without any bleeding events during the study. The frequency of thrombocytopenia has been higher in adult patients (likely driven by cirrhotic patients which were not included in the present paediatric study).

Platelet Levels (x10^9 cells/L)	(N=111)
Normal, >=100.0	92 (82.9%)
<100.0 - 75.0	17 (15.3%)
<75.0 - 50.0	1 (0.9%)
<50.0 - 20.0	1 (0.9%)

As previously mentioned (Adverse Events and Laboratory Abnormalities that Led to Dose Modification of Study Treatment), the proportion of patients in need of dose modifications for reasons of neutropenia and ALT increases was similar or lower as compared to what was seen in adult studies. In the Pegasys SmPC, specific dose modifications are recommended in the case of neutropenia, thrombocytopenia (at present only for adults), and ALT increases. CHMP noted that the present PI recommendations are somewhat different for adults and paediatric patients (presently age 5 and above) and that in addition in the present study protocol somewhat different rules were applied. CHMP considered that the MAH initial proposal could result in a complicated SmPC and has asked for further clarification.

With regard to the dose modification for low neutrophil counts, the MAH explained the reasons for which the dose modification recommendations differ in case of neutropenia between adult and paediatric patients and within the paediatric population between CHB and CHC patients. For children a more conservative approach in line with that used in the pivotal paediatric studies (NV17424 and YV25718) is proposed. CHMP considered that it is reasonable to use this conservative approach for children and to maintain the adult recommendations, which are well established since the Pegasys initial marketing authorization. The MAH proposal was endorsed by CHMP.

CHMP further noted that the differences in the recommendations proposed for children with CHB and CHC were minor and requested that a harmonized recommendation should be acceptable and should not impact the benefit-risk. Recommendations for dose modifications for CHB were also applied for children with CHC in the Pegasys PI. It was also agreed that ANC cut-off intervals should be maintained and should also be included for the adult population.

With regard to the dose modification for low platelet counts, the MAH highlighted that the approved rules for discontinuation and dose-modification scheme for low platelet counts in adults are essentially the same as those in paediatric patients. The MAH has however proposed changes to the recommendations for adults in the SmPC for consistency. The interval 25,000 to < 50,000 should be used instead of merely < 50,000 to decrease the risk for medication errors. CHMP agreed to this proposal.

With regard to the dose modification recommendation for high ALT levels, CHMP agreed that the differences observed between adults and children are justified by a more conservative approach applied for the paediatric population.

VITAL SIGNS, PHYSICAL FINDINGS

The tables below provide an overview of growth parameters at Week 48 of treatment and Week 24 of follow-up for study YV25718 (present study) and study NV17424 (the study in children with chronic hepatitis C).

Growth Parameters at Week 48 of Treatment: Study YV25718 and Study NV17424

	YV25718		NV17424	
	Group A+C PEG-IFN	Group B Untreated	PEG-IFN+RBV	PEG-IFN
Height	**n=108**	**n=47**	**n=37**	**n=22**
Mean Z-score change	-0.07	-0.01	-0.32	-0.39
Mean percentile change	-1.9	-0.5	-8.4	-9.8
Number of patients with >15 percentile drop	7 (6.5%)	1 (2.1%)	11 (22.4%)	6 (25.0%)
Weight	**n=106**	**n=47**	**n=49**	**n=24**
Mean Z-score change	-0.21	-0.08	-0.54	-0.34
Mean percentile change	-4.7	-2.4	-12.2	-10.9
Number of patients with >15 percentile drop	12 (11.3%)	4 (8.5%)	19 (38.8%)	8 (33.3%)

Growth Parameters at Week 24 of Follow-up: Study YV25718 and Study NV17424

	YV25718		NV17424	
	Group A+C PEG-IFN	Group B Untreated	PEG-IFN+RBV	PEG-IFN
Height	**n=110**	**n=15**	**n=48**	**n=20**
Mean Z-score change	0.10	-0.08	-0.21	0.25
Mean percentile change	-1.7	-1.9	-6.4	-6.5
Numbers (%) with >15 percentile drop	13 (11.8)	1 (6.7)	10 (21.0)	3 (15.0)
Week 12	2/109 (1.8)			
Week 24	6/110 (5.5)			
Week 36	4/109 (3.7)			
Week 48	7/108 (6.5)			
12 week FU	11/111 (9.9)			
24 week FU	13/110 (11.8)			
Weight	**n=110**	**n=15**	**n=49**	**n=20**
Mean Z-score change	-0.06	-0.32	-0.14	0.05
Mean percentile change	-1.9	-7.8	-4.1	0.9
Number of patients with >15 percentile drop	13 (11.8%)	3 (20.0%)	6 (12.5%)	1 (5.0%)

Height

Z-Scores

In the pooled safety population (Group A + Group C), the mean change from baseline in the height for age Z-score (which expresses the given variable as a number of standard deviations below or above the reference mean value of a given age and sex) was -0.01 at Week 24, -0.07 at Week 48 on treatment, and -0.10 at Week 24 of Follow-up. Similar changes were observed in the untreated Group B (-0.07, -0.01, and -0.08, respectively).

Changes in Percentile

Mean height for age percentile showed little variation throughout the study in the pooled safety population; 59.4 at baseline, 58.1 Week 48 of treatment, and 56.8 at Week 24 of follow-up time-points. At Week 48 of treatment, the proportion of patients with > 15% drop in height for age percentile was 6%, and by Week 24 of follow-up, this proportion was 12%. In the untreated Group B, the mean height for age percentile was 49.7 at baseline, 50.2 at Week 48 of the principal observation period, and 53.6 at Week 24 of follow-up. The proportion of patients in group B with > 15% drop in the height for age percentile was 2% at Week 48 principal observation period, and 7% by Week 24 of follow-up.

CHMP noted that it is already established that the treatment of children/adolescents with IFN carries a risk for a reduced final height (see introduction to Safety section), and that the risk for non-reversible decreases in mean height percentiles (i.e. without a substantial catch-up when treatment is stopped) is most likely highest when therapy is given a time of the growth spurt during puberty.

CHMP also noted that the reduction in height for age percentiles in this study seemed lower than in the previous study undertaken in CHC patients (see introduction to safety). It was discussed that the differences in reductions at post treatment follow-up between studies could be a result of the

proportions of individuals most vulnerable (linked to age/growth spurts). Although CHMP agreed that this issue needed long term follow-up, the MAH was asked to provide scatter plots and box plots on changes in height for age percentiles *by baseline age*, from BL to week 48 and from BL to 24 weeks FU, using pooled data from the present study (YV25718) and from the previous paediatric study in CHC infected patients (N17424) and to redo the exercise in later presentations of long term data (presumably 2- and 5-years follow-up). The age categories to be used for the box plots were agreed to be 3-5 years, 6-8 years, 9-12 years, 13-15 years and 16-17 years. In addition to the analyses requested, the MAH also analysed these data by gender and for each study separately. Finally, in a further effort to understand the potential effect of PEG-IFN on growth during puberty, the MAH conducted additional height-for-age percentile analyses using gender-specific age ranges for puberty.

The MAH provided the requested additional information. Although there was no apparent pattern of percentile change from baseline that could give further guidance to the prescriber in addition to the existing boxed warning with regards to growth and development, CHMP agreed that a greater risk of growth impairment especially during puberty cannot be ruled out and considered that the current wording in section 4.4 of the Pegasys SmPC "Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition" was adequate.

Post-Marketing Experience in Paediatric Patients

In total, 355 cases (727 AEs) involving paediatric patients treated with PEG-IFN were identified in the safety database. These cases involved mostly adolescents (aged ≥12 to < 18 years; 196 [55.2%]) and children (aged ≥2 years to <12 years; 117 [33.0%]); 39 cases (11.0%) were from children aged 3 to 5 years. The reported cases concerned primarily paediatric patients treated with PEG-IFN for CHC (168 cases [47%]).

The AEs that were reported were those typically seen/reported in the adult studies and in the paediatric studies discussed in this report. No new safety signals were seen.

2.5.1. Discussion and conclusions on clinical safety

Apart from the risk of reduced height, the safety profile of a in these 111 children (around half below the age of 12, and 18 children (16%) below the age of 5) seems broadly similar to the safety profile reported in adults. The frequency of the most common AEs (pyrexia and headache) was reported in similar frequencies as in adults, while other typical AEs (such as fatigue) were reported in lower frequencies, perhaps because terms are interpreted differently, or may be hard to ask about.

The rate of neuropsychiatric events in the present study was similar or lower to that seen in adults; there were two reported depressive episodes; both were mild and resolved without the halt of therapy.

No severe infections were seen, and the frequency and degree of neutropenia was similar or lower than that seen in adults. ALT flares, as a marker of HBV clearance, were seen in similar frequencies and severities as in adults.

Only one patient stopped therapy due to an AE (ALT increase >10 x ULN) and the event resolved.

Specific SmPC recommendations for which levels of lab abnormalities (neutropenia, thrombocytopenia, ALT increases) should trigger dose reductions were clarified.

A main issue for the use of peg-IFN in children is the risk for a shortened final height, in particular when treatment is given at the time of growth spurt in puberty (i.e. no chance for catch up post treatment). In the present study 6.5% of the children had a >15% reduction in height for age percentiles during treatment (12% at 24 weeks post treatment FU). In a prior study with peg-IFN 2a

+/- ribavirin for the treatment of CHC in children aged 5-18 years, 13/68 (20%) had a >15% decrease in this parameter at that time point, and in a prior study with PEG-IFN 2b (CHC, paediatric population) the figure was around 40%, where it was already shown that this reduction remained long term. There is presently no data to support that there is any relevant difference between interferons with regards the risk for height reductions. Differences in reductions at post treatment follow-up between studies would likely rather be a result of proportions of individuals most vulnerable (i.e. at growth spurt during puberty when treated).

Pooled data from the CHB and CHC studies in children were analysed by gender and for each study separately. Moreover, the MAH has provided height-for-age percentile analyses using gender-specific age ranges for puberty. Although there was no apparent pattern of percentile change from baseline that could give further guidance to the prescriber in addition to the existing boxed warning with regards to growth and development, CHMP agreed that a greater risk of growth impairment especially during puberty cannot be ruled out and that the current wording in section 4.4 of the SmPC "Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition" is considered adequate.

One additional amendment to Section 4.4 of the SmPC is inserted to clarify that growth inhibition is not only an issue with combination therapy but also Pegasys monotherapy.

CHMP noted that the box warning in section 4.4 of the Pegasys SmPC referring to "growth and development" ended with a wording stating that "there are no data on long-term effects on sexual maturation" and discussed the validity of this statement. To date, no data on the effect of Pegasys on sexual maturation are available. CHMP also noted that Tanner stages will be recorded for assessing sexual maturation in the ongoing study NV25361, which has a follow-up of 5 years after end of 48 weeks of treatment with PEG-IFN in combination with lamivudine or entecavir (for 56 weeks) compared with untreated controls (114 paediatric patients in total). It was acknowledged that no data were available for IFN α2b that and only limited data were available for PEG-IFN α2b. CHMP agreed to leave the current wording unchanged until more data is available.

2.5.2. PSUR cycle

The PSUR cycle remains unchanged.

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

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.3 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.3 with the following content:

Safety concerns

The list of safety concerns were updated as follows:

Summary of safety concerns	
Important identified risks	**<u>For PEG-IFN alfa-2a or PEG-IFN alfa-2a and ribavirin combination therapy:</u>** Psychiatric and CNS events, including depression, suicidal ideation, attempted suicide, suicide, aggression, nervousness, confusion, concentration impairment, and substance abuse, Blood and lymphatic system events, including neutropenia, thrombocytopenia, anemia, aplastic anemia, and pancytopenia Endocrine system disorders, including hyperthyroidism, hypothyroidism, and diabetes mellitus Cardiac events, including angina, MI, cardiac failure and atrial fibrillation Hepatobiliary disorders, including hepatic failure Hypersensitivity reactions, including hypersensitivity, anaphylaxis, and urticaria Autoimmune disorders, including SLE, RA, and ITP Serious infections, including cellulitis, bronchitis, sepsis, and UTI Ocular disorders, including retinopathy, retinal hemorrhage, retinal detachment, optic neuropathy, retinal vascular disorder, and visual disturbance Pulmonary disorders, including dyspnea, pneumonia, and interstitial pneumonitis Skin disorders, including psoriasis, sarcoidosis, EM, SJS, and TENS Teratogenic risk associated with ribavirin Impairment in height and weight gain during treatment in pediatric patients
Important potential risks	• Possible persistence or *de novo* development of neuropsychiatric events after stopping treatment in pediatric patients. • Possible persistence or *de novo* development of thyroid dysfunction after stopping treatment and its potential impact on growth in pediatric patients. • Potential of medication errors in dosing in pediatric patients
Missing information	• Safety and efficacy in HCV patients aged 3 to 5 years old. • Safety and efficacy in HIV/HCV patients aged 3 to 17 years old. • Safety and efficacy in previous non-responder HCV patients aged 3 to 17 years old. • Safety and efficacy in immunotolerant HBV patients aged 3 to 17 years old. • Use of Pegasys in pediatric patients with renal impairment.

Pharmacovigilance plan

The PV plan was updated as follows:

Study	Objective	Safety concerns addressed	Status	Date for Submission of interim or final reports
NV25361	To evaluate the efficacy of Pegasys + lamivudine or Pegasys + entecavir, compared with an untreated control group in pediatric patients with chronic hepatitis B in the immune-tolerant phase, as measured by loss of HBsAg 24 weeks post-end of treatment/end of untreated observation. The treatment will be for a total of 56 weeks for Pegasys + Lamivudine or Pegasys + entecavir. The patients will be followed up closely for further 6 months after stopping treatment and then yearly for 5 years	Safety and efficacy in immunotolerant HBV patients aged 3-17 years old Impairment in height and weight gain during treatment in pediatric patients Possible persistence or de novo development of neuropsychiatric events after stopping treatment in pediatric patients Possible persistence or de novo development of thyroid dysfunction after stopping treatment and its potential on growth in pediatric patients	Ongoing	Submissions planned after: Primary endpoint Q4 2019 5-year follow-up planned for Q2 2024
YV25718 (previously known as WV18447) – HBV Pediatric IMAC study	To evaluate the long-term effects of Pegasys on certain efficacy and safety measures in immunoactive HBV patients aged 3-17 years old Treatment with Pegasys was for 48 weeks. The long-term follow-up period will last up to 5 years after end of treatment.	Safety and efficacy in immunoactive HBV patients aged 3-17 years old. Possible persistence or de novo development of neuropsychiatric events after stopping treatment in pediatric patients Possible persistence or de novo development of thyroid dysfunction after stopping treatment and its potential on growth in pediatric patients	Ongoing	Submission planned after: 5-year follow-up Q3 2020

Risk minimisation measures

The RMMs were updated as follows:

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Important identified risks:		
Psychiatric and CNS Events	Section 4.3 (Contraindication) of the Pegasys EU SmPC. Section 4.4 (Special warnings and precautions for use) contains a boxed warning describing the spectrum of neuropsychiatric disorders. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Blood and Lymphatic System Events	Section 4.2 (Posology and method of administration) of the Pegasys EU SmPC provides recommendations for the management of low ANC (dose adjustment of Pegasys), low platelet count (dose adjustment of Pegasys), and treatment-emergent anemia (dose adjustment of ribavirin). Section 4.4 (Special warnings and precautions for use) of the EU SmPC describes the spectrum of hematological abnormalities observed. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Endocrine System Disorders	Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes the spectrum of these events and recommendations for their management. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Cardiac Events	Section 4.3 (Contraindication) of the Pegasys EU SmPC. Section 4.4 (Special warnings and precautions for use) of the EU SmPC describes the spectrum of these events. AEs are listed in EU SmPC Section 4.8 (Undesirable effects). <u>Use of Pegasys in combination with ribavirin</u> Section 4.4 (Special warnings and precautions for use) of the Copegus EU SmPC describes the ischemic cardiac events that may result from anemia. Dosage modification guidelines for the management of treatment-emergent anemia are provided in Section 4.2 ((Posology and method of administration) of the Pegasys EU SmPC and Copegus EU SmPC.	None proposed

Hepatobiliary Disorders	Section 4.3 (Contraindication) of the Pegasys EU SmPC. Section 4.4 (Special warnings and precautions for use) of the EU SmPC details the spectrum of occurrence of the hepatic decompensation and providing recommendations for management. Instructions in Section 4.2 (Posology and method of administration) of the Pegasys EU SmPC discuss the occurrence of the event and provide recommendations for dose management based upon liver function parameters. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Hypersensitivity Reactions	Section 4.3 (Contraindication) of the Pegasys EU SmPC. Section 4.4 (Special warnings and precautions for use) of the EU SmPC describes the spectrum of hypersensitivity reactions and provides recommendations for managing these events. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Autoimmune Disorders	Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes the spectrum of occurrence of these events and recommendations for management. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Serious Infections	Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes the spectrum of occurrence of these events and recommendations for management. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Ocular Disorders	Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes the spectrum of ocular events and provides recommendations for managing these events. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Pulmonary Disorders	Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes the spectrum of such events. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Skin Disorders	Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes the spectrum of skin disorders and provides recommendation for managing psoriasis. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Teratogenic risk associated with ribavirin	Pegasys EU SmPC Section 4.6 (Fertility, pregnancy and lactation)	None proposed

	Copegus EU SmPC Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use)Section 4.6 (Fertility, pregnancy and lactation)	
Impairment in height and weight gain during treatment in pediatric patients	A boxed warning in Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes growth and development in children and adolescents. Section 4.8 (Undesirable effects) of the EU SmPC also described growth inhibition observed in pediatric patients.	None proposed
Potential Risks		
Possible persistence or *de novo* development of neuropsychiatric events after stopping treatment in pediatric patients	A boxed warning in Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC describes the spectrum of neuropsychiatric reactions. AEs are listed in EU SmPC Section 4.8 (Undesirable effects).	None proposed
Possible persistence or *de novo* development of thyroid dysfunction after stopping treatment and its potential impact on growth in pediatric patients**.**	A boxed warning in Section 4.4 (Special warnings and precautions for use) of the Pegasys EU SmPC the spectrum of these events and recommendations for their management. Hypothyroidism and hyperthyroidism are listed as AEs in EU SmPC Section 4.8 (Undesirable effects), as well as further information on thyroid function.	None proposed
Potential of medication errors in dosing in pediatric patients	Dosing by BSA category and dosing graph included in the EU SmPC.	None proposed
Missing Information:		
Safety and efficacy in HCV patients aged 3 to 5 years old	Section 4.2 (Posology and method of administration) of the Pegasys EU SmPC states “There is limited experience with Pegasys in treating paediatric patients with CHC aged 3 to 5 years”	None proposed
Safety and efficacy in HIV/HCV patients aged 3 to 17 years old	Section 4.2 (Posology and method of administration) of the Pegasys EU SmPC states “There are no data in paediatric patients coinfected with HCV/HIV”	None proposed
Safety and efficacy in previous non-responder HCV patients aged 3 to 17 years old	Section 4.2 (Posology and method of administration) of the Pegasys EU SmPC states “There is limited experience with Pegasys in treating paediatric patients with CHC (…) who have failed to be adequately treated previously”	None proposed
Safety and efficacy in immunotolerant HBV patients aged 3 to 17 years old	None	None proposed

Use of Pegasys in pediatric patients with renal impairment	Section 4.2 (Posology and method of administration) of the EU SmPC states "There are no data in paediatric patients with renal impairment"	None proposed

2.7. Update of the Product information

Changes to the Pegasys SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 are introduced. The Package Leaflet is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant. The changes of the Product Information have been assessed as not requiring the need for a specific consultation. This was considered acceptable.

3. Benefit-Risk Balance

In study YV25718, Pegasys was administered for 48 weeks to 111 children aged 3-17 with HBeAg positive CHB and ALT levels above the normal (prior to entry), indicative for entrance to the immune active stage. A control group of 50 children received no treatment but had the chance to start therapy after the week 48 time point. Around half of the patients were below the age of 12, and again, around half had an ALT elevation at baseline of < 2 X ULN.

3.1. Favourable effects

The vast majority of children with CHB do have a spontaneous HBe seroconversion after the entrance to the immune active phase, when followed long term (80-100%, see introduction section 2.1), although very few have an immune clearance (HBs seroconversion). However, in those responding to PEG-IFN treatment, the immune active stage(which precedes the HBe seroconversion) is shortened and the risk of fibrosis development is consequently lowered. The overall response rate (i.e. HBe seroconversion at 24 weeks post treatment) of 26% is similar, or somewhat lower than that seen in adult studies. The Odds ratio for HBe seroconversion in the treated vs. the untreated patients was around 5 in this study (at 6 months follow-up); the immune clearance rate (HBsAg seroconversion) is low also with therapy, but considerably higher than in the untreated patients in this study (8% vs. 0% at 24 weeks of follow-up).

Efficacy Endpoints at 24 Weeks after the End-of-Treatment: ITT Population			
	Treated (N=101) (%), [95% CI]	Untreated (N=50) (%), [95% CI]	Odds Ratio [95% CI]
HBeAg seroconversion	26 (26) [18, 35]	3 (6) [1, 17]	5.4 [2, 19]
HBV genotype A	3/9 (33.3)	1/3 (33.3)	1.0 (0.04,78.4)
B	7/21 (33.3)	0/6 (0.0)	-
C	13/34 (38.2)	1/23 (4.3)	13.62 (1.7,604.5)
D	3/31 (9.7)	1/18 (5.6)	1.8 (0.1,101.2)
Other	0/6 (0.0)	0/0	-
ALT <1xULN	0/7 (0)	0/5	-

>=1xULN - <2xULN	9/41 (22.2)	0/19	-
>=2xULN - <5xULN	15/43 (34.9)	1/17 (5.9)	8.6 (1.1,383.0)
>=5xULN - <10xULN	2/8 (25.0)	2/9 (22.2)	1.2 (0.06,20.7)
>=10xULN	0/2 (0.0)	0/0	-
HBsAg seroconversion	8 (8) [4,15)	0 (0) [0, 7]	-
Normal ALT	52 (51) [41,62]	6 (12) [5,24]	7.8 [3,24]
HBV-DNA < 2000 IU/mL	29 (29)	1 (2)	19.7
undetectable	17 (17)	1 (2)	9.9

3.2. Uncertainties and limitations about favourable effects

It is well known that response rates differ by HBV genotype. Of those genotypes studied (mainly A-D), genotype D, the one at least historically most prevalent in southern parts of Europe, the one at least historically most prevalent in southern parts of Europe, and also in Eastern Europe/Russia responds less well to PEG-IFN therapy. In adults treated with 48 weeks of peg-IFN the HBe seroconversion rates were around 20-25% for this genotype as compared to 30-40% for the others. In the present study only 10% (3/31) of the genotype D-infected patients responded to therapy (table next page). To what extent this very low figure was an effect of the genotype per se, or other negative predictive factors potentially over represented in that subpopulation in this study was further explored. It was noted that normal to minimally increased ALT levels were more frequent in these children. HBeAg levels were also higher, potentially reflecting that children with subtype D (mainly included in Russia and Ukraine) to a greater extent were included despite not having entered the immune active stage. Hence, other factors than subtype per se may at least in part explain the very low response rate in genotype D-infection in the present study.

Exploratory subgroup analyses of the primary endpoint of HBeAg seroconversion by genotype were supportive of a treatment benefit across HBV genotypes B, C and D. In the case of HBV genotype A, an odds ratio (OR) of 1.0 was observed, but the number of patients with this genotype was too low (9 in Group A and 3 in Group B) to enable a meaningful assessment of the treatment effect. In the specific case of HBV genotype D, which is considered as a less responsive genotype (Sunbul 2014), a less profound treatment effect on HBeAg seroconversion rate was observed (9.7%) comparing to HBV genotypes B and C (33.3%-38.2%).

The MAH also analysed to what extent factors other than genotype D may explain HBeAg seroconversion rate of <10% in this study. Baseline characteristics of the treated patients with HBV genotype D were compared with those with non-D genotypes to investigate whether any baseline factors that are predictive of worse response may have contributed to the lower response rate in HBV genotype D patients.

The inclusion criteria to this study could have been seen as liberal with regards to ALT levels to be included and during what time span prior to baseline at the MAH was asked to discuss. It was clarified that the inclusion criteria used in study YV25718 were chosen to ensure patients were in the immune-active phase of the disease (i.e. defined by positive HBeAg, HBV DNA >2000 IU/mL, ALT elevated, active inflammation on liver biopsy [McMahon 2008]). The ALT criterion aligns with the previous adult Pegasys CHB studies. Moreover, this ALT inclusion criterion is consistent with the current treatment guidelines (i.e. AASLD [Terrault et al 2016], EASL [EASL 2017], APASL [Sarin et al 2016]), which state that patients with minimally elevated ALT levels (1-2 × ULN) can still be considered for treatment. Indeed, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2013 paediatric CHB guideline treatment algorithm advocates liver biopsy and subsequent treatment consideration in children with elevated ALT levels (Sokal et al 2013). Upon CHMP request, the MAH

revised section 4.1 of the Pegasys SmPC to highlight that the indication concerns children with persistently elevated ALT levels (i.e. the marker for entrance to the immune active stage) and included references to sections 4.2, 4.4 and 5.1. Also, the response at week 12 of therapy (HBV-DNA decline from baseline) seemed predictive for e-antigen seroconversion (aim of therapy). Although the data is too limited and variable to provide a definite stopping rule, the data is presented as part of section 5.1 of the Pegasys SmPC for transparency.

Since, in general, lower baseline ALT level, higher HBV-DNA and higher HBsAg level are associated with poorer response to PEG-IFN treatment, these factors may have contributed to the lower HBeAg seroconversion rate observed in patients with HBV genotype D in YV25718 study. In a further effort to understand what factors may influence response in patients with genotype D, baseline and demographic characteristics of these patients were analyzed by whether patients achieved HBeAg seroconversion at Week 24 of follow-up. However, as only 3 out of 31 patients with genotype D experienced seroconversion, it was not possible to draw reliable conclusions from this analysis. The MAH further noted that the 9.7% response rate observed in the paediatric study YV25718 was in line with the results of a meta-analysis of pivotal and post-marketing data exclusively in patients treated with PEG-IFN, recently undertaken by the MAH, in which the response rate was 10.3%. Despite the limitations of these analyses, CHMP agreed that genotype D will be included in the approved paediatric indication and that section 5.1 of the Pegasys SmPC will show response rates by genotype.

Furthermore, the MAH provided data on the treatment of HBV genotypes other than A-D. Despite the fact that the included numbers were low, CHMP agreed that the approved paediatric indication for Pegasys in CHB paediatric patients will also include these patients.

3.3. Unfavourable effects

Treatment with IFNs carries a long list of well-established and common side effects, including neutropenia, thrombocytopenia, influenza-like side effects and neuropsychiatric side effect. The frequency and severity of these side effects seems similar in children compared to adults. Of note, the comparison of subjective side effects in children and adults should be done cautiously, since the reporting and understanding of such events for small children is certainly not easy. Furthermore, there is a risk of inducing autoimmune disorders, of which thyroid disease is most prevalent.

On top of the side effects seen in adults, children are at risk for a reduced final length. Length per age percentiles is substantially reduced during therapy. That was shown for both non-pegylated interferons and PEG-IFN α2a and 2b. Long term follow-up (5 years) was so far more successfully performed in children treated with PEG-IFN α2b than for children treated with PEG-IFN α2a (Pegasys), both in the treatment of hepatitis C-infection. For the former PEG-IFN α2b, it was shown that impaired growth largely recovered posttreatment following 24 weeks of therapy, but only partially so for those treated for 48 weeks.

3.4. Uncertainties and limitations about unfavourable effects

Effects on length in children treated with IFNs and recovery rates post treatment differ between studies, including in cross-study comparisons of PEG-IFN α2a. Available data does not provide sufficient evidence for a differential risk between interferons, and there is still a need to collect further long term data after treatment with PEG-IFN α2a. Study YV25718 aims to follow all patients for 5 years post treatment. It is important that the MAH makes all efforts to minimize the loss to follow-up, so that the issue of impact on height can be adequately followed, in addition to following the course of the hepatitis B-infection in responders as well as non-responders. As part of the present procedure the

company was asked to further elaborate on length impairment by age at starting PEG-IFN therapy; an exercise that should be repeated in future follow-ups of this study.

The MAH provided the requested additional information. Although there was no apparent pattern of percentile change from baseline that could give further guidance to the prescriber in addition to the existing boxed warning with regards to growth and development, CHMP agreed that a greater risk of growth impairment especially during puberty cannot be ruled out and considered that the current wording in section 4.4 of the Pegasys SmPC "Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition" was adequate.

3.5. Benefit-risk assessment and discussion

3.5.1. Importance of favourable and unfavourable effects

CHB runs a benign disease course in most children, and the risk for developing significant/more severe fibrosis during childhood is low also without treatment. In many cases therapy can therefore be deferred (also if ALT levels are somewhat increased), having side effects and moderate efficacy in mind. In cases where treatment is deemed to be adequate, the efficacy of PEG-IFN α2a is likely similar to that seen in adults. For those, (around 25% responding to therapy) there is a decreased risk of fibrosis development, and in longer term, a decreased risk of hepatocellular cancer. The response rate was correlated to the level of ALT increase at baseline, which is well established from studies in adults. Following questions and requests from CHMP, section 4.1 of the Pegasys SmPC therefore clarifies that the indication only concerns children with persistently elevated ALT levels (i.e. marker of immune activation).

Further, response rates in genotype D-infected children, constituting around one third of study subjects, were very low (around 10%). To some extent, the figure is likely explained by other baseline factors, since further analyses indicated that normal or minimally increased ALT levels were more frequent in the genotype D-infected children in the present study. In adult studies the difference in outcomes by genotype was less pronounced. Hence, a genotype specific indication is not considered necessary by the CHMP, but the data is reflected in section 5.1 of the SmPC. Of note, genotypes other than A-D have not been studied, neither in children nor adults, which is reflected in the SmPC.

Moreover, another factor that may have affected the delayed HBeAg-seroconversion in paediatric responders in this study vs. adult responders was the mean baseline HBeAg level, which was higher in children than in adults. The difference in decline of HBeAg and HBV-DNA between responders and non-responders opens for predictions of the likelihood of response early during treatment (for example at week 12). The MAH was asked to provide a similar analysis on the paediatric data. Despite the exploratory nature of the analyses and small n numbers, the response in patients with lower decline in HVB-DNA at week 12 seemed poorer compared to those patients who achieved a steeper decline in HBV-DNA. For transparency, this is reflected in section 5.1 of the Pegasys SmPC.

The common side effects seemed to be similar in frequency in children compared to adults, although AE reporting from young children would likely be associated with some methodological problems. The frequency of severe AEs was reported to be low, and therapy was stopped due to an AE in only 1/111 treated in this study. The majority of thyroid laboratory abnormalities, an event linked to interferon therapy, were isolated and single events of high FT3 not accompanied by TSH or FT4 abnormalities. None of these abnormalities was reported as an AE, except two high TSH abnormalities AEs which did not require treatment. Perhaps the main safety issue is the risk of reduced adult stature, where treatment of paediatric patients with interferons in this and prior trials yielded variable but overall

substantial proportions of patients with marked reductions in height by age percentiles, which in many cases seem only partially reversible.

There is presently no data to support that there is any relevant difference between interferons with regards the risk for height reductions. Differences in reductions at post treatment follow-up between studies would likely rather be a result of proportions of individuals most vulnerable (i.e. at growth spurt during puberty when treated). Of note, a greater risk of growth impairment especially during puberty cannot be ruled out and the current wording in section 4.4 of the Pegasys SmPC was updated accordingly. One additional amendment to Section 4.4 of the SmPC is inserted to clarify that growth inhibition is not only an issue with combination therapy but also Pegasys monotherapy.

3.5.2. Balance of benefits and risks

The benefit risk balance for the revised proposed indication is currently considered positive. Relevant sections of the SmPC (including section 4.1) were updated to certify a more adequate selection for whom to treat. In order to emphasize the need for the prescribers to consult section 4.2, 4.4, and 5.1 for decision making, CHMP agreed that the following wording “with respect to the decision to initiate treatment in paediatric patients, see section 4.2, 4.4, and 5.1” is added to the Pegasys SmPC. A more conservative writing which minimizes the risk for the treatment of children, who barely have entered the immune active stage, is warranted, having response rates and safety issues in mind. Further, despite some limitations, the results of exploratory analyses conducted by the MAH can be considered supportive of therapy of all genotypes.

3.5.3. Discussion on the Benefit-Risk Balance

The views around which children with CHB should be treated vary between regions and countries. To treat children with weekly injections of PEG-IFN for 1 year, with associated side effects, and a fairly low probability of response may indeed be questioned in most cases, having the general disease course in mind. However, daily therapy with direct antivirals (conversion rate similar), per se well tolerated, may also be problematic in some cases, taking for example adherence into account, and less established knowledge when such therapy can be safely stopped. While treatment likely could be deferred during childhood and adolescents in many cases, there is still a group of paediatric patients where therapy would be indicated.

3.6. Conclusions

The overall benefit/risk balance of Pegasys for treatment of non-cirrhotic children and adolescents 3 years of age and older with HBeAg-positive CHB, who show evidence of viral replication and persistently elevated serum ALT levels, as well as for all other approved indications, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include the use of Pegasys in the treatment of paediatric patients from 3 to less than 18 years of age with chronic Hepatitis B in the immune-active phase; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from study YV25718. The Package Leaflet is updated in accordance. An updated RMP (version 8.3) was agreed.

Paediatric data

The CHMP reviewed the paediatric data of study YV25718 subject to the agreed Paediatric Investigation Plan EMEA-000298-PIP01-08-M05. The results of this study are reflected in the Pegasys SmPC and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the use of Pegasys in the treatment of paediatric patients from 3 to less than 18 years of age with chronic Hepatitis B in the immune-active phase; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from study YV25718. The Package Leaflet is updated in accordance. An updated EU RMP (version 8.3) was agreed.

Summary

Please refer to Scientific Discussion Pegasys-H-C-395-II-91